THE STATE OF SOUTH CAROLINA
In The Supreme Court

APPEAL FROM SPARTANBURG COUNTY
Court of Common Pleas

Roger L. Couch, Circuit Court Judge

Case No. 2007-CP-42-1438

State of South Carolina ex. rel. Alan Wilson in his capacity as Attorney General of the State of South Carolina, ... Respondent,

v.

Ortho-McNeill-Janssen Pharmaceuticals, Inc., f/k/a Janssen Pharmaceutica, Inc., and/or Janssen, L.P., and Johnson & Johnson, Inc., ... Defendants.

Of whom Ortho-McNeill-Janssen Pharmaceuticals, Inc. is ..... Appellant.

RECORD ON APPEAL - VOLUME VII

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INDEX TO RECORD ON APPEAL

PAGE

VOLUME ONE

I. ORDERS/JUDGMENTS

Order of Remand, dated July 10, 2007 1

Order Denying the State's Motion for Non-Jury Determination, dated August 27, 2011 7

Order Regarding Defendant's Motions for Summary Judgment and Parties' Motions *in Limine*, dated February 25, 2011 8

Penalty Order, dated June 3, 2011 27

Order Denying Defendant's Motion for Judgment Notwithstanding the Verdict or, in the Alternative, for a New Trial, dated December 20, 2011 44

Order Denying Defendant's Motion to Alter or Amend the Judgment and/or for a New Trial, dated December 20, 2011 50

Order Granting the State's Motion to Transfer Case and Certify the Case for Review by this Court, dated February 27, 2012 56

II. PLEADINGS

Complaint, filed April 23, 2007 58

Second Amended Complaint, filed March 19, 2010 102

Defendants' Answer to Plaintiff's Second Amended Civil Action Complaint, filed April 11, 2010 121

III. TRANSCRIPTS

Hearing Transcript, February 2, 2011 143

MOTIONS 143

Transcript of Trial, March 7-22, 2011 182

MOTIONS 194

PLAINTIFF'S OPENING STATEMENT 320

PUBLISHED DEPOSITION OF MAGALI HAAS 366

PUBLISHED DEPOSITION OF SALLY BERRY 399

TESTIMONY OF WILLIAM WIRSHING

Direct Examination by Mr. Trammell 414

VOLUME TWO (Begins at R. 501)

Cross Examination by Mr. Campion 593

Redirect Examination by Mr. Trammell 674

TESTIMONY OF LAURA PLUNKETT

Direct Examination by Mr. Trammell 687

Cross Examination by Mr. Murphy 885

VOLUME THREE (Begins at R. 1001)

Redirect Examination by Mr. Trammell 1038

Re-Cross Examination by Mr. Murphy 1078

Redirect Examination by Mr. Trammell 1084

PUBLISHED DEPOSITION OF EDWARD BRANN 1087

PUBLISHED DEPOSITION OF DONNA OHYE 1116

TESTIMONY OF ANGIE ALDERMAN

Direct Examination by Mr. White 1139

Cross Examination by Mr. Pugh 1175

Redirect Examination by Mr. White 1177

PUBLISHED DEPOSITION OF GAHAN PANDINA 1186

PUBLISHED DEPOSITION OF RILEY SMITH 1208

TESTIMONY OF JAMES ASSEY

Direct Examination by Mr. Coggins 1214

Cross Examination by Mr. Murphy 1230

Redirect Examination by Mr. Coggins 1236

Re-Cross Examination by Mr. Murphy 1244

Redirect Examination by Mr. Coggins 1245

Re-Cross Examination by Mr. Murphy 1248

PUBLISHED DEPOSITION OF RONALD KALMEIJER.....1249

PUBLISHED DEPOSITION OF JOHN JACOPPI.....1251

PUBLISHED DEPOSITION OF PHILOMENA MCARTHUR.....1256

PUBLISHED DEPOSITION OF PATRICIA DESANTIS 1282

PUBLISHED DEPOSITION OF AMY GROGG 1284

PUBLISHED DEPOSITION OF OLGA MITELMAN 1295

TESTIMONY OF DAVID PATTERSON

Direct Examination by Mr. Coggins.....1299

Redirect Examination by Mr. Coggins 1316

Re-Cross Examination by Mr. Pugh 1317

PUBLISHED DEPOSITION OF IVO CAERS.....1320

MOTION.....1331

TESTIMONY OF RAMY MAHMOUD

Direct Examination by Mr. Campion.....1371

VOLUME FOUR (Begins at R. 1484)

Cross Examination by Mr. Trammell 1484

Redirect Examination by Mr. Campion.....1645

Re-Cross Examination by Mr. Trammell.....1665

TESTIMONY OF IVO CAERS

Direct Examination by Mr. Campion.....1672

MOTION.....1722

TESTIMONY OF IVO CAERS

Cross Examination by Mr. Simmons 1726

TESTIMONY OF MICHAEL CHESTER

Direct Examination by Mr. Pugh 1763

Cross Examination by Mr. Coggins 1819

MOTION 1887

TESTIMONY OF MICHAEL CHESTER

Cross Examination by Mr. Coggins 1906

Redirect Examination by Mr. Pugh 1919

Re-Cross Examination by Mr. Coggins 1922

TESTIMONY OF SHELDON BRADSHAW

Direct Examination by Mr. Murphy 1925

VOLUME FIVE (Begins at R. 1980)

Cross Examination by Mr. Simmons 1980

TESTIMONY OF ROBERT BANK

Direct Examination by Mr. Murphy 1987

Cross Examination by Mr. White 2005

Redirect Examination by Mr. Murphy 2024

Re-Cross Examination by Mr. White 2025

TESTIMONY OF BRENDA RATLIFF

Direct Examination by Mr. Murphy 2029

Cross Examination by Mr. White 2043

Redirect Examination by Mr. Murphy 2058

Re-Cross Examination by Mr. White 2060

PUBLISHED DEPOSITION OF JOHN WILLIAMS 2082

PUBLISHED DEPOSITION OF PAM DERUITER 2084

MOTIONS 2086

TESTIMONY OF DAVID FABBRI

Direct Examination by Mr. Pugh 2103

Cross Examination by Mr. Coggins 2140

Redirect Examination by Mr. Pugh 2210

Re-Cross Examination by Mr. Coggins 2216

Redirect Examination by Mr. Pugh 2217

TESTIMONY OF JOHN NEWCOMER

Direct Examination by Mr. Murphy 2221

Cross Examination by Mr. Trammell 2269

Redirect Examination by Mr. Murphy 2313

PUBLISHED DEPOSITION OF EDWARD BRANN 2339

MOTIONS 2340

PLAINTIFF'S CLOSING ARGUMENT 2418

DEFENDANTS' CLOSING ARGUMENT 2454

PLAINTIFF'S CLOSING ARGUMENT 2457

CHARGE BY THE COURT 2469

VOLUME SIX (Begins at R. 2480)

Transcript of Penalty Hearing, April 18-19, 2011 2539

PLAINTIFF'S OPENING STATEMENT 2546

TESTIMONY OF JAMES WOODLOCK

Direct Examination by Mr. Coggins 2559

Cross Examination by Mr. Murphy 2595

Redirect Examination by Mr. Coggins 2607

Re-Cross Examination by Mr. Murphy 2612

TESTIMONY OF JAY SMITH

Direct Examination by Mr. Coggins 2616

Cross Examination by Mr. Pugh 2629

PLAINTIFF'S PRESENTATIONS 2646

DEFENDANT'S OPENING STATEMENT 2712

TESTIMONY OF JOHN NEWCOMER

Direct Examination by Mr. Murphy 2743

Cross Examination by Mr. Trammell 2760

Redirect Examination by Mr. Murphy 2767

Re-Cross Examination by Mr. Trammell 2769

TESTIMONY OF WILLIAM WECKER

Direct Examination by Mr. Campion 2770

Cross Examination by Mr. Trammell 2812

Redirect Examination by Mr. Campion 2834

Re-Cross Examination by Mr. Trammell 2836

PLAINTIFF'S CLOSING STATEMENT 2875

DEFENDANT'S CLOSING STATEMENT 2889

IV. CHARGES

Plaintiff the State of South Carolina's Proposed Requests for Charge, filed March 17, 2011 2903

Defendants' Requested Jury Instructions, filed March 17, 2011 2913

Plaintiff the State of South Carolina's Request for Charge No. 1; Amended Request for Charge No. 6; Request for Charge No. 7; Request for Charge No. 8; and Amended Proposed Form of Verdict, filed March 18, 2011 2957

VOLUME SEVEN (Begins at R. 2966)

Plaintiff the State of South Carolina's Objections to Defendants' Requested Jury Instructions, filed March 18, 2011 2966

Defendants' Requested Verdict Sheet, filed March 18, 2011 2985

Defendants' Objections to Plaintiff's Proposed Requests for Charge and Proposed Verdict Sheet and Defendants' Request for Corrective Instruction, filed March 20, 2011 3000

Verdicts as to Johnson & Johnson, Inc. and Ortho-McNeil-Janssen Pharmaceutica, Inc., f/k/a Janssen Pharmaceutica Inc., and/or Janssen L.P., filed March 22, 2011 3030

V. EXHIBITS

Plaintiff's Trial Exhibits:

P0077 Risperdal Business Plan 2004 3034

P0164 Letter from R. Katz to V. Wagner-Weber, dated May 1, 2000 3087

P0165 E-mail from S. Dodd to R. Mahmoud and others, dated July 20, 2000 3089

P0166 E-mail from A. Grogg to J. Vandenbossche and others, dated August 1, 2000 3094

P0167 E-mail from A. Grogg to J. Vandenbossche and others, dated August 1, 2000 3095

P0200 Letter from L. Stockbridge to T. McIntyre, dated January 5, 1999 3102

P0232 Letter from T. Abrams to A. Shetty, dated April 19, 2004 3107

P0254 E-mail from R. Mahmoud to N. Dac and others, dated October 10, 2000 3112

P0280 August 2008 Risperdal Package Insert 3115

P0357 Diabetes Package Insert Revision, Field Training, dated November 2003 3127

P0387 Field Training, dated October 31, 2003 3157

P0435 Risperdal Hyperglycemia/Diabetes Labeling power point, IDC, dated January 13, 2004 3197

P0438 Letter from Janssen Pharmaceutica Inc. to Healthcare Providers, dated July 21, 2004 3229

P0442 Trial 113 Topline Results, dated September 9, 1999....3231

P0462 E-mail from S. Reines to G. Pruden, dated October 23, 2003....3246

P0477 E-mail from S. Reines to J. Grebb, dated November 30, 2003 3247

P0520 Letter from R. Katz to C. McGowan, dated September 12, 2003 3249

P0571 Letter from R. Temple to R. Wasserman, dated December 29, 1993 3253

P0631 1996 Risperdal Package Insert (published in 1997 Physicians' Desk Reference)....3257

P0640 2006 Risperdal Package Insert....3263

P0641 March 2006 Risperdal Package Insert (published in 2007 Physicians' Desk Reference) 3270

P0643 1994 Risperdal Package Insert....3278

P0648 July 1998 Risperdal Package Insert....3283

P0649 May 1999 Risperdal Package Insert 3287

P0653 December 2000 Risperdal Package Insert 3291

P0656 Revised July 2002 Risperdal Package Insert....3295

P0657 March 2003 Risperdal Package Insert 3299

P0661 December 2003 Risperdal Package Insert 3303

P0662 February 2005 Risperdal Package Insert 3311

P0665 October 2006 Risperdal Package Insert....3351

P1027 Letter from S. Danese to R. Wasserman, dated February 9, 1994 3397

VOLUME EIGHT (Begins at R. 3406)

P1078 Risperdal 2003 Business Plan Summary 3406

P1105 E-mail from C. Shaw to B. Goff, dated September 17, 2003 3493

P1224 October 2001 Risperdal Package Insert.....3496

P1264 Risperdal 2000 Business Plan.....3501

P1552 Risperdal Growth Acceleration, dated February 26, 2001 3552

P1564 Differential Effects of Antipsychotics on Type II Diabetes, presented May 3-5, 2001.....3676

P1662 Janssen First Cycle 1999 3680

P1670 Risperdal Q&A, dated July 26, 1996.....3747

P1728 Letter from E. Brann to R. Katz, dated August 10, 2000 3753

P1731 Letter from D. Ohye to T. Abrams, dated April 28, 2004 3758

P1736 Letter from Janssen Pharmaceutica Inc. to Healthcare Providers, dated November 10, 2003.....3762

P1741 Janssen submission to FDA, dated August 8, 2000.....3764

P2049 September 1996 Risperdal Package Insert 3777

P2061 April 1995 Risperdal Package Insert.....3781

P2352 Draft letter from Janssen Pharmacuetica Inc. to Healthcare Providers, dated November 2003.....3788

P2353 Draft letter from Janssen Pharmacuetica Inc. to Healthcare Providers, dated November 2003.....3790

P2354 Draft letter from Janssen Pharmacuetica Inc. to Healthcare Providers, dated November 2003.....3791

P2364 E-mail from S. Reines to J. Waldstreicher, dated April 28, 2004 3792

P2610 Letter from Janssen Pharmaceutica Inc. to Healthcare Providers, dated April 16, 2003 3795

P2613 E-mail from S. Reines to F. Grossman, dated March 10, 2004.....3801

P2614 E-mail from S. Reines to F. Grossman, dated June 10, 2004.....3805

P2618 Risperdal Training Meeting.....3806

VOLUME NINE (Begins at R. 3906)

P2651 E-mail from G. Pruden to R. Mahmoud, dated October 5, 2003 3973

P2653 Abbreviated Clinical Study Report, Trial 113, dated December 18, 1997 – February 26, 1999 3976

VOLUME TEN (Begins at R. 4406)

P2653 Abbreviated Clinical Study Report, Trial 113, dated December 18, 1997 – February 26, 1999, Cont. 4406

VOLUME ELEVEN (Begins at R. 4906)

P2653 Abbreviated Clinical Study Report, Trial 113, dated December 18, 1997 – February 26, 1999, Cont. 4906

VOLUME TWELVE (Begins at R. 5406)

P2653 Abbreviated Clinical Study Report, Trial 113, dated December 18, 1997 – February 26, 1999, Cont. 5406

P2662 Draft letter from Janssen Pharmacuetica Inc. to Healthcare Providers, dated November 2003 5430

P2682 Memo Regarding Medication Problem, Trial 113, dated September 22, 1999 5431

Plaintiff's Penalty Hearing Exhibits:

P1 Letter from S. Pugh to D. Coggins, dated April 13, 2011 5436

P6 Sample Call Note Data 5439

P7 Call Note Report Generated by James Woodlock 5441

P8 Call Note Report Generated by James Woodlock 5443

P9 Call Note Example 5446

P17 Court Filings (Offered; not admitted into evidence) 5447

P18 Johnson & Johnson 2010 Annual Report 5590

P19 Johnson & Johnson 2004 Annual Report 5668

P20 Johnson & Johnson 2003 Annual Report 5746

P21 Plaintiff's Calculations Regarding Potential Violations 5820

P22 Johnson & Johnson 10-K for Fiscal Year Ended January 2, 2011 (Offered; not admitted into evidence) 5825

P2720 Plaintiff's Calculations Regarding Sample Quantity Data 5835

P2722 Plaintiff's Calculations Regarding Number of Sales Calls When Samples Were Left 5836

Defendants' Trial Exhibits:

D0351 Letter from Janssen Pharmaceutica Inc. to Healthcare Providers with Risperdal Package Insert, dated November 10, 2003 5837

D0442 Letter from Janssen Pharmaceutica Inc. to Healthcare Providers, dated July 21, 2004 5843

D0498 August 2007 Risperdal Package Insert 5851

VOLUME THIRTEEN (Begins at R. 5899)

D0807 Volume 1 of the 2000 Submission to FDA 5899

D0821 Volume 15 of the 2000 Submission to FDA 6165

VOLUME FOURTEEN (Begins at R. 6384)

D0841 Letter from R. Katz to E. Brann, dated March 3, 2002 6384

D0843 Letter from R. Katz to M. Zoschg, dated December 4, 2003 6418

D0919 Letter from S. Merchant to R. Katz, dated March 29, 2004 6457

VOLUME FIFTEEN (Begins at R. 6884)

D3097 Letter from R. Katz to V. Wagner-Weber, dated May 1, 2000 7051

D3140 Letter from E. Brann to R. Katz, dated September 24, 2003 7053

D3175 Letter from R. Katz to C. McGowan, dated September 11, 2003 7063

D3179 Letter from S. Merchant to R. Katz, dated November 26, 2003 7066

D3180 Letter from R. Katz to S. Merchant, dated November 21, 2003 7077

D4337 Chapter 4 of the 2004 Version of the FDA's Regulatory Procedures Manual 7080

D6211 Letter from S. Merchant to R. Katz, dated April 18, 2002 7119

D6253 Letter from M. Brony to D. Ohye, dated October 14, 2004.....7315

D7008 Expert Report of William E. Wecker, Ph.D., dated December 3, 2010 (Referred to in Trial Transcript as "Def. Exh. A.") 7318

D7174 Chart of South Carolina Department of Health and Human Services Drug Utilization Review Program – Patient Drug History Profile 7367

D7185 "Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes," The Journal of Clinical and Applied Research and Education Diabetes Care, 27:2 (2004); 596-601 7375

VOLUME SIXTEEN (Begins at R. 7382)

D7186 SC-DMH Laboratory Monitoring Guidelines for Antipsychotic Medications 7382

D7294 IND 31,931 Risperidone Tablets Annual Report July 1, 1998 – June 30, 1999.....7388

D7336 Letter from W. Murray Yarbrough to T. Engles, dated September 19, 2003.....7489

D7337 South Carolina Medicaid & SHP Claims Data, June 2003-October 2004 (Referred to in Trial Transcript as "Def. Exh. B").....7494

D7338 South Carolina Medicaid & SHP Claims Data, November 2004-December 2005 (Referred to in Trial Transcript as "Def. Exh. C").....7495

Defendants' Penalty Hearing Exhibits:

D2 2007 Zyprexa Package Insert (Offer of proof; not admitted into evidence).....7496

D5 South Carolina Fee for Service, State Health Plan, and HMO Claims Data – Antipsychotic Prescriptions by Month 7532

D6 Calculation of Net Cost of Risperdal to the State (Columns 1-7 admitted).....7533

Court's Exhibits:

C-2 Federal Regulations 7540

C-3 Court's Rulings on Objections to Openings 7584

C-4 Defendants' Offer of Proof 7586

C-5 Charge by Court 7654

C-6 Question from the Jury 7670

C-7 Question from the Jury 7671

Physical Exhibit:

P5 Hard Drive containing sales call data produced by Defendants 7672

VI. MISCELLANEOUS AND OTHER MOTIONS

Tolling Agreement, dated February 20, 2007 7673

Notice of Removal, filed May 22, 2007 7678

Plaintiff the State of South Carolina's Motion to Exclude the Testimony of Certain Risperdal Prescribers at Trial, filed July 2, 2010 7737

Defendants' Motion *in Limine* and Memorandum of Law in Support Thereof to Preclude the Introduction into Evidence of the April 19, 2004 DDMAC Letter and Any Evidence of or Reference to the Letter at Trial, filed January 7, 2011 7747

Plaintiff the State of South Carolina's Notice of Motion and Motion to Exclude the Expert Testimony of Sheldon Bradshaw, filed January 13, 2011 7817

VOLUME SEVENTEEN (Begins at R. 7837)

Plaintiff the State of South Carolina's Motion to Exclude the Expert Testimony of Dr. William E. Wecker, filed January 13, 2011 7837

Plaintiff the State of South Carolina's Response in Opposition to Defendants' Motion *in Limine* to Preclude the Introduction of Evidence of the April 19, 2004 DDMAC Letter and Any Evidence of or Reference to the Letter at Trial, filed January 18, 2011 8093

Defendants' Memorandum of Law in Opposition to Plaintiff's Motion to Exclude the Testimony of Certain Risperdal Prescribers at Trial, filed January 20, 2011 8102

Plaintiff the State of South Carolina's Response in Opposition to Defendants' Motion for Summary Judgment as to Plaintiff's Unfair Trade Practices Claim Based on November 10, 2003 Mailing, filed January 21, 2011 8171

VOLUME EIGHTEEN (Begins at R. 8325)

Plaintiff the State of South Carolina's Response in Opposition to Defendants' Motion for Summary Judgment as to Plaintiff's Unfair Trade Practices Act Claim Based on the FDA Approved Package Insert, filed January 21, 2011 8325

Defendants' Memorandum of Law in Opposition to Plaintiff's Motion to Exclude the Expert Testimony of Dr. William E. Wecker, filed January 21, 2011 8344

Plaintiff the State of South Carolina's Reply to Defendants' Response in Opposition to the State's Motion to Exclude the Expert Witness Testimony of Defendants' Expert Witness, Dr. William E. Wecker, filed January 31, 2011 8483

Defendants' Objections to Plaintiff's Opening Statement, filed March 8, 2011 8525

Plaintiff the State of South Carolina's Response in Opposition to Defendants' Objections to Plaintiff's Opening Statement, filed March 14, 2011 8530

Defendants' Motion for a Directed Verdict and Memorandum of Law in Support Thereof, filed March 14, 2011 8600

Plaintiff the State of South Carolina's Response in Opposition to Defendants' Motion for a Directed Verdict, filed March 15, 2011 8632

Defendants' Reply in Support of Motion for a Directed Verdict, filed March 15, 2011 8664

Plaintiff the State of South Carolina's Motion for a Directed Verdict as to Defendants' Eighth Affirmative Defense on Statute of Limitations, filed March 21, 2011 8667

Defendants' Offer of Proof for the Expert Testimony of Dr. William E. Wecker, filed March 21, 2011 8696

VOLUME NINETEEN (Begins at R. 8803)

Defendants' Offer of Proof for the Post-2007 FDA-Approved Package Insert for Zyprexa and the 2010 FDA-Approved Package Insert for Latuda, filed March 21, 2011 8803

Defendants' Renewed Motion for a Directed Verdict and Memorandum of Law in Support Thereof, filed March 21, 2011 8870

Defendant Ortho-McNeil-Janssen Pharmaceuticals Inc.'s Motion and Memorandum in Support Thereof for Judgment Notwithstanding the Verdict or, in the Alternative, for a New Trial, filed April 1, 2011 9030

Plaintiff's Pre-trial Brief to the Court (Civil Penalty Phase), filed April 15, 2011 9107

Janssen's Penalty Hearing Brief, filed April 15, 2011 9115

Plaintiff the State of South Carolina's Memorandum of Law in Support of its Response in Opposition to Defendant's Motion for Judgment Notwithstanding the Verdict or, in the Alternative, for a New Trial, filed April 15, 2011 9225

VOLUME TWENTY (Begins at R. 9303)

Defendant's Offer of Proof for the Testimony of Prescriber Physicians; and Robert L. Bank, M.D., and Brenda Ratliff, M.D., filed April 18, 2011 9343

Plaintiff the State of South Carolina's Post Civil Penalties Hearing Submission, filed May 3, 2011 9401

Defendant Ortho-McNeil-Janssen Pharmaceuticals Inc.'s Post-Penalty Hearing Brief, filed May 3, 2011 9426

Reply Memorandum of Law in Support of Defendant Ortho-McNeil-Janssen Pharmaceuticals Inc.'s Motion for Judgment Notwithstanding the Verdict or, in the Alternative, for a New Trial, filed May 3, 2011 9440

Defendant Ortho-McNeil-Janssen Pharmaceuticals Inc.'s Motion and Memorandum of Law in Support Thereof to Alter or Amend the Judgment and/or for a New Trial, June 13, 2011 9455

Plaintiff the State of South Carolina's Response in Opposition to Defendant's Motion to Alter or Amend the Judgment and/or For a New Trial, filed July 7, 2011 9492

Defendant Ortho-McNeil-Janssen Pharmaceuticals Inc.'s Reply in Support of its Motion to Alter or Amend the Judgment and/or for a New Trial, filed July 15, 2011 9525

VII. CERTIFICATE OF COUNSEL

STATE OF SOUTH CAROLINA COUNTY OF SPARTANBURG STATE OF SOUTH CAROLINA ex. rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina, PLAINTIFF, v. ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA, INC., and/or JANSSEN, L.P., AND JOHNSON & JOHNSON, INC. DEFENDANTS.	IN THE COURT OF COMMON PLEAS FOR THE SEVENTH JUDICIAL CIRCUIT Civil Action No.: 2007-CP-42-1438 PLAINTIFF THE STATE OF SOUTH CAROLINA'S OBJECTIONS TO DEFENDANTS' REQUESTED JURY INSTRUCTIONS

TO: STEVEN J. PUGH AND KENNETH A. MURPHY, ATTORNEYS FOR DEFENDANTS

Plaintiff, the State of South Carolina, *ex rel.* Alan Wilson,[1] in his capacity as Attorney General of the State of South Carolina (hereinafter, "the State"), by and through the undersigned counsel, hereby submits its Objections to the Requested Jury Instructions submitted by Defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. f/k/a Janssen Pharmaceutica, Inc., and/or Janssen, L.P., and Johnson & Johnson, Inc. (collectively, "Janssen" or "Defendants").

The State submits these specific objections without waiving their motions, objections, responses, and other submissions raised with the Court prior to and during the trial of the case, and the State does not waive any of the Court's prior rulings. The State may also submit supplemental objections relative to Defendants' proposed instructions and/or verdict forms as

[1] Pursuant to South Carolina Rule of Civil Procedure 25(d)(1), the Honorable Alan Wilson has been substituted for the Honorable Henry McMaster as Attorney General for the State of South Carolina.

may be required by the filing of additional requested instructions by Defendants and any ruling by the Court following the submission of parties' instructions.

More specifically, by submitting specific objections to certain of Defendants' requested jury instructions herein, the State does not concede that those other requested jury instructions can or should be properly submitted to the jury. Accordingly, these objections are made without waiving the State's objections to certain other of Defendants' requested jury instructions, particularly those which are at all inconsistent with applicable South Carolina law, this Court's prior rulings, or the State's own Proposed Requests to Charge.

Further, the State does not concede that those other requested jury instructions of Defendants, or any issues relating thereto, can or should be properly submitted to the jury. In addition, these objections are made without waiving the State's objections regarding specific claims or affirmative defenses of Defendants. For example, without limiting the foregoing, the State submits specific objections to particular portions of Defendants' requested instruction No. 29 – (Statute of Limitations) without waiving its argument that this affirmative defense is inapplicable to the State's case in that the statute of limitations cannot serve as a bar to the State's claims under the South Carolina Unfair Trade Practices Act ("SCUTPA"). Similarly, the State also submits objections to portions of Defendants' requested instructions regarding the applicability of various federal preemption-based affirmative defenses without waiving its arguments that the State's SCUTPA claims are not preempted by purported FDA authorization or permit of Defendants' labeling which the FDA ultimately deemed false and misleading and violative of federal regulations or without waiving its arguments that the enforcement of SCUTPA's provisions does not otherwise contravene *Buckman v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001) or federal safety requirements.

A. PLAINTIFF'S OBJECTIONS TO DEFENDANTS' REQUESTED INSTRUCTION NO. 6 – (Expert Witness Testimony – General Charge)

Plaintiff objects to Defendants' Requested Instruction No. 6 because it substantially adds elements and information for the jury to consider that are unsupported by South Carolina law. For example, Defendants' citation to the Rules of Evidence 702 and 703 govern the admissibility of expert testimony, not jury's consideration of expert testimony that has already been deemed admissible by the Court. Additionally, the following language added to the Defendants' proposed instruction is not found in the standard Requests for Charge and appears to be a conglomeration of cherry-picked support, if any support is offered at all:

> An expert's opinion, however, must be based upon facts within his or her own knowledge or upon hypothetical questions supported by the evidence and relating t the particular matter upon which the expert opinion is sought. An expert opinion must be based on the facts sufficient to form a basis for the opinion. You may not consider the testimony of an expert where the factual basis for such opinion is vague.
>
> If you are satisfied that there is an evidentiary showing of the facts upon which the expert based his or her opinion, then the expert's conclusions and opinions constitute evidence to be considered by you in connection with all of the other testimony and evidence in the case.

B. PLAINTIFF'S OBJECTION TO DEFENDANTS' REQUESTED INSTRUCTION NO. 13 – (Burden of Proof)

The State objects to this requested instruction because it is contrary to South Carolina law, and, more specifically, it misstates, modifies, conflates and confuses legal standards in a manner that will lead to jury confusion and misdirection. In particular, "[t]he statute clearly requires that in order to recover pursuant to [SCUTPA] one must prove . . . three elements by the greater weight or preponderance of the evidence." *Charleston Lumber Company, Inc. v. Miller Housing Corp.*, 458 S.E.2d 431, 438 (S.C. Ct. App. 1995), *reversed on other grounds by Charleston Lumber Co., Inc. v. Miller Housing Corp.*, 525 S.E.2d 869 (S.C. 2000). Thus,

Defendants' proposed instruction is an improper attempt to impose a heightened standard upon the State's civil action, to which a preponderance or greater weight of the evidence standard applies. *See, e.g., Welch v. Clifton Mfg. Co.*, 33 S.E. 739, 746 (1899). Moreover, Defendants cite no case in which this elevated standard of proof has been applied in a SCUTPA action.

C. PLAINTIFF'S OBJECTIONS TO DEFENDANTS' REQUESTED INSTRUCTION NO. 14 – (Penal Statute)

Plaintiff objects to this requested instruction because it is contrary to South Carolina law and even Defendants' cited cases. In particular, the words "you must give Defendants the benefit of every doubt in your mind" and "any doubt as to the State's claim should be resolved in favor of the Defendants and against the State" do not appear in the cited cases, and Defendants offer no authority for including them in the jury charge. Defendants cite no case in which a South Carolina jury was so instructed. In each of the cited cases, the higher courts are determining the rule of construction applicable to *their* review of the lower tribunal's decision. *See, e.g., State ex rel. Moody v. Stem*, 50 S.E.2d 175, 176 (S.C. 1948) ("With these rules of construction in mind, we turn to the penalty statute . . . ."). Also, the instruction is an improper attempt to impose a beyond a reasonable doubt standard upon (or an even more stringent 'beyond any doubt' standard) on the State's civil action, to which a preponderance or greater weight of the evidence standard applies. *See, e.g., Welch v. Clifton Mfg. Co.*, 33 S.E. 739, 746 (1899). Finally, such an instruction is, at least in part, contrary to the standard instruction on circumstantial evidence—i.e., that "[i]n a civil case, proof of circumstances warranting a given inference is sufficient because proof of certainty is not required in a civil suit. [E]very other reasonable conclusion need not be excluded." It is therefore likely to mislead and confuse the jury. Ralph King Anderson, Jr., *South Carolina Requests for Charge – Civil*, 2009, § 1-4; *see, e.g., Cox v. Lund*, 334 S.E.2d 116 (1985) (stating that, in civil actions, every other reasonable

conclusion need not be excluded; proof of circumstances warranting a given inference is sufficient in such cases). The instruction is also unfairly one-sided.

D. PLAINTIFF'S OBJECTION TO DEFENDANTS' REQUESTED INSTRUCTION NO. 15 – (General Jury Charge)

The State objects to this requested instruction because it misstates, modifies, and conflates standards applicable to rendering a verdict and awarding damages. Defendants improperly rely on *Young v. Warr*, 165 S.E.2d 797, 801 (1969) for the stated proposition. The *Young* court explained that "[i]t is only when the verdict is so grossly excessive and the amount awarded so shockingly disproportionate to the injuries as to indicate that the jury was moved or actuated by passion, caprice, prejudice, or other consideration not found on the evidence that it becomes the duty of this court, as well as of the trial court, to set aside the verdict absolutely." *Id.* However, the court additionally cautioned that it is not required that the trial judge set aside the verdict where it is deemed excessive in the sense that it indicates undue liberality on the part of the jury. *Id.* In that connection, the court emphasized that "[a] verdict which may be supported by any rational view of the evidence and bears a reasonable relationship to the character and extent of the injury and damage sustained, is not excessive." *Id.*

Importantly, the State has not asserted claims for damages or any claim for which a jury could otherwise award an excessive verdict for which Defendants' proposed instruction could arguably apply. Indeed, the issue of any award to the State through damages, penalties, or otherwise is not before the jury. (Order of Feb. 25, 2011 at 4.) Rather, the jury will determine pursuant to S.C. Code Ann. §§ 39-5-20 and 39-5-110(a) only whether Defendants' conduct at issue is unlawful and willful, respectively.

E. PLAINTIFF'S OBJECTIONS TO DEFENDANTS' REQUESTED INSTRUCTION NO. 16 – (South Carolina Unfair Trade Practices Act)

Plaintiff objects to Defendants' Requested Instruction No. 16 because it is cumulative of Defendants' Proposed Instructions Nos. 18 and 19, is contrary to South Carolina law, and invites jury confusion. Plaintiff specifically objects to the paragraph beginning "In general, an unfair act . . ." to the end of the proposed instruction. Plaintiff incorporates by reference as if repeated in full herein its objections to Defendants' Proposed Instructions Nos. 18 and 19, *infra*.

F. PLAINTIFF'S OBJECTIONS TO DEFENDANTS' REQUESTED INSTRUCTION NO. 17 – (First Amendment Considerations)

Plaintiff objects to Defendants' Requested Instruction No. 17 because it invites jury confusion and misstates the law applicable to this case. For example, the instruction addresses whether any statement the State alleges to be a violation of the South Carolina Unfair Trade Practices Act "is capable of being proved true or false," then adds the requirement that the State prove the falsity of the statement and actual malice. SCUTPA, of course, merely requires that the State show that the statement had a "tendency to deceive"—there is no requirement that falsity or actual malice be shown. *Gentry v. Yonce*, 522 S.E.2d 137 (S.C. 1999). Indeed, States may regulate commercial speech "to require that a commercial message appear in such a form, or include such additional information, warnings, and disclaimers, as are necessary to prevent its being deceptive." *Va. State Bd. of Pharm. v. Va. Citizens Consumer Council*, 425 U.S. 748, 772 n.24 (1976); *accord, 44 Liquormart v. R.I.*, 517 U.S. 484, 498-99 (1996) (citing *Ohralik v. Ohio State Bar Ass'n.*, 436 U.S. 447, 456 (1978) (commercial speech "occurs in an area traditionally subject to government regulation"). Further, if Defendants intend to assert an affirmative defense under the First Amendment to the United States Constitution and Article I of the Constitution of the State of South Carolina, then the burden is improperly stated in this

instruction; the burden of establishing an affirmative defense is on the defendant. *McClain v. Anderson Free Press*, 232 S.C. 448, 102 S.E.2d 750 (1958) (finding that, in action for libel, where answer pleads affirmative defense of qualified privilege, burden of proof is upon defendant to establish such defense by a preponderance of the evidence); *Lorick & Lowrance, Inc. v. Julius H. Walker & Co.*, 153 S.C. 309, 150 S.E. 789 (1929)(when a defendant interposes an affirmative defense, he becomes as to that matter the actor in the suit, and burden of proof rests upon him to establish his affirmative defense by preponderance of the evidence). If Defendants desire to challenge the constitutionality of SCUTPA as applied to them or to these facts, then it must do so through pre- or post trial motion, as it has failed to make such a challenge at the pre-trial stage. The First Amendment cases cited by Defendants do not change the above result.

G. PLAINTIFFS' OBJECTION TO DEFENDANTS' REQUESTED INSTRUCTION NO. 18 – (Deceptive Trade Practice)

The State objects to this requested instruction because it is contrary to South Carolina law. SCUTPA provides that "[u]nfair methods of competition and unfair or deceptive acts or practices in the conduct of any trade or commerce are . . . unlawful." S.C. Code Ann. § 39-5-20. The act or practice complained of must be unfair or deceptive and whether an act or practice is unfair or deceptive within the meaning of SCUTPA depends upon the surrounding facts and the impact of the transaction on the marketplace. *See Wright v. Craft*, 640 S.E.2d 486, 500 (S.C. Ct. App. 2006). Proof of common law fraud is not required to establish a violation. *See Inman v. Hyatt Chrysler Plymouth, Inc.*, 363 S.E.2d 691, 692 (S.C. 1988); *State ex rel. McLeod v. C & L Corp.*, 313 S.E.2d 334, 338 (S.C. Ct. App. 1984). Rather, to be actionable under SCUTPA, the unfair or deceptive act or practice complained of must have an impact on the public interest. Unfair or deceptive acts or practices in the conduct of trade or commerce have an impact upon

the public interest if the acts or practices have the potential for repetition, which may be shown in numerous ways. Thus, in order to prove a "deceptive" violation of SCUTPA, "there is no need to show that a claim or representation was intended to deceive, but only that it had the capacity or effect or tendency to deceive." *McLeod*, 313 S.E.2d at 338.

Contrary to Defendants' proposed instruction, therefore, the State is not required to prove that "false representations of fact" were made by Defendants as to Risperdal. "Even a truthful statement may be deceptive." *Wright*, 640 S.E.2d at 500. Additionally, in evaluating whether the November 2003 "Dear Doctor" letter or Risperdal package insert or label had a tendency to deceive, the jury is not required to make these considerations in light of the relative sophistication of the medical community recipients or prescribers, but may also consider the general consuming public, or reasonable consumer. Similarly, the materiality of Defendants' misstatements with respect to prescribing decisions is irrelevant to the determination of potential deceptiveness; the State is not required to demonstrate causation or reliance to prove a violation of SCUTPA. Further, in order to demonstrate public interest, the State is not required to present "proof of specific facts establishing that members of the South Carolina public or South Carolina physicians were, or were likely to be, adversely affected by the deceptive conduct." As explained above, the State may show the same kind of actions occurred in the past, thus making it likely they will continue to occur absent deterrence; that the company's procedures create a potential for repetition of the unfair and deceptive acts; or, *any other* evidence demonstrating the potential for repetition. *See id.*; *Daisy Outdoor Adver. Co. v. Abbott*, 473 S.E.2d 47, 49 (S.C. 1996). In fact, the South Carolina Supreme Court has "expressly reject[ed] any rigid, bright line test that delineates in minute detail exactly what a plaintiff must show to satisfy the potential for repetition/public impact." *Daisy*, 473 S.E.2d at 51.

H. PLAINTIFF'S OBJECTION TO DEFENDANTS' REQUESTED INSTRUCTION NO. 19 – (Unfair Trade Practice)

The State objects to this requested instruction because it is contrary to South Carolina law. SCUTPA provides that "[u]nfair methods of competition and unfair or deceptive acts or practices in the conduct of any trade or commerce are . . . unlawful." S.C. Code Ann. § 39-5-20. The act or practice complained of must be unfair or deceptive and whether an act or practice is unfair or deceptive within the meaning of SCUTPA depends upon the surrounding facts and the impact of the transaction on the marketplace. *See Wright v. Craft*, 640 S.E.2d 486, 500 (S.C. Ct. App. 2006). Proof of common law fraud is not required to establish a violation. *See Inman v. Hyatt Chrysler Plymouth, Inc.*, 363 S.E.2d 691, 692 (S.C. 1988); *State ex rel. McLeod v. C & L Corp.*, 313 S.E.2d 334, 338 (S.C. Ct. App. 1984). Rather, to be actionable under SCUTPA, the unfair or deceptive act or practice complained of must have an impact on the public interest. Unfair or deceptive acts or practices in the conduct of trade or commerce have an impact upon the public interest if the acts or practices have the potential for repetition which may be shown in numerous ways. Thus, in order to prove an "unfair" violation of SCUTPA, all that need be shown is that the practice is "offensive to public policy or . . . is immoral, unethical, or oppressive." *Wright*, 640 S.E.2d at 498; *Wogan v. Kunze*, 623 S.E.2d 107, 120 (S.C. Ct. App. 2005).

Contrary to Defendants' proposed instruction, therefore, the State is not required to prove that the November 2003 "Dear Doctor" letter or Risperdal package insert or label "was likely to cause substantial injury to South Carolina consumers" or demonstrate any proof relative to "any substantial injury." South Carolina case law makes clear that while "substantial injury" may be probative of "unfairness" under SCUTPA, it is not required to prove a violation thereof. *See, e.g., id.* Even under Defendants' proposed FTC standard, "substantial injury" is not required to

prove "unfairness" under the FTC Act. *See Spiegel, Inc. v. Federal Trade Comm'n*, 540 F.2d 287, 293 (7th Cir. 1976) ("A practice is unfair when it offends established policy and when the practice is immoral, unethical, oppressive, unscrupulous *or* substantially injurious to consumers.") (emphasis added). Further, in order to demonstrate public interest, the State is not required to present "proof of specific facts establishing that members of the South Carolina public or South Carolina physicians were, or were likely to be, adversely affected by the unfair conduct." Nor is it required to demonstrate that public policy was violated. As explained above, the State may show the same kind of actions occurred in the past, thus making it likely they will continue to occur absent deterrence; that the company's procedures create a potential for repetition of the unfair and deceptive acts; or, *any other* evidence demonstrating the potential for repetition. *See id.*; *Daisy Outdoor Adver. Co. v. Abbott*, 473 S.E.2d 47, 49 (S.C. 1996). In fact, the South Carolina Supreme Court has "expressly reject[ed] any rigid, bright line test that delineates in minute detail exactly what a plaintiff must show to satisfy the potential for repetition/public impact." *Daisy*, 473 S.E.2d at 51.

I. PLAINTIFF'S OBJECTION TO DEFENDANTS' REQUESTED INSTRUCTION NO. 20 – (Regulated Activity Exemption)

The State objects to this requested instruction because it is not supported by South Carolina case law and is likely to lead to jury confusion. In particular, this instruction may lead the jury to believe that the FDA's initial approval of Risperdal's labeling or use for certain indications, equates to the FDA's authorization or permit of Defendants' labeling which it later deemed false and misleading and violative of federal regulations. In truth, Defendants' labeling cannot qualify as "permitted" for purposes of statutory exemption in light of Defendants' failure to strengthen Risperdal's warnings, as they were required to do by the FDA, once they became aware of reasonable evidence of an association between Risperdal use and a serious hazard. *See*

21 C.F.R. 201.57(e) (2006). In other words, the fact that the FDA had intermediately "approved" Risperdal's labeling, therefore, cannot absolve Defendants from their duty to update the labeling to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product." *See* 21 C.F.R. § 314.70(c)(6)(iii)(A), (C); *accord Wyeth v. Levine*, 129 S. Ct. 1187, 1197 (2009). Further, the Court denied as a matter of law Defendants' motion for summary judgment on this issue; the issue is not before the jury. (Order of Feb. 25, 2011 at 7.)

J. PLAINTIFF'S OBJECTIONS TO DEFENDANTS' REQUESTED INSTRUCTION NO. 21 – (Violation of FDCA)

Plaintiff objects to Defendants' Requested Instruction No. 21 because it is irrelevant to the State's claim under the South Carolina Unfair Trade Practices Act and will invite jury confusion. It is also contrary to South Carolina law and rules of evidence. First, the State brings no claim for violation of the federal Food, Drug & Cosmetic Act ("FDCA"), nor asks the jury to decide whether any federal law or Food & Drug Administration ("FDA") rules and regulations have been violated. Second, South Carolina law permits the jury to consider evidence of regulatory violations to support a finding of willful conduct, including in the context of an award of punitive damages. *See, e.g., Ravan v. Greenville County*, 434 S.E.2d 296, 303 (S.C. Ct. App. 1993) (citing *Rhodes v. Lawrence*, 302 S.E.2d 343, 344 (S.C. 1983) and *Tant v. Dan River, Inc.*, 345 S.E.2d 495, 496 (1986)); *Cooper by Cooper v. County of Florence*, 412 S.E.2d 417, 419 (S.C. 1991). Third, the evidence that the proposed instruction purports to address is admissible and may be considered by the jury under S.C.R. Evid. 404(b) as evidence of motive, absence of mistake or accident, and intent. Fourth, the evidence that the proposed instruction purports to

address is admissible and may be considered by the jury under S.C.R. Evid. 406 as evidence of habit or routine practice of the Defendants.

K. PLAINTIFF'S OBJECTIONS TO DEFENDANTS' REQUESTED INSTRUCTION NO. 22 – (Nondisclosures to the FDA)

Plaintiff objects to Defendants' Requested Instruction No. 22 because it is contrary to South Carolina law and rules of evidence. First, South Carolina law permits the jury to consider evidence of regulatory violations to support a finding of willful conduct, including in the context of an award of punitive damages. *See, e.g., Ravan v. Greenville County*, 434 S.E.2d 296, 303 (S.C. Ct. App. 1993) (citing *Rhodes v. Lawrence*, 302 S.E.2d 343, 344 (S.C. 1983) and *Tant v. Dan River, Inc.*, 345 S.E.2d 495, 496 (1986)); *Cooper by Cooper v. County of Florence*, 412 S.E.2d 417, 419 (S.C. 1991). Second, the evidence that the proposed instruction purports to address is admissible and may be considered by the jury under S.C.R. Evid. 404(b) as evidence of motive, absence of mistake or accident, and intent. Third, the evidence that the proposed instruction purports to address is admissible and may be considered by the jury under S.C.R. Evid. 406 as evidence of habit or routine practice of the Defendants. Fourth, this lawsuit does not contravene *Buckman v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001) because enforcement of SCUTPA provisions against the Defendants "parallel [and do not contravene] federal safety requirements . . . ." *Id.*; *see Wyeth v. Levine*, 129 S. Ct. 1187, 1202 n.10 (2009) (observing that the FDA regarded state law as complementing the agency's mission on consumer protection).

L. PLAINTIFF'S OBJECTIONS TO DEFENDANTS' REQUESTED INSTRUCTION NO. 23 – (Benefit of Prescription Drugs)

Plaintiff objects to Defendants' Requested Instruction No. 23 because it is prejudicially one-sided and unsupported by South Carolina law. The case cited by Defendants does not contain the language of the proposed instruction, and it did not involve any jury instruction

regarding the benefits of prescription drugs. Further, the State has already acknowledged in its opening statement that Risperdal works in some patients and it has presented expert testimony in its case in chief supporting that proposition. The self-serving instruction is, therefore, probative of nothing and better suited for Defendants' closing argument.

M. PLAINTIFF'S OBJECTIONS TO DEFENDANTS' REQUESTED INSTRUCTION NO. 24 – (Disagreement with the FDA)

Plaintiff objects to Defendants' Requested Instruction No. 24 because it is an inaccurate proposition and because it mischaracterizes the evidence in a manner that unfairly and prejudicially favors Defendants. It will also mislead and confuse the jury. It is most certainly the case that Defendants may have a "disagreement with the FDA," the subject matter of which also violates the South Carolina Unfair Trade Practices Act. That, in fact, is the case before this Court, given Defendants' characterization of their dealings with the FDA as a disagreement or 'scientific debate,' and the State's position that Defendants violated FDA regulations. Defendants' only cited authority for this proposed instruction is the First Amendment to the United States Constitution. The First Amendment does not support this instruction any more than it supported Defendants' Requested Instruction No. 17, and the State incorporates by reference its objections to Requested Instruction No. 17 as if repeated in full herein.

N. PLAINTIFF'S OBJECTIONS TO DEFENDANTS' REQUESTED INSTRUCTION NO. 25 – (Off-Label Use)

Plaintiff objects to Defendants' Requested Instruction No. 25 because it is an inaccurate proposition and because it mischaracterizes the evidence in a manner that unfairly and prejudicially favors Defendants. It will also mislead and confuse the jury. It is most certainly the case that Defendants' unlawful promotion of Risperdal for off-label uses may, under certain circumstances, also constitute a violation of the South Carolina Unfair Trade Practices Act.

Buckman does not state or suggest that off-label promotion of prescription drugs cannot constitute a violation of state unfair trade practices law. *Buckman*, an express preemption case, is limited to state law claims for fraud directed at the FDA, and the State here has disclaimed any such theories of recovery.

O. PLAINTIFF'S OBJECTIONS TO DEFENDANTS' REQUESTED INSTRUCTION NO. 26 – (Consideration of Promotional Materials, Off-Label Uses, Etc.)

Plaintiff objects to Defendants' Requested Instruction No. 26 because it is an inaccurate proposition and because it mischaracterizes the evidence in a manner that unfairly and prejudicially favors Defendants. It will also mislead and confuse the jury. It is most certainly the case that Defendants' unlawful promotion of Risperdal for off-label uses may, under certain circumstances, also constitute a violation of the South Carolina Unfair Trade Practices Act. *Buckman* does not state or suggest that off-label promotion of prescription drugs cannot constitute a violation of state unfair trade practices law. *Buckman*, an express preemption case, is limited to state law claims for fraud directed at the FDA, and the State here has disclaimed any such theories of recovery. Also, South Carolina law permits the jury to consider evidence of regulatory violations to support a finding of willful conduct, including in the context of an award of punitive damages. *See, e.g., Ravan v. Greenville County*, 434 S.E.2d 296, 303 (S.C. Ct. App. 1993) (citing *Rhodes v. Lawrence*, 302 S.E.2d 343, 344 (S.C. 1983) and *Tant v. Dan River, Inc.*, 345 S.E.2d 495, 496 (1986)); *Cooper by Cooper v. County of Florence*, 412 S.E.2d 417, 419 (S.C. 1991). In addition, the evidence that the proposed instruction purports to address is admissible and may be considered by the jury under S.C.R. Evid. 404(b) as evidence of motive, absence of mistake or accident, and intent. The evidence that the proposed instruction purports to address is also admissible and may be considered by the jury under S.C.R. Evid. 406 as evidence of habit or routine practice of the Defendants. Finally, the evidence is relevant to

whether Defendants' violations of the Unfair Trade Practices Act were capable of repetition, and therefore involving the public interest.

P. PLAINTIFF'S OBJECTIONS TO DEFENDANTS' REQUESTED INSTRUCTION NO. 27 – (CBE Submissions)

Plaintiff objects to Defendants' Requested Instruction No. 27 because it is an inaccurate, inapplicable statement of the law relative to the facts of this case. Defendants have on repeated occasion attempted to admit evidence of a 2008 amendment to the FDA's "changes being effected" ("CBE") procedure for updating prescription drug labels. Among other changes, that amendment augmented the standard for strengthening a prescription drug label warning absent FDA approval, requiring evidence of a "causal association" rather than the prior standard—i.e., "reasonable evidence of an association" where a "causal relationship need not have been proved." The Court has ruled that this evidence is inadmissible because it is irrelevant in that the amendment has not been shown by the Defendants to have been in effect during the time period for which the State seeks penalties. Likewise, the instruction should not be given to the jury.

Q. PLAINTIFF'S OBJECTION TO DEFENDANTS' REQUESTED INSTRUCTION NO. 28 – (Willfulness)

The State objects to this requested instruction because it is contrary to South Carolina law, Defendants' cited case law, and is likely to lead to jury confusion. The express language of the applicable statute, S.C. Code Ann. § 39-5-110(c), requires only that Defendants "knew or should have known that [their] conduct was a violation of § 39-5-20." Defendants, however, argue that the State must additionally show that the conduct was prohibited. South Carolina courts as well as Defendants' cited case law make clear that in order to demonstrate willfulness the State need only show that "in the exercise of due diligence, a person of ordinary prudence engaged in trade or commerce could have ascertained that his conduct violates the Act," without

more. *Haley v. Nursery Co. v. Forrest*, 381 S.E.2d 906, 909 (S.C. 1989) (quoting *State v. Nest Egg Society Today, Inc.*, 348 S.E.2d 381 (S.C. Ct. App. 1986)).

R. PLAINTIFF'S OBJECTION TO DEFENDANTS' REQUESTED INSTRUCTION NO 29 – (Statute of Limitations)

The State objects to this requested instruction because it is contrary to South Carolina law, and, more specifically, it misstates, modifies, conflates and confuses legal standards in a manner that will lead to jury confusion and misdirection. To start, contrary to Defendants' contentions that "the law affords voluntary ignorance no protection," and the "statute of limitations requires very little to begin running," the facts must be taken in the light most favorable to the Plaintiff and Defendants bear the burden of proof of establishing their statute of limitations defense. *See Johnston v. Bowen*, 437 S.E.2d 45, 47 (S.C. 1993); *see also Lorick & Lowrance, Inc. v. Julius H. Walker & Co.*, 153 S.C. 309, 150 S.E. 789 (1929). Further, the knowledge of the Attorney General is distinguishable from any other potential plaintiff. The Attorney General of South Carolina is the only South Carolina government official who may bring a claim for civil penalties under SCUTPA. *See* S.C. Code Ann. § 39-5-110. And, despite Defendants' assertion that a plaintiff must take steps to identify whether it has been wronged, "the government has no 'affirmative duty to take action to discover information which it does not possess . . .'". *State v. Von Dohlen*, 471 S.E.2d 689, 693 (S.C. 1996). This is particularly true where the plaintiff, or Attorney General, could not have discovered essential information relative to his claim thus warranting the equitable tolling of the applicable statute of limitations. *See Hooper v. Ebenezer Senior Servs. & Rehab. Ctr.*, 687 S.E.2d 29, 32-33 (S.C. 2009).

S. PLAINTIFF'S OBJECTIONS TO DEFENDANTS' REQUESTED INSTRUCTION NO. 30 – (Separate Defendants)

Plaintiff objects to Defendants' Requested Instruction No. 30 because this Court has already ruled that there is sufficient evidence of Johnson & Johnson's culpability to submit the State's case against that entity to the jury, and Defendants have not filed a no-evidence summary judgment motion as to Johnson & Johnson nor otherwise sought their independent dismissal from this case. If, upon conclusion of the trial, Defendants contend there is insufficient evidence to support a verdict or penalties award against Johnson & Johnson, then Defendants may seek post trial or appellate relief on that ground. Further, it is equally true that when the facts show not only stock ownership, common officers and the like, but that the subsidiary company was a mere agency or department of the holding company, or that it was an instrumentality to subserve some special purpose of the holding company, particularly where the public interests are involved, the Court will deal with the substance of the transaction as if separate corporate entities did not exist. *State ex rel. Daniel v. Broad River Power Co*, 153 S.E. 537, 545 (S.C. 1930). The "public interests" are unquestionably involved here because the State has brought this action to recover civil penalties for Defendants' violations of SCUTPA in marketing a prescription drug with potentially fatal side effects. (*See* discussion, *supra* at § E.) The State does not have to satisfy the *Dumas* factors. Although Johnson & Johnson is a holding company In *Mid-South Management Co. v. Sherwood Development Corp.*, the Court of Appeals of South Carolina affirmed the application of the alter ego theory to the parent and subsidiary situation, and considered whether the corporate veil could be pierced under the alter ego theory separate and apart from whether the corporate veil could be pierced under the two-prong test with the *Dumas* factors. 649 S.E.2d 135, 140-44. Additionally, while the State's case unquestionably involves the "public interests," *Broad River* did not hold that the "pubic interests" must be involved to

impose liability on a holding company for the torts of its operating companies. Nor did *Broad River* hold that a holding company must be of a public service character to be held liable, although Defendants fall within that category as well.

Respectfully submitted,

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March 18, 2011
Spartanburg, South Carolina

Attorneys for the State of South Carolina

STATE OF SOUTH CAROLINA COUNTY OF SPARTANBURG	IN THE COURT OF COMMON PLEAS FOR THE SEVENTH JUDICIAL CIRCUIT
STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina, Plaintiff, v. ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA INC., and/or JANSSEN, L.P. and JOHNSON & JOHNSON, INC., Defendants.	Civil Action No. 2007-CP-42-1438 **DEFENDANTS' REQUESTED VERDICT SHEET**

Defendants, Ortho-McNeil-Janssen Pharmaceuticals, Inc. and Johnson & Johnson (erroneously named as Johnson & Johnson, Inc.), by and through their undersigned counsel and pursuant to Rule 49 of the South Carolina Rules of Civil Procedure, request that the Court submit to the Jury the attached verdict sheet with special interrogatories.

FILED
CLERK OF COURT
SPARTANBURG COUNTY
2011 MAR 18 PM 1:33
M. HOPE BLACKLEY

Respectfully Submitted,

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March 18, 2011.

FILED
CLERK OF COURT
SPARTANBURG COUNTY
2011 MAR 18 PM 1:33
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STATE OF SOUTH CAROLINA COUNTY OF SPARTANBURG	IN THE COURT OF COMMON PLEAS FOR THE SEVENTH JUDICIAL CIRCUIT
STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina, Plaintiff, v. ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA INC., and/or JANSSEN, L.P. and JOHNSON & JOHNSON, INC., Defendants.	Civil Action No. 2007-CP-42-1438 **JURY VERDICT SHEET** **PART 1 of 4** **(November 2003 Mailing)** **Ortho-McNeil-Janssen Pharmaceuticals, Inc.**

WE, THE JURY, FIND AS FOLLOWS:

1. (a) Do you find that the challenged statements contained in the November 2003 mailing are expressions of opinion that cannot be proven true or false?

Yes ___ No ___

If your answer to question 1.(a) is "yes," proceed to Jury Verdict Sheet Part 3 of 4. If your answer to question 1.(a) is "no," proceed to question 1.(b).

1. (b) Do you find, by clear and convincing evidence, that the challenged statements contained in the November 2003 mailing are false **and** that defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. made the challenged statements contained in the November 2003 mailing with knowledge that they were false, or with a degree of awareness that they were probably false?

Yes ___ No ___

If your answer to question 1.(b) is "no," proceed to Jury Verdict Sheet Part 2 of 4. If your answer to question 1.(b) is "yes," proceed to question 2.

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SPARTANBURG COUNTY
2011 MAR 18 PM 1:33
M. HOPE BLACKLEY

Foreman

2. On what date do you find that the State knew or should have known of the conduct of which it complains with respect to the November 2003 mailing?

_____/__/_____
Month/Day/Year

Please proceed to question 3.(a).

3. (a) Do you find that the challenged statements in the November 2003 mailing contain false representations of fact as to Risperdal **and** that the challenged statements in the November 2003 mailing had a tendency to deceive or were likely to deceive South Carolina physicians?

Yes __ No __

If your answer to question 3.(a) is "no," proceed to question 4.(a). If your answer to question 3.(a) is "yes," proceed to question 3.(b).

3. (b) Do you find the challenged statements in the November 2003 mailing were material to South Carolina physicians' decisions to prescribe Risperdal?

Yes __ No __

If your answer to question 3.(b) is "no," proceed to question 4.(a). If your answer to question 3.(b) is "yes," proceed to question 3.(c).

3. (c) Do you find that the State presented specific facts showing that the November 2003 mailing had an adverse public impact?

Yes __ No __

If your answer to question 3.(c) is "no," proceed to question 4.(a). If your answer to question 3.(c) is "yes," proceed to question 3.(d).

3. (d) Do you find, with respect to the State's claim that the November 2003 mailing was a deceptive trade practice, that defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. willfully violated the South Carolina Unfair Trade Practices Act?

Yes __ No __

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Please proceed to question 4.(a).

4. (a) Do you find the November 2003 mailing caused or was likely to cause substantial injury to South Carolina consumers and the alleged injury was not trivial or merely speculative?

Yes __ No __

If your answer to question 4.(a) is "no," proceed to Jury Verdict Sheet Part 2 of 4. If your answer to question 4.(a) is "yes," proceed to question 4(b).

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Foreman

4. (b) Do you find that substantial injury to consumers from the November 2003 mailing was not reasonably avoidable by consumers **and** that any substantial injury to consumers from the November 2003 mailing is not outweighed by countervailing benefits to consumers or physicians?

Yes ___ No ___

If your answer to question 4.(b) is "no," proceed to Jury Verdict Sheet Part 2 of 4. If your answer to question 4.(b) is "yes," proceed to question 4.(c).

4. (c) Do you find that the State presented specific facts showing that the November 2003 mailing had an adverse public impact?

Yes ___ No ___

If your answer to question 4.(c) is "no," proceed to Jury Verdict Sheet Part 2 of 4. If your answer to question 4.(c) is "yes," proceed to question 4.(d).

4. (d) Do you find, with respect to the State's claim that the November 2003 mailing was an unfair trade practice, that defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. willfully violated the South Carolina Unfair Trade Practices Act?

Yes ___ No ___

Proceed to Jury Verdict Sheet Part 2 of 4.

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M. HOPE BLACKLEY

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STATE OF SOUTH CAROLINA COUNTY OF SPARTANBURG	)	IN THE COURT OF COMMON PLEAS FOR THE SEVENTH JUDICIAL CIRCUIT
STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina, Plaintiff, v. ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA INC., and/or JANSSEN, L.P. and JOHNSON & JOHNSON, INC., Defendants.	)	Civil Action No. 2007-CP-42-1438 **JURY VERDICT SHEET** **PART 2 of 4** **(November 2003 Mailing)** **Johnson & Johnson, Inc.**

PLEASE NOTE: YOU MUST COMPLETE JURY VERDICT SHEET PART 1 BEFORE BEGINNING THIS JURY VERDICT SHEET

WE, THE JURY, FIND AS FOLLOWS:

1. (a) Do you find that the challenged statements contained in the November 2003 mailing are expressions of opinion that cannot be proven true or false?

Yes ___ No ___

If your answer to question 1.(a) is "yes," proceed to Jury Verdict Sheet Part 3 of 4. If your answer to question 1.(a) is "no," proceed to question 1.(b).

1. (b) Do you find, by clear and convincing evidence, that the challenged statements contained in the November 2003 mailing are false **and** that defendant Johnson & Johnson, Inc. made the challenged statements contained in the November 2003 mailing with knowledge that they were false, or with a degree of awareness that they were probably false?

Yes ___ No ___

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HOPE BLACKLEY

If your answer to question 1.(b) is "no," stop deliberation as to this statement and proceed to Jury Verdict Sheet Part 3 of 4. If your answer to question 1.(b) is "yes," proceed to question 2.

Foreman

2. On what date do you find that the State knew or should have known of the conduct of which it complains with respect to the November 2003 mailing?

_____/__/_____
Month/Day/Year

Please proceed to question 3.(a).

3. (a) Do you find that the challenged statements in the November 2003 mailing contain false representations of fact as to Risperdal **and** that the challenged statements in the November 2003 mailing had a tendency to deceive or were likely to deceive South Carolina physicians?

Yes __ No __

If your answer to question 3.(a) is "no," proceed to question 4.(a). If your answer to question 3.(a) is "yes," proceed to question 3.(b).

3. (b) Do you find the challenged statements in the November 2003 mailing were material to South Carolina physicians' decisions to prescribe Risperdal?

Yes __ No __

If your answer to question 3.(b) is "no," proceed to question 4.(a). If your answer to question 3.(b) is "yes," proceed to question 3.(c).

3. (c) Do you find that the State presented specific facts showing that the November 2003 mailing had an adverse public impact?

Yes __ No __

If your answer to question 3.(c) is "no," proceed to question 4.(a). If your answer to question 3.(c) is "yes," proceed to question 3.(d).

3. (d) Do you find, with respect to the State's claim that the November 2003 mailing was a deceptive trade practice, that the State presented proof that defendant Johnson & Johnson, Inc. willfully violated the South Carolina Unfair Trade Practices Act?

Yes __ No __

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Please proceed to question 4.(a).

4. (a) Do you find the November 2003 mailing caused or was likely to cause substantial injury to South Carolina consumers and the alleged injury was not trivial or merely speculative?

Yes __ No __

If your answer to question 4.(a) is "no," proceed to Jury Verdict Sheet Part 3 of 4. If your answer to question 4.(a) is "yes," proceed to question 4(b).

_____
Foreman

4. (b) Do you find that substantial injury to consumers from the November 2003 mailing was not reasonably avoidable by consumers **and** that any substantial injury to consumers from the November 2003 mailing is not outweighed by countervailing benefits to consumers or physicians?

Yes ___ No ___

If your answer to question 4.(b) is "no," proceed to Jury Verdict Sheet Part 3 of 4. If your answer to question 4.(b) is "yes," proceed to question 4.(c).

4. (c) Do you find that the State presented specific facts showing that the November 2003 mailing had an adverse public impact?

Yes ___ No ___

If your answer to question 4.(c) is "no," proceed to Jury Verdict Sheet Part 3 of 4. If your answer to question 4.(c) is "yes," proceed to question 4.(d).

4. (d) Do you find, with respect to the State's claim that the November 2003 mailing was an unfair trade practice, that the State presented proof that defendant Johnson & Johnson, Inc. willfully violated the South Carolina Unfair Trade Practices Act?

Yes ___ No ___

Proceed to Jury Verdict Sheet Part 3 of 4.

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M. HOPE BLACKLEY

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STATE OF SOUTH CAROLINA COUNTY OF SPARTANBURG	)	IN THE COURT OF COMMON PLEAS FOR THE SEVENTH JUDICIAL CIRCUIT
STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina, Plaintiff, v. ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA INC., and/or JANSSEN, L.P. and JOHNSON & JOHNSON, INC., Defendants.	)	Civil Action No. 2007-CP-42-1438 **JURY VERDICT SHEET** **PART 3 of 4** **(Risperdal product label or package insert)** **Ortho-McNeil-Janssen Pharmaceuticals, Inc.**

PLEASE NOTE: YOU MUST COMPLETE JURY VERDICT SHEET PARTS 1 AND 2 BEFORE BEGINNING THIS JURY VERDICT SHEET

WE, THE JURY, FIND AS FOLLOWS:

1. (a) Do you find that the challenged statements contained in the Risperdal package insert or product label are expressions of opinion that cannot be proven true or false?

Yes ___ No ___

If your answer to question 1.(a) is "yes," stop deliberation and alert the Court Officer that you have completed the Verdict Sheets. If your answer to question 1.(a) is "no," proceed to question 1.(b).

1. (b) Do you find, by clear and convincing evidence, that the challenged statements contained in the Risperdal package insert or product label are false **and** that defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. made the challenged statements contained in the Risperdal package insert with knowledge that they were false, or with a degree of awareness that they were probably false?

Yes ___ No ___

If your answer to question 1.(b) is "no," proceed to Jury Verdict Sheet Part 4 of 4. If your answer to question 1.(b) is "yes," proceed to question 2.

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M. HOOD BICKLEY

Foreman

2. On what date do you find that the State knew or should have known of the conduct of which it complained with respect to the Risperdal package insert or product label?

_____/__/_____
Month/Day/Year

Please proceed to question 3.

3. Do you find that the federal Food and Drug Administration allowed, authorized, or permitted the Risperdal package insert or product label?

Yes __ No __

If your answer to question 3 is "no," proceed to question 4.(a). If your answer to question 3 is "yes," stop deliberation and alert the Court Officer that you have completed the Verdict Sheet.

4. (a) Do you find that the Risperdal package insert or product label failed to disclose information as to the risk of weight gain, a condition known as hyperglycemia, diabetes, and a condition known as hyperprolactinemia **and** that the Risperdal package insert had a tendency to or was likely to deceive South Carolina physicians?

Yes __ No __

If your answer to question 4.(a) is "no," proceed to question 5.(a). If your answer to question 4.(a) is "yes," proceed to question 4.(b).

4. (b) Do you find the language of the Risperdal package insert or product label challenged as deceptive was material to South Carolina physicians' decisions to prescribe Risperdal?

Yes __ No __

If your answer to question 4.(b) is "no," proceed to question 5.(a). If your answer to question 4.(b) is "yes," proceed to question 4.(c).

4. (c) Do you find the State presented specific facts showing that the language of the Risperdal package insert or product label had an adverse public impact?

Yes __ No __

If your answer to question 4.(c) is "no," proceed to question 5.(a). If your answer question 4.(c) is "yes," proceed to question 4.(d).

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M. HOPE BLACKLEY

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Foreman

4. (d) Do you find, with respect to the State's claim that the Risperdal package insert or product label was a deceptive trade practice, that defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. willfully violated the South Carolina Unfair Trade Practices Act?

Yes ___ No ___

Proceed to question 5.(a).

5. (a) Do you find the Risperdal package insert caused or was likely to cause substantial injury to South Carolina consumers as a result of a failure to disclose information as to the risk of weight gain, a condition known as hyperglycemia, diabetes, and a condition known as hyperprolactinemia **and** the alleged injury that was not trivial or merely speculative?

Yes ___ No ___

If your answer to question 5.(a) is "no," proceed to Jury Verdict Sheet 4 of 4. If your answer to question 5.(a) is "yes," proceed to question 5.(b).

5. (b) Do you find that substantial injury to consumers from the Risperdal package insert or product label was not reasonably avoidable by consumers **and** that any substantial injury to consumers from the Risperdal package insert or product label is not outweighed by countervailing benefits to consumers or physicians?

Yes ___ No ___

If your answer to question 5.(b) is "no," proceed to Jury Verdict Sheet Part 4 of 4. If your answer to question 5.(b) is "yes," proceed to question 5.(c).

5. (c) Do you find that the State presented specific facts showing that the Risperdal package insert or product label had an adverse public impact?

Yes ___ No ___

If your answer to question 5.(c) is "no," proceed to Jury Verdict Sheet Part 4 of 4. If your answer to question 5.(c) is "yes," proceed to question 5.(d).

5. (d) Do you find, with respect to the State's claim that the Risperdal package insert was an unfair trade practice, that defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. willfully violated the South Carolina Unfair Trade Practices Act?

Yes ___ No ___

Proceed to Jury Verdict Sheet Part 4 of 4.

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HOPE BLACKLEY

Foreman

STATE OF SOUTH CAROLINA COUNTY OF SPARTANBURG	IN THE COURT OF COMMON PLEAS FOR THE SEVENTH JUDICIAL CIRCUIT
STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina, Plaintiff, v. ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA INC., and/or JANSSEN, L.P. and JOHNSON & JOHNSON, INC., Defendants.	Civil Action No. 2007-CP-42-1438 **JURY VERDICT SHEET** **PART 4 of 4** **(Risperdal Package Insert or Product Label)** **Johnson & Johnson, Inc.**

PLEASE NOTE: YOU MUST COMPLETE JURY VERDICT SHEET PARTS 1 THROUGH 3 BEFORE BEGINNING THIS JURY VERDICT SHEET

WE, THE JURY, FIND AS FOLLOWS:

1. (a) Do you find that the challenged statements contained in the Risperdal package insert or product label are expressions of opinion that cannot be proven true or false?

Yes ___ No ___

If your answer to question 1.(a) is "yes," stop deliberation and alert the Court Officer that you have completed the Verdict Sheet. If your answer to question 1.(a) is "no," proceed to question 1.(b).

1. (b) Do you find, by clear and convincing evidence, that the challenged statements contained in the Risperdal package insert or product label are false **and** that defendant Johnson & Johnson, Inc. made the challenged statements contained in the Risperdal package insert with knowledge that they were false, or with a degree of awareness that they were probably false?

Yes ___ No ___

If your answer to question 1.(b) is "no," stop deliberation and alert the Court Officer that you have completed the Verdict Sheet. If your answer to question 1.(b) is "yes," proceed to question 2.

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CLERK OF COURT
SPARTANBURG COUNTY
2013 MAR 18 PM 3:23
PAMELA BLACKLEY

Foreman

2. On what date do you find that the State knew or should have known of the unlawful conduct of which it complained with respect to the Risperdal package insert or product label?

_____ / __ / _____
Month/Day/Year

Please proceed to question 3.

3. Do you find that the federal Food and Drug Administration allowed, authorized, or permitted the Risperdal package insert or product label?

Yes ___ No ___

If your answer to question 3 is "no," proceed to question 4.(a). If your answer to question 3 is "yes," alert the Court Officer that you have completed the Verdict Sheet.

4. (a) Do you find that the Risperdal package insert or product label failed to disclose information as to the risk of weight gain, a condition known as hyperglycemia, diabetes and a condition known as hyperprolactinemia **and** that the Risperdal package insert had a tendency to or was likely to deceive South Carolina physicians?

Yes ___ No ___

If your answer to question 4.(a) is "no," proceed to question 5.(a). If your answer to question 4.(a) is "yes," proceed to question 4.(b).

4. (b) Do you find the language of the Risperdal package insert or product label challenged as deceptive was material to South Carolina physicians' decisions to prescribe Risperdal?

Yes ___ No ___

If your answer to question 4.(b) is "no," proceed to question 5.(a). If your answer to question 4.(b) is "yes," proceed to question 4.(c).

4. (c) Do you find the State presented specific facts showing that the language of the Risperdal package insert or product label had an adverse public impact?

Yes ___ No ___

If your answer to question 4.(c) is "no," proceed to question 5.(a). If your answer to question 4.(c) is "yes," proceed to question 4.(d).

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SPARTANBURG COUNTY
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M. ROPE BLACKLEY

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Foreman

4. (d) Do you find, with respect to the State's claim that the Risperdal package insert or product label was a deceptive trade practice, that defendant Johnson & Johnson, Inc. willfully violated the South Carolina Unfair Trade Practices Act?

Yes ___ No ___

Proceed to question 5.(a).

5. (a) Do you find the Risperdal package insert caused or was likely to cause substantial injury to South Carolina consumers as a result of a failure to disclose information as to the risk of weight gain, a condition known as hyperglycemia, diabetes, and a condition known as hyperprolactinemia **and** the alleged injury that was not trivial or merely speculative?

Yes ___ No ___

If your answer to question 5.(a) is "no," stop deliberation and alert the Court Officer that you have completed the Verdict Sheet. If your answer to question 5.(a) is "yes," proceed to question 5.(b).

5. (b) Do you find that substantial injury to consumers from the Risperdal package insert or product label was not reasonably avoidable by consumers **and** that any substantial injury to consumers from the Risperdal package insert or product label is not outweighed by countervailing benefits to consumers or physicians?

Yes ___ No ___

If your answer to question 5.(b) is "no," stop deliberation and alert the Court Officer that you have completed the Verdict Sheet. If your answer to question 5.(b) is "yes," proceed to question 5.(c).

5. (c) Do you find that the State presented specific facts showing that the Risperdal package insert or product label had an adverse public impact?

Yes ___ No ___

If your answer to question 5.(c) is "no," stop deliberation and alert the Court Officer that you have completed the Verdict Sheet. If your answer to question 5.(c) is "yes," proceed to question 5.(d).

5. (d) Do you find, with respect to the State's claim that the Risperdal package insert was an unfair trade practice, that defendant Johnson & Johnson, Inc. willfully violated the South Carolina Unfair Trade Practices Act?

Yes ___ No ___

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SPARTANBURG COUNTY
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M. HOPE BLACKLEY

Foreman

Please alert the Court Officer that you have completed the Verdict Sheet.

SO SAY WE ALL.

DATED this _____ day of March, 2011.

_____

Foreperson

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SPARTANBURG COUNTY
2011 MAR 18 PM 1:33
M. HOPE BLACKLEY

STATE OF SOUTH CAROLINA COUNTY OF SPARTANBURG	IN THE COURT OF COMMON PLEAS FOR THE SEVENTH JUDICIAL CIRCUIT
STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina, Plaintiff, v. ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC. f/k/a JANSSEN PHARMACEUTICA, INC., and/or JANSSEN, L.P. and JOHNSON & JOHNSON, INC., Defendants.	Civil Action No. 2007-CP-42-1438 **DEFENDANTS' OBJECTIONS TO PLAINTIFF'S PROPOSED REQUESTS FOR CHARGE AND PROPOSED VERDICT SHEET** **DEFENDANTS' REQUEST FOR CORRECTIVE INSTRUCTION**

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SPARTANBURG COUNTY
2011 MAR 21 AM 8:
M. MOSS BLANKLEY

Defendants, Ortho-McNeil-Janssen Pharmaceuticals, Inc. and Johnson & Johnson (erroneously named as Johnson & Johnson, Inc.), by and through the undersigned counsel, hereby submit the following objections to Plaintiff's Proposed Requests for Charge and Proposed Verdict Sheet, together with a request for a corrective instruction.

Defendants may also submit supplemental objections relative to the State's requests for charge and/or proposed verdict form and/or to any modification or addition to the State's requests for charge and/or in response to the Court's rulings on the requests for instructions. Defendants submit these specific objections without waiving any arguments or objections raised earlier. These objections are made without waiving Defendants' objections to certain other of the State's proposed requests for charge, particularly those that are inconsistent with applicable South Carolina law, this Court's prior rulings, or Defendants' Requested Jury Instructions. By submitting these objections to certain of the State's proposed requests for charge, Defendants do not concede that other proposed requests for charge, or any issues relating thereto, can or should be submitted to the jury.

A. **Objection to Plaintiff's Request To Charge No. 2 (Unfair Trade Practices Act – When Act Or Practice Is Unfair)**

Defendants object to Plaintiff's Request to Charge No. 2 as incomplete. South Carolina courts have stated that an act is "unfair" when it is "offensive to public policy or when it is immoral, unethical, or oppressive." *See, e.g., Gentry v. Yonce*, 337 S.C. 1, 12-13, 522 S.E.2d 137, 143 (1999). At the same time, the South Carolina courts have acknowledged the legislative mandate that in determining whether an act is unfair or deceptive, "the courts will be guided by the interpretations given by the Federal Trade Commission and the Federal Courts to § 5(a)(1) of the Federal Trade Commission Act (15 U.S.C. § 45(a)(1), as from time to time amended." *See* S.C. Code § 39-5-20; *see also Plowman v. Bagnal*, 316 S.C. 283, 287, 450 S.E.2d 36, 38 (1994) (relying on federal case construing Federal Trade Commission Act); *State ex rel. McLeod v. VIP Enters., Inc.*, 286 S.C. 501, 504, 335 S.E.2d 243, 244 (Ct. App. 1985) (same). That statutory mandate, obviously, does not require that South Carolina courts defer to interpretations of the Federal Trade Commission Act that are inconsistent with binding South Carolina authority, but it does call for deference to interpretations that are consistent with South Carolina decisional law or instructive where there is an absence of South Carolina law on the specific issue presented – for example, those that clarify the meaning and scope of the "unfairness" provision of the Federal Trade Commission Act, which, like the South Carolina Unfair Trade Practices Act ("SCUTPA"), prohibits both "unfair" and "deceptive" trade practices.

The Federal Trade Commission (the "FTC"), in furtherance of the Federal Trade Commission Act, has provided the public and the courts with guidance on what constitutes an "unfair" trade practice: the act or practice must cause substantial injury that is not (i) trivial or merely speculative, (ii) outweighed by any offsetting consumer or competitive benefits that the act or practice produces, and (iii) reasonably avoidable by consumers.

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GREENVILLE COUNTY
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RICHARD L. HOPE

Notably, the FTC observed that the "immoral, unethical, oppressive, or unscrupulous . . . test [similar to the South Carolina test] was presumably included in order to be sure of reaching all the purposes of the underlying statute, which forbids 'unfair' acts or practices." FTC Policy Statement on Unfairness (Dec. 17, 1980). The FTC specifically noted that "[t]he test has proven, however, to be largely duplicative. Conduct that is truly unethical or unscrupulous will almost always injure consumers or violate public policy as well." *Id.*

It is clear, then, that the State's charge does not adequately explain the requirements of "unfairness" under SCUTPA. Defendants submit that Defendants' Requested Instructions Nos. 16 and 19 more accurately reflect the law.

B. Objection To Plaintiff's Request To Charge No. 3 (Unfair Trade Practices Act – Capacity To Deceive)

Defendants object to Plaintiff's Request to Charge No. 3 as incomplete. The FTC Policy Statement on Deception clarifies the meaning of "deceptive" by explaining that an act or practice is deceptive when it has a "tendency to mislead" or – stated differently – is "likely to mislead." That explanation is not inconsistent with South Carolina law and thus should "guide" this Court's interpretation of the SCUTPA "deception" requirement. Accordingly, Defendants submit that Defendants' Requested Instructions Nos. 16 and 18 are a more complete statement of the law.

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SPARTANBURG COUNTY
2011 MAR 1 AM 8:04
M. POPPELL CRILEY

C. Objection To Plaintiff's Request To Charge No. 5 (Unfair Trade Practices Act – Willfulness)

Defendants object to Plaintiff's Request to Charge No. 5 as incomplete. Defendants' Proposed Instruction No. 28 more accurately reflects the applicable law. *See, e.g., Gentry v. Yonce*, 337 S.C. 1, 522 S.E.2d 137 (1999); *Haley Nursery Co. v. Forrest*, 298 S.C. 520, 381 S.E.2d 906 (1989); *S.C. ex rel. Medlock v. Nest Egg Soc'y Today, Inc.*, 290 S.C. 124, 348 S.E.2d 381 (1986); *Trans World Airlines, Inc. v. Air Line Pilots Assoc., Int'l*, 469 U.S. 111 (1985).

D. **Objection To Plaintiff's Amended Request to Charge No. 6 (Statute of Limitations)**

Defendants object to Plaintiff's Amended Request to Charge No. 6 as to the statute of limitations. The proposed charge is incomplete, provides insufficient guidance to the jury with respect to constructive notice and the discovery rule, and, in some respects, is inconsistent with well-settled South Carolina law. *See* Defendants' Requested Instruction No. 29. In particular, the State's proposed instruction essentially asks that the Court instruct the jury that the State is not subject to the same principles governing the application of the statute of limitations as anyone else. The only South Carolina court to address the issue, however, held the exact opposite. *Willcox v. Stroup*, 358 B.R. 824 (D.S.C. 2006); *see also State of Delaware ex rel. Brady v. Pettinaro Enters.*, 870 A.2d 513, 532 (Del. Ch. Ct. 2005) ("Given the public policy underlying statutes of limitation in general – to compel timely pursuit of claims and to avoid the adjudication of stale claims and these apt criminal law analogies, in particular – I cannot accept the State's strange argument that the [statute's] limitation period did not start to run until the Attorney General received complaints from consumers. To do so would be to condone torpor on the part of consumers, as well as the State itself."); *Pettinaro Enters.*, 870 A2d at 533 ("I realize, of course, that as a practical matter, state agencies may be reliant on citizen complaints to trigger their investigations as to even blatantly unlawful conduct. But that reality does not allow the State the luxury to recline in a leather chair, believing that the statute of limitations will only run once some aggrieved citizen gets around to making a complaint.") (footnote omitted).

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RICHLAND COUNTY
2014 MAR 1 AM 8:34
M. HOPE BLACKLEY

In addition, Defendants object to the jury, and not the Court, deciding the limited statute of limitations issue as to whether the doctrine of equitable tolling is applicable to the State's SCUTPA claim. *See Hooper v. Ebenezer Senior Svcs. & Rehab. Ctr.*, 386 S.C 108, 115, 687 S.E.2d 29, 32 (2009) ("Equitable tolling is judicially created; it stems from the

judiciary's inherent power to formulate rules of procedure where justice demands it."). Defendants also object to any instruction as to equitable tolling because the present case does not present any extraordinary circumstances to support its application. *See, e.g.*, *Hooper*, 386 S.C. at 117, 687 S.E.2d at 33 ("[E]quitable tolling is a doctrine that should be used sparingly and only when the interests of justice compel its use."); *Am. Legion Post 15 v. Horry Cty.*, 381 S.C. 576, 583-84, 674 S.E.2d 181, 182, 184 (Ct. App. 2009) ("Equitable tolling is reserved for extraordinary circumstances. . . . In this case, we find no extraordinary circumstances or active misleading by the [defendant] to warrant tolling the statutory period of limitations. Nothing prevented the [plaintiffs] from learning of the governing statutes, as we find is required for due diligence.").

E. Objection To Plaintiff's Request To Charge No. 7 (Disregard Rejected Or Stricken Evidence)

1. Bradshaw

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SPARTANBURG COUNTY
2011 MAR 2 AM 8:38
M. HOPE BLACKLEY

Defendants object to the portion of Plaintiff's Request to Charge No. 7 seeking a special instruction as to the testimony of Defendants' expert, Mr. Bradshaw. Earlier, the Court granted the State's request to strike certain answers of Mr. Bradshaw during Mr. Bradshaw's testimony and instructed the jury to disregard the answers because they "violate[d] a previous ruling that this court had made." *See* Trial Tr. vol. IX, 2060:12-2076:10, Mar. 17, 2011. The Court's ruling as to the Bradshaw testimony was based on the following representation by the State's counsel:

> MR. SIMMONS: Your Honor, these are copies of the 2002, 2004, 2006, and 2008 regulations at issue.
>
> Judge, the 2002, the 2004, and the 2006 all provide under E, warnings, which is at issue here:
>
> "The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug. A causal relationship need not have been proved."

> This witness testified, again, Your Honor, specifically that there was a causal relationship.
>
> THE COURT: Required.
>
> MR. SIMMONS: And, if fact, Your Honor, we would submit to you that's not even the standard under the 2008.

Trial Tr. vol IX, 2065:11-2066:3, Mar. 17, 2011. Counsel for the State also argued:

> MR. TRAMMELL: Your Honor, that's the critical difference in the '08 reg. The '08 reg has causal where he's interposing it in every previous version of it.
>
> THE COURT: It doesn't say causal.
>
> MR. TRAMMELL: It doesn't say causal. At no time when there are facts at issue in this case was the standard causal. And it's a critical distinction.

Id. at 2069:21-2070:4.

The "2006" regulation counsel presented to the Court was the April 1, 2006 regulation. As of June 30, 2006, the regulation was revised to provide as follows: In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a **causal** association with a drug; a causal relationship need not have been definitively established." 21 C.F.R. § 201.57(c)(6)(i) (effective June 30, 2006) (a true and correct copy is attached hereto as Ex. A) (emphasis added).[1] According to the FDA, the June 30, 2006 regulation was meant to "*codify* the agency's *longstanding* view concerning when a change to the labeling of an approved drug, biologic, or medical device may be

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2011 MAR 2 AM 8:3
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[1] The regulation effective until June 30, 2006 stated "The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R. § 201.57(e) (effective until June 30, 2006).

made in advance of the agency's review and approval of such change." 73 Fed. Reg. 49603, 49603 (Aug. 22, 2008) (emphasis added).

The State presented expert testimony that the label was inadequate, in at least some respects, through at least 2007. *See, e.g.*, Trial Tr. vol. III, 624:20-626:13, Mar. 9, 2011. Therefore, not only is the requested instruction improper, but also the jury should be given a corrective instruction that the FDA regulation was revised as of June 30, 2006 to include the word "causal," that the FDA has stated that the revision was intended to "codify," or set forth in the regulation itself, the FDA's longstanding position as to when a warning may be added to a label without prior FDA approval, and that the jury is entitled to consider the testimony of Mr. Bradshaw that was previously stricken. The following Bradshaw testimony should then be republished to the jury:

> **Q. The jury has heard some discussion throughout the course of the trial about various sections of the warning – of the label – including warnings, precautions, adverse reactions, and such.**
>
> **The question I have for you, Mr. Bradshaw, is, what is the standard for determining whether the warning section ought to be amended?**
>
> A. Sure. The Code of Federal Regulations contains all of the different standards for when you can add different information, um, to a label. And in order to add a warning to a label, there has to be reasonable likelihood of a causal relationship between the drug and whatever has been warned about.
>
> In other words, the FDA doesn't want information about adverse events unless there's actual scientific information showing that the drug actually causes the incidence in question, so as to avoid, you know, sort of junking up the label with just every possible adverse event that someone may have while taking the drug that's totally unconnected with the drug.
>
> As a result, only those – only information where there's a causal relationship between the drug and the adverse event can find its way into a warning.

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CLERK OF COURT
SPARTANBURG COUNTY
2011 MAR 21 AM 8:34
M. HOPE BLACKLEY

. . . .

Q. Now, you can pull that down. There's also been testimony that the jury has heard regarding something known as changes being effected, or CBE.

Can you explain to the jury precisely what is CBE or changes being effected?

A. Sure. In the FDA regulations, there are three ways to, um, submit a supplement to amend labeling. The most common and preferred method is called a prior approval supplement, which means you submit a supplement to the FDA to make a labeling change. The FDA reviews that supplement and then if it agrees with it, will approve it, or there may be some back and forth between the FDA and the company. But ultimately, the FDA approves the supplement, and then the – the, uh, manufacturer then makes that change to the label and after they have the FDA's approval.

But the FDA recognizes that there are some cases – and that process can take, you know, a while. It can take a year to have this back-and-forth.

But the FDA recognizes that there are sometimes manufacturers get new information that's significant and needs to be added to the label right away. And so they created a mechanism called the changes-being-effected supplement. And this allows the company – again, these are exceptions to the ordinary rule that you have to have the FDA's approval in advance.

But there's this narrow exception called the CBE that has two requirements, and if you satisfy them, you can submit a supplement to the agency. After waiting 30 days, you can go ahead and make those changes to your labeling, and then at some point in the future, the FDA will get back to you as to whether they accept or reject the changes.

In the two circumstances that you have to meet, it has to be newly-acquired evidence. So it can't be evidence that the FDA is already aware of, has already taken into account in their labeling. And it has to be something that's literally newly acquired evidence by the company. And then the second requirement is that it has to meet that legal standard set forth in the regulation, so if you're going to add a warning, it not only has to be newly acquired evidence, but you actually have to have evidence that there's a causal relationship.

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SPARTANBURG COUNTY
2011 MAR 21 AM 8:34
M. HOPE BLACKLEY

Trial Tr. vol. IX, 2050:12-2051:14, 2058:2-2060:1, Mar. 17, 2001.

2. **Brann**

The additional portion of the instruction proposed by the State as to the testimony of Mr. Brann also is improper and would prejudice Defendants and mislead the jury. Defendants incorporate by reference Defendants' Memorandum of Law in Opposition to Plaintiff's Motion for Jury Instruction and Sanctions Related to the Deposition Testimony of Edward Brann.

F. Objection To Plaintiff's Request To Charge No. 8 (Drug Labeling)

Defendants object to Plaintiff's Request to Charge No. 8 seeking an instruction based on *Wyeth v. Levine*, 129 S. Ct. 1187 (2009). The State repeatedly has stated that its claim under SCUTPA is not a claim for "failure to warn," *see* Pl.'s Opp'n to Defs.' Mot. for Summ. J. on Pl.'s SCUTPA Claim based on FDA-Approved Package Insert (filed Jan. 21, 2011) at 5 ("But the State is not bringing common law negligence, failure to warn, or other fraud claims. . . ."), which is the context in which the *Wyeth* decision is applicable. Moreover, the proposed charge is incomplete, inaccurate, and misleading, for it does not give a full and fair explanation of the circumstances in which a label may be updated and does not address the requirement that the FDA approve all revisions of the label. Further, the proposed charge as to a duty to update a package insert is inconsistent with the proposed instructions to the jury as to what constitutes an unfair or deceptive trade practice. The State cites no law that a breach of a "manufacturer's responsibility for the content of its label" constitutes an unfair or deceptive trade practice. For these reasons, the State's proposed instruction would only serve to confuse or mislead the jury as to the relevant inquiry for the State's SCUTPA claim.

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SPARTANBURG COUNTY
2011 MAR 21 AM 8:34
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G. Objection To Plaintiff's Proposed Verdict Sheet

Defendants object to Plaintiff's proposed verdict sheet. As its claim against Defendants, the State alleges that Johnson & Johnson *and* Janssen each engaged in unfair *and* deceptive trade practices in violation of SCUTPA by distributing the FDA-approved package insert for Risperdal *and* by disseminating a November 10, 2003 mailing from Janssen to South Carolina physicians. This claim presents a number of considerations, including but not limited to, the following. First, the State is required to present different proof to establish an unfair trade practice and a deceptive trade practice. Second, should the jury return a verdict in favor of the State, it will be important to know whether the verdict was based on the package insert or the November 2003 mailing. Third, the jury must consider the claim against each defendant separately. Fourth, the jury must determine not only whether Defendants' conduct violated SCUTPA, but, if it did, whether that conduct was willful. Finally, South Carolina law is clear that "*generally*, statute of limitations issues are for the jury, rather than the court, to resolve." *Dunbar v. Carlson*, 341 S.C. 261, 269, 533 S.E.2d 913, 917 (Ct. App. 2000) (citation omitted) (emphasis added). This relates particularly to factual issues. *See, e.g.*, *Arant v. Kressler*, 327 S.C. 225, 229, 489 S.E.2d 206, 208 (1997) (stating when there is conflicting testimony regarding time of discovery of facts giving notice of a medical malpractice claim, the date on which discovery should have been made becomes an issue for the jury to decide). Notably, the State included in its original proposed verdict sheet a question specifically requesting the jury decide whether

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SPARTANBURG COUNTY
2011 MAR 1 8:4
M. DUPREE KELLY

the statute of limitations operated as a bar to its claim. Defendants submit that their proposed verdict sheet is appropriate given the complexity of the State's claim.

Respectfully Submitted,

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2011 MAR 21 AM 8:34
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March 20, 2011.

EXHIBIT A

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2011 MAR 21 AM 6:34
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Code of Federal Regulations Currentness
Title 21. Food and Drugs
Chapter I. Food and Drug Administration, Department of Health and Human Services (Refs & Annos)
Subchapter C. Drugs: General
Part 201. Labeling (Refs & Annos)
Subpart B. Labeling Requirements for Prescription Drugs and/or Insulin

§ 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).

<Text of section effective June 30, 2006.>

The requirements in this section apply only to prescription drug products described in § 201.56(b)(1) and must be implemented according to the schedule specified in § 201.56(c), except for the requirement in paragraph (c)(18) of this section to reprint any FDA-approved patient labeling at the end of prescription drug labeling or accompany the prescription drug labeling, which must be implemented no later than June 30, 2007.

(a) Highlights of prescribing information. The following information must appear in all prescription drug labeling:

(1) Highlights limitation statement. The verbatim statement "These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product)."

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SPARTANBURG COUNTY
2011 MAR 23 P 2:34
J. HOPE BAILEY

(2) Drug names, dosage form, route of administration, and controlled substance symbol. The proprietary name and the established name of the drug, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (the act) or, for biological products, the proper name (as defined in § 600.3 of this chapter) including any appropriate descriptors. This information must be followed by the drug's dosage form and route of administration. For controlled substances, the controlled substance symbol designating the schedule in which the controlled substance is listed must be included as required by § 1302.04 of this chapter.

(3) Initial U.S. approval. The verbatim statement "Initial U.S. Approval" followed by the four-digit year in which FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients. The statement must be placed on the line immediately beneath the established name or, for biological products, proper name of the product.

(4) Boxed warning. A concise summary of any boxed warning required by paragraph (c)(1) of this section, not to exceed a length of 20 lines. The summary must be preceded by a heading, in upper-case letters, containing the word "WARNING" and other words that are appropriate to identify the subject of the warning. The heading and the summary must be contained within a box and bolded. The following verbatim statement must be placed immediately following the heading of the boxed warning: "See full prescribing information for complete boxed warning."

(5) Recent major changes. A list of the section(s) of the full prescribing information, limited to the labeling sections described in paragraphs (c)(1), (c)(2), (c)(3), (c)(5), and (c)(6) of this section, that contain(s) substantive labeling changes that have been approved by FDA or authorized under § 314.70(c)(6) or (d)(2), or §

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601.12(f)(1) through (f)(3) of this chapter. The heading(s) and, if appropriate, the subheading(s) of the labeling section(s) affected by the change must be listed together with each section's identifying number and the date (month/year) on which the change was incorporated in labeling. These labeling sections must be listed in the order in which they appear in the full prescribing information. A changed section must be listed under this heading in Highlights for at least 1 year after the date of the labeling change and must be removed at the first printing subsequent to the 1 year period.

(6) Indications and usage. A concise statement of each of the product's indications, as required under paragraph (c)(2) of this section, with any appropriate subheadings. Major limitations of use (e.g., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted. If the product is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class in the following manner: "(Drug) is a (name of class) indicated for (indication(s))."

(7) Dosage and administration. A concise summary of the information required under paragraph (c)(3) of this section, with any appropriate subheadings, including the recommended dosage regimen, starting dose, dose range, critical differences among population subsets, monitoring recommendations, and other clinically significant clinical pharmacologic information.

(8) Dosage forms and strengths. A concise summary of the information required under paragraph (c)(4) of this section, with any appropriate subheadings (e.g., tablets, capsules, injectable, suspension), including the strength or potency of the dosage form in metric system (e.g., 10-milligram tablets) and whether the product is scored.

(9) Contraindications. A concise statement of each of the product's contraindications, as required under paragraph (c)(5) of this section, with any appropriate subheadings.

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2011 MAR 15 AM 8:34
J. HOPE ACKLEY

(10) Warnings and precautions. A concise summary of the most clinically significant information required under paragraph (c)(6) of this section, with any appropriate subheadings, including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm.

(11) Adverse reactions.

(i) A list of the most frequently occurring adverse reactions, as described in paragraph (c)(7) of this section, along with the criteria used to determine inclusion (e.g., incidence rate). Adverse reactions important for other reasons (e.g., because they are serious or frequently lead to discontinuation or dosage adjustment) must not be repeated under this heading in Highlights if they are included elsewhere in Highlights (e.g., Warnings and Precautions, Contraindications).

(ii) For drug products other than vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at (insert current FDA phone number and Web address for voluntary reporting of adverse reactions)."

(iii) For vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or VAERS at (insert the current VAERS phone number and Web address for voluntary reporting of adverse reactions)."

(iv) For manufacturers with a Web site for voluntary reporting of adverse reactions, the Web address of the direct link to the site.

(12) Drug interactions. A concise summary of the information required under paragraph (c)(8) of this section,

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with any appropriate subheadings.

(13) Use in specific populations. A concise summary of the information required under paragraph (c)(9) of this section, with any appropriate subheadings.

(14) Patient counseling information statement. The verbatim statement "See 17 for Patient Counseling Information" or, if the product has FDA-approved patient labeling, the verbatim statement "See 17 for Patient Counseling Information and (insert either FDA-approved patient labeling or Medication Guide)."

(15) Revision date. The date of the most recent revision of the labeling, identified as such, placed at the end of Highlights.

(b) Full prescribing information: Contents. Contents must contain a list of each heading and subheading required in the full prescribing information under § 201.56(d)(1), if not omitted under § 201.56(d)(4), preceded by the identifying number required under § 201.56(d)(1). Contents must also contain any additional subheading(s) included in the full prescribing information preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(c) Full prescribing information. The full prescribing information must contain the information in the order required under paragraphs (c)(1) through (c)(18) of this section, together with the headings, subheadings, and identifying numbers required under § 201.56(d)(1), unless omitted under § 201.56(d)(4). If additional subheadings are used within a labeling section, they must be preceded by the identifying number assigned in accordance with § 201.56(d)(2).

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SPARTANBURG COUNTY
2011 MAR 22 P 2:34
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(1) Boxed warning. Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information.

(2) 1 Indications and usage. This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

(i) This section must include the following information when the conditions listed are applicable:

(A) If the drug is used for an indication only in conjunction with a primary mode of therapy (e.g., diet, surgery, behavior changes, or some other drug), a statement that the drug is indicated as an adjunct to that mode of therapy.

(B) If evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group), or if the indication is approved based on a surrogate endpoint under § 314.510 or § 601.41 of this chapter, a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the "Clinical Studies" section for a discussion of the available evidence.

(C) If specific tests are necessary for selection or monitoring of the patients who need the drug (e.g., microbe susceptibility tests), the identity of such tests.

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(D) If information on limitations of use or uncertainty about anticipated clinical benefits is relevant to the recommended intervals between doses, to the appropriate duration of treatment when such treatment should be limited, or to any modification of dosage, a concise description of the information with reference to the more detailed information in the "Dosage and Administration" section.

(E) If safety considerations are such that the drug should be reserved for specific situations (e.g., cases refractory to other drugs), a statement of the information.

(F) If there are specific conditions that should be met before the drug is used on a long term basis (e.g., demonstration of responsiveness to the drug in a short term trial in a given patient), a statement of the conditions; or, if the indications for long term use are different from those for short term use, a statement of the specific indications for each use.

(ii) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition.

(iii) Any statements comparing the safety or effectiveness of the drug with other agents for the same indication must, except for biological products, be supported by substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, such statements must be supported by substantial evidence.

(iv) For drug products other than biological products, all indications listed in this section must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

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2018 MAR 21 AM 8:34
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(v) For biological products, all indications listed in this section must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(3) 2 Dosage and administration.

(i) This section must state the recommended dose and, as appropriate:

(A) The dosage range,

(B) An upper limit beyond which safety and effectiveness have not been established, or beyond which increasing the dose does not result in increasing effectiveness,

(C) Dosages for each indication and subpopulation,

(D) The intervals recommended between doses,

(E) The optimal method of titrating dosage,

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(F) The usual duration of treatment when treatment duration should be limited,

(G) Dosing recommendations based on clinical pharmacologic data (e.g., clinically significant food effects),

(H) Modification of dosage needed because of drug interactions or in special patient populations (e.g., in children, in geriatric age groups, in groups defined by genetic characteristics, or in patients with renal or hepatic disease),

(I) Important considerations concerning compliance with the dosage regimen,

(J) Efficacious or toxic concentration ranges and therapeutic concentration windows of the drug or its metabolites, if established and clinically significant. Information on therapeutic drug concentration monitoring (TDM) must also be included in this section when TDM is necessary.

(ii) Dosing regimens must not be implied or suggested in other sections of the labeling if not included in this section.

(iii) Radiation dosimetry information must be stated for both the patient receiving a radioactive drug and the person administering it.

(iv) This section must also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams of active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed (e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the reconstituted drug, when important; essential information on drug-incompatibilities if the drug is mixed in vitro with other drugs or diluents; and the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.")

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(4) 3 Dosage forms and strengths. This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible, including:

(i) The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets), and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation; and

(ii) A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. The National Drug Code number(s) for the drug product must not be included in this section.

(5) 4 Contraindications. This section must describe any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit. Those situations include use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed (e.g., if severe hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication). If no contraindications are known, this section must state "None."

(6) 5 Warnings and precautions.

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(i) General. This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

(ii) Other special care precautions. This section must contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug (e.g., precautions not required under any other specific section or subsection).

(iii) Monitoring: Laboratory tests. This section must identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information must be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be performed before, during, and after therapy.

(iv) Interference with laboratory tests. This section must briefly note information on any known interference by the product with laboratory tests and reference the section where the detailed information is presented (e.g., "Drug Interactions" section).

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SPARTANBURG COUNTY
2011 MAR 28 P 3:34
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(7) 6 Adverse reactions. This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

(i) Listing of adverse reactions. This section must list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. The list or lists must be preceded by the information necessary to interpret the adverse reactions (e.g., for clinical trials, total number exposed, extent and nature of exposure).

(ii) Categorization of adverse reactions. Within a listing, adverse reactions must be categorized by body system, by severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in decreasing order of frequency. If frequency information cannot be reliably determined, adverse reactions must be listed in decreasing order of severity.

(A) Clinical trials experience. This section must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse reactions that occurred below the specified rate are included, they must be included in a separate listing. If comparative rates of oc-

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currence cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), adverse reactions must be grouped within specified frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified, if frequency ranges cannot be determined. For adverse reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.

(B) Postmarketing experience. This section of the labeling must list the adverse reactions, as defined in paragraph (c)(7) of this section, that are identified from domestic and foreign spontaneous reports. This listing must be separate from the listing of adverse reactions identified in clinical trials.

(iii) Comparisons of adverse reactions between drugs. For drug products other than biological products, any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions must be based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, any such claim must be based on substantial evidence.

(8) 7 Drug interactions.

(i) This section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them. The mechanism(s) of the interaction, if known, must be briefly described. Interactions that are described in the "Contraindications" or "Warnings and Precautions" sections must be discussed in more detail under this section. Details of drug interaction pharmacokinetic studies that are included in the "Clinical Pharmacology" section that are pertinent to clinical use of the drug must not be repeated in this section.

(ii) This section must also contain practical guidance on known interference of the drug with laboratory tests.

(9) 8 Use in specific populations. This section must contain the following subsections:

(i) 8.1 Pregnancy. This subsection may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus. For all other drugs, this subsection must contain the following information:

(A) Teratogenic effects. Under this subheading, the labeling must identify one of the following categories that applies to the drug, and the labeling must bear the statement required under the category:

(1) Pregnancy category A. If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling must state: "Pregnancy Category A. Studies in pregnant women have not shown that (name of drug) increases the risk of fetal abnormalities if administered during the first (second, third, or all) trimester(s) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (name of drug) should be used during pregnancy only if clearly needed." The labeling must also contain a description of the human studies. If animal reproduction studies are also available and they fail to demonstrate a risk to the fetus, the labeling must also state: "Reproduction studies have been performed in (kinds of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of im-

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paired fertility or harm to the fetus due to (name of drug)." The labeling must also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(2) Pregnancy category B. If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the labeling must state: "Pregnancy Category B. Reproduction studies have been performed in (kind(s) of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed." If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling must state: "Pregnancy Category B. Reproduction studies in (kind(s) of animal(s)) have shown (describe findings) at (x) times the human dose. Studies in pregnant women, however, have not shown that (name of drug) increases the risk of abnormalities when administered during the first (second, third, or all) trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (name of drug) should be used during pregnancy only if clearly needed." The labeling must also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(3) Pregnancy category C. If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling must state: "Pregnancy Category C. (Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." The labeling must contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling must state: "Pregnancy Category C. Animal reproduction studies have not been conducted with (name of drug). It is also not known whether (name of drug) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (Name of drug) should be given to a pregnant woman only if clearly needed." The labeling must contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

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SPARTANBURG COUNTY
2011 OCT 18 P 3:
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(4) Pregnancy category D. If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling must state: "Pregnancy Category D. See 'Warnings and Precautions' section." Under the "Warnings and Precautions" section, the labeling must state: "(Name of drug) can cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus."

(5) Pregnancy category X. If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any

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possible benefit (for example, safer drugs or other forms of therapy are available), the labeling must state: "Pregnancy Category X. See 'Contraindications' section." Under "Contraindications," the labeling must state: "(Name of drug) may (can) cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) (Name of drug) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus."

(B) Nonteratogenic effects. Under this subheading the labeling must contain other information on the drug's effects on reproduction and the drug's use during pregnancy that is not required specifically by one of the pregnancy categories, if the information is relevant to the safe and effective use of the drug. Information required under this heading must include nonteratogenic effects in the fetus or newborn infant (for example, withdrawal symptoms or hypoglycemia) that may occur because of a pregnant woman's chronic use of the drug for a preexisting condition or disease.

(ii) 8.2 Labor and delivery. If the drug has a recognized use during labor or delivery (vaginal or abdominal delivery), whether or not the use is stated in the Indications and Usage section, this subsection must describe the available information about the effect of the drug on the mother and the fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary, and the effect of the drug on the later growth, development, and functional maturation of the child. If any information required under this subsection is unknown, it must state that the information is unknown.

(iii) 8.3 Nursing mothers.

(A) If a drug is absorbed systemically, this subsection must contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring must be described.

(B) If a drug is absorbed systemically and is known to be excreted in human milk, this subsection must contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or if the drug has a known tumorigenic potential, the labeling must state: "Because of the potential for serious adverse reactions in nursing infants from (name of drug) (or, "Because of the potential for tumorigenicity shown for (name of drug) in (animal or human) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling must state: "Caution should be exercised when (name of drug) is administered to a nursing woman."

(C) If a drug is absorbed systemically and information on excretion in human milk is unknown, this subsection must contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or has a known tumorigenic potential, the labeling must state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from (name of drug) (or, "Because of the potential for tumorigenicity shown for (name of drug) in (animal or human) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling must state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (name of drug) is administered to a nursing woman."

(iv) 8.4 Pediatric use.

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STATE OF DELAWARE
2011 JUN 14 P 4:
IN THE SUPREME COURT OF THE STATE OF DELAWARE

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(A) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(H) of this section, the terms pediatric population(s) and pediatric patient(s) are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(B) If there is a specific pediatric indication different from those approved for adults that is supported by adequate and well-controlled studies in the pediatric population, it must be described under the "Indications and Usage" section, and appropriate pediatric dosage information must be given under the "Dosage and Administration" section. The "Pediatric use" subsection must cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. Data summarized in this subsection should be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or "Clinical Studies" section. As appropriate, this information must also be contained in the "Contraindications" and/or "Warnings and Precautions" section(s).

(C) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they must be summarized in the "Pediatric use" subsection and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage must be given under the "Dosage and Administration" section. The "Pediatric use" subsection of the labeling must also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information must also be contained in the "Contraindications" and/or "Warnings and Precautions" section(s).

(D)(1) When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the "Pediatric use" subsection of the labeling must contain either the following statement or a reasonable alternative:

The safety and effectiveness of (drug name) have been established in the age groups ____ to ____ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (drug name) in these age groups is supported by evidence from adequate and well-controlled studies of (drug name) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population).

(2) Data summarized in the preceding prescribed statement in this subsection must be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or the "Clinical Studies" section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose response information should be described in the "Clinical Pharmacology" section. Pediatric dosing instructions must be included in the "Dosage and Administration" section. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients must be cited briefly in the "Pediatric use" subsection and, as appropriate, in the "Contraindications," "Warnings and Precautions," and "Dosage and Administration" sections.

(E) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the "Pediatric use" subsection must

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SPARTANBURG COUNTY
2011 MAY 18 P 4:
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contain an appropriate statement such as "Safety and effectiveness in pediatric patients below the age of (____) have not been established." If use of the drug in this pediatric population is associated with a specific hazard, the hazard must be described in this subsection, or, if appropriate, the hazard must be stated in the "Contraindications" or "Warnings and Precautions" section and this subsection must refer to it.

(F) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection must contain the following statement: "Safety and effectiveness in pediatric patients have not been established." If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard must be described in this subsection, or, if appropriate, the hazard must be stated in the "Contraindications" or "Warnings and Precautions" section and this subsection must refer to it.

(G) If the sponsor believes that none of the statements described in paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(F) of this section are appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

(H) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk must be made, generally in the "Contraindications" or "Warnings and Precautions" section.

(v) 8.5 Geriatric use.

(A) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population must be described under the "Indications and Usage" section, and appropriate geriatric dosage must be stated under the "Dosage and Administration" section. The "Geriatric use" subsection must cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the "Geriatric use" subsection must pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection must be discussed in more detail, if appropriate, under "Clinical Pharmacology" or the "Clinical Studies" section. As appropriate, this information must also be contained in the "Warnings and Precautions" and/or "Contraindications" section(s).

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(B) Specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, must be contained in the "Geriatric use" subsection and must reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biologics license application, or a supplement or amendment to one of these applications (e.g., postmarketing studies or adverse drug reaction reports). The "Geriatric use" subsection must contain the following statement(s) or reasonable alternative, as applicable, taking into account available information:

(1) If clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection must include the following statement:

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Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

(2) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection must contain the following statement:

Of the total number of subjects in clinical studies of (name of drug), ____ percent were 65 and over, while ____ percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

(3) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the "Geriatric use" subsection must contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate, must refer to more detailed discussions in the "Contraindications," "Warnings and Precautions," "Dosage and Administration," or other sections.

(C)(1) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they must be described briefly in the "Geriatric use" subsection and in detail under the "Clinical Pharmacology" section. The "Clinical Pharmacology" and "Drug Interactions" sections ordinarily contain information on drug/disease and drug/drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to use concomitant drugs.

(2) If a drug is known to be substantially excreted by the kidney, the "Geriatric use" subsection must include the statement:

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

(D) If use of the drug in the elderly appears to cause a specific hazard, the hazard must be described in the "Geriatric use" subsection, or, if appropriate, the hazard must be stated in the "Contraindications" or "Warnings and Precautions" section, and the "Geriatric use" subsection must refer to those sections.

(E) Labeling under paragraphs (c)(9)(v)(A) through (c)(9)(v)(C) of this section may include statements, if they are necessary for safe and effective use of the drug, and reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that:

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Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of (name of drug) and observed closely.

(F) If the sponsor believes that none of the requirements described in paragraphs (c)(9)(v)(A) through (c)(9)(v)(E) of this section are appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

(vi) Additional subsections. Additional subsections may be included, as appropriate, if sufficient data are available concerning the use of the drug in other specified subpopulations (e.g., renal or hepatic impairment).

(10) 9 Drug abuse and dependence. This section must contain the following information, as appropriate:

(i) 9.1 Controlled substance. If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled must be stated.

(ii) 9.2 Abuse. This subsection must state the types of abuse that can occur with the drug and the adverse reactions pertinent to them, and must identify particularly susceptible patient populations. This subsection must be based primarily on human data and human experience, but pertinent animal data may also be used.

(iii) 9.3 Dependence. This subsection must describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and must identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details must be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state and the principles of treating the effects of abrupt withdrawal must be described.

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(11) 10 Overdosage. This section must be based on human data. If human data are unavailable, appropriate animal and in vitro data may be used. The following specific information must be provided:

(i) Signs, symptoms, and laboratory findings associated with an overdosage of the drug;

(ii) Complications that can occur with the drug (for example, organ toxicity or delayed acidosis);

(iii) Concentrations of the drug in biologic fluids associated with toxicity or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the "Clinical Pharmacology" section also may be referenced here, if applicable to overdoses;

(iv) The amount of the drug in a single dose that is ordinarily associated with symptoms of overdosage and the amount of the drug in a single dose that is likely to be life threatening;

(v) Whether the drug is dialyzable; and

(vi) Recommended general treatment procedures and specific measures for support of vital functions (e.g., proven antidotes, gastric lavage, forced diuresis, or as per Poison Control Center). Such recommendations must be based on data available for the specific drug or experience with pharmacologically related drugs. Unqualified

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recommendations for which data are lacking for the specific drug or class of drugs must not be stated.

(12) 11 Description.

(i) This section must contain:

(A) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug or, for biological products, the proper name (as defined in § 600.3 of this chapter) and any appropriate descriptors;

(B) The type of dosage form(s) and the route(s) of administration to which the labeling applies;

(C) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for drug labels or §§ 610.60 and 610.61 of this chapter for biological product labels;

(D) If the product is sterile, a statement of that fact;

(E) The pharmacological or therapeutic class of the drug;

(F) For drug products other than biological products, the chemical name and structural formula of the drug; and

(G) If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics.

(ii) If appropriate, other important chemical or physical information, such as physical constants or pH, must be stated.

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2011 MAR 21 AM 8:25
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(13) 12 Clinical pharmacology.

(i) This section must contain information relating to the human clinical pharmacology and actions of the drug in humans. Pharmacologic information based on in vitro data using human biomaterials or pharmacologic animal models, or relevant details about in vivo study designs or results (e.g., drug interaction studies), may be included in this section if essential to understand dosing or drug interaction information presented in other sections of the labeling. This section must include the following subsections:

(A) 12.1 Mechanism of action. This subsection must summarize what is known about the established mechanism(s) of the drug's action in humans at various levels (e.g., receptor, membrane, tissue, organ, whole body). If the mechanism of action is not known, this subsection must contain a statement about the lack of information.

(B) 12.2 Pharmacodynamics. This subsection must include a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug's clinical effect in preventing, diagnosing, mitigating, curing, or treating disease, or those related to adverse effects or toxicity. Exposure-response relationships (e.g., concentration-response, dose-response) and time course of pharmacodynamic response (including short-term clinical response) must be included if known. If this information is unknown, this subsection must contain a statement about the lack of information. Detailed dosing or monitoring recommendations based on pharmacodynamic information that appear in other sections (e.g., "Warnings and Precautions" or "Dosage and Administration") must not be repeated in this subsection, but the lo-

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cation of such recommendations must be referenced.

(C) 12.3 Pharmacokinetics. This subsection must describe the clinically significant pharmacokinetics of a drug or active metabolites, (i.e., pertinent absorption, distribution, metabolism, and excretion parameters). Information regarding bioavailability, the effect of food, minimum concentration (C_{min}), maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve (AUC), pertinent half-lives ($t_{1/2}$), time to reach steady state, extent of accumulation, route(s) of elimination, clearance (renal, hepatic, total), mechanisms of clearance (e.g., specific enzyme systems), drug/drug and drug/food (e.g., dietary supplements, grapefruit juice) pharmacokinetic interactions (including inhibition, induction, and genetic characteristics), and volume of distribution (V_d) must be presented if clinically significant. Information regarding nonlinearity in pharmacokinetic parameters, changes in pharmacokinetics over time, and binding (plasma protein, erythrocyte) parameters must also be presented if clinically significant. This section must also include the results of pharmacokinetic studies (e.g., of metabolism or interaction) that establish the absence of an effect, including pertinent human studies and in vitro data. Dosing recommendations based on clinically significant factors that change the product's pharmacokinetics (e.g., age, gender, race, hepatic or renal dysfunction, concomitant therapy) that appear in other sections (e.g., "Warnings and Precautions," "Dosage and Administration" or "Use in Specific Populations") must not be repeated in this subsection, but the location of such recommendations must be referenced.

(ii) Data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use may be included under this section only under the following circumstances:

(A) In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement "The following in vitro data are available but their clinical significance is unknown."

(B) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled studies, as defined in § 314.126(b) of this chapter, to be necessary for the safe and effective use may be included in this section only if a waiver is granted under § 201.58 or § 314.126(c) of this chapter.

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2011 APR 22 AM 8:38
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(14) 13 Nonclinical toxicology. This section must contain the following subsections as appropriate:

(i) 13.1 Carcinogenesis, mutagenesis, impairment of fertility. This subsection must state whether long term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If results from reproduction studies or other data in animals raise concern about mutagenesis or impairment of fertility in either males or females, this must be described. Any precautionary statement on these topics must include practical, relevant advice to the prescriber on the significance of these animal findings. Human data suggesting that the drug may be carcinogenic or mutagenic, or suggesting that it impairs fertility, as described in the "Warnings and Precautions" section, must not be included in this subsection of the labeling.

(ii) 13.2 Animal toxicology and/or pharmacology. Significant animal data necessary for safe and effective use of the drug in humans that is not incorporated in other sections of labeling must be included in this section (e.g., specifics about studies used to support approval under § 314.600 or § 601.90 of this chapter, the absence of chronic animal toxicity data for a drug that is administered over prolonged periods or is implanted in the body).

(15) 14 Clinical studies. This section must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively. Ordinarily, this section will describe the studies that support effectiveness for the labeled indication(s), including discussion of study design, population, endpoints, and results, but must not include an encyclopedic listing of all, or even most, studies performed as part of the product's clinical development program. If a specific important clinical study is mentioned in any section of the labeling required

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under §§ 201.56 and **201.57** because the study is essential to an understandable presentation of the information in that section of the labeling, any detailed discussion of the study must appear in this section.

(i) For drug products other than biological products, any clinical study that is discussed in prescription drug labeling that relates to an indication for or use of the drug must be adequate and well-controlled as described in § 314.126(b) of this chapter and must not imply or suggest indications or uses or dosing regimens not stated in the "Indications and Usage" or "Dosage and Administration" section. For biological products, any clinical study that is discussed that relates to an indication for or use of the biological product must constitute or contribute to substantial evidence and must not imply or suggest indications or uses or dosing regimens not stated in the "Indications and Usage" or "Dosage and Administration" section.

(ii) Any discussion of a clinical study that relates to a risk from the use of the drug must also refer to the other sections of the labeling where the risk is identified or discussed.

(16) 15 References. When prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions, the labeling may include a reference to the source of the information.

(17) 16 How supplied/storage and handling. This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information must include, as appropriate:

(i) The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets) and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation;

(ii) The units in which the dosage form is ordinarily available for prescribing by practitioners (e.g., bottles of 100);

(iii) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, imprinting, and National Drug Code number; and

(iv) Special handling and storage conditions.

(18) 17 Patient counseling information. This section must contain information necessary for patients to use the drug safely and effectively (e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects). Any FDA-approved patient labeling must be referenced in this section and the full text of such patient labeling must be reprinted immediately following this section or, alternatively, accompany the prescription drug labeling. Any FDA-approved patient labeling printed immediately following this section or accompanying the labeling is subject to the type size requirements in paragraph (d)(6) of this section, except for a Medication Guide to be detached and distributed to patients in compliance with § 208.24 of this chapter. Medication Guides for distribution to patients are subject to the type size requirements set forth in § 208.20 of this chapter.

(d) Format requirements. All labeling information required under paragraphs (a), (b), and (c) of this section must be printed in accordance with the following specifications:

(1) All headings and subheadings required by paragraphs (a) and (c) of this section must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Reverse type is not permitted as a form of highlighting.

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2011 MAR 21 AM 8:30
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(2) A horizontal line must separate the information required by paragraphs (a), (b), and (c) of this section.

(3) The headings listed in paragraphs (a)(5) through (a)(13) of this section must be presented in the center of a horizontal line.

(4) If there are multiple subheadings listed under paragraphs (a)(4) through (a)(13) of this section, each subheading must be preceded by a bullet point.

(5) The labeling information required by paragraphs (a)(1) through (a)(4), (a)(11)(ii) through (a)(11)(iv), and (a)(14) of this section must be in bold print.

(6) The letter height or type size for all labeling information, headings, and subheadings set forth in paragraphs (a), (b), and (c) of this section must be a minimum of 8 points, except for labeling information that is on or within the package from which the drug is to be dispensed, which must be a minimum of 6 points.

(7) The identifying numbers required by § 201.56(d) and paragraphs (c)(1) through (c)(18) of this section must be presented in bold print and must precede the heading or subheading by at least two square em's (i.e., two squares of the size of the letter "m" in 8 point type).

(8) The information required by paragraph (a) of this section, not including the information required under paragraph (a)(4) of this section, must be limited in length to an amount that, if printed in 2 columns on a standard sized piece of typing paper (8 1/2 by 11 inches), single spaced, in 8 point type with 1/2-inch margins on all sides and between columns, would fit on one-half of the page.

(9) Sections or subsections of labeling that are identified as containing recent major changes under paragraph (a)(5) of this section must be highlighted in the full prescribing information by the inclusion of a vertical line on the left edge of the new or modified text.

(10) For the information required by paragraph (b) of this section, each section heading must be in bold print. Each subheading within a section must be indented and not bolded.

[71 FR 3988, Jan. 24, 2006]

SOURCE: 40 FR 13998, March 27, 1975; 51 FR 8182, March 7, 1986; 51 FR 43904, Dec. 5, 1986; 52 FR 2111, Jan. 20, 1987; 53 FR 4135, Feb. 12, 1988; 54 FR 39635, Sept. 27, 1989, 57 FR 54300, Nov. 18, 1992; 58 FR 45201, Aug. 26, 1993; 62 FR 51515, Oct. 1, 1997; 63 FR 26698, May 13, 1998; 64 FR 400, Jan. 5, 1999, unless otherwise noted.

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

21 C. F. R. § 201.57, 21 CFR § 201.57

Current through March 30, 2006; 71 FR 16060

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STATE OF SOUTH CAROLINA	)	IN THE COURT OF COMMON PLEAS
COUNTY OF SPARTANBURG	)	
Ex. Rel. Alan Wilson in his capacity as Attorney General of the State of South Carolina,	)	C.A.No.: 07-CP-42-1438
Plaintiff	)	
v.	)	
Ortho-McNeil-Janssen Pharmaceuticals, Inc., f/k/a Janssen Pharmaceutica, Inc., And/or Janssen, L.P., And Johnson & Johnson, Inc., Defendants.	)	

VERDICT AS TO ORTHO-MCNEIL-JANSSEN PHARMACEUTICA, INC., f/k/a JANSSEN PHARMACEUTICA, INC., and/or JANSSEN L.P.

1. As to the question of whether or not the above Defendant engaged in unfair or deceptive acts or practices in the conduct of any trade or commerce in the "dear doctor" letter of November 10, 2003, we the jury unanimously find for:

_____ The Defendant

_✓_ The Plaintiff

(If you found for the Plaintiff on Question #1 then you must answer question 1A.)

1A. Were the violations of the Unfair Trade Practices Act, by the Defendant willful?

R. 3030

✓ Yes

___ No

2. As to the question of whether or not the above Defendant engaged in unfair or deceptive acts or practices in the conduct of any trade or commerce in its label (package insert), we the jury unanimously find for:

_____ The Defendant

✓ The Plaintiff

(If you found for the Plaintiff on Question #2 then you must answer question 2A.)

2A. Were the violations of the Unfair Trade Practices Act, by the Defendant, willful?

✓ Yes

___ No

The above verdicts are the unanimous verdict of the jury, this 22 day of March, 2011.

Robert Ellison

FOREPERSON

NO. 272 P. 3
MAY. 11. 2011 11:08AM 123

STATE OF SOUTH CAROLINA	)	IN THE COURT OF COMMON PLEAS
	)	
COUNTY OF SPARTANBURG	)	
	)	
Ex. Rel. Alan Wilson in his capacity as Attorney General of the State of South Carolina,	)	C.A.No.: 07-CP-42-1438
	)	
Plaintiff	)	
	)	
v.	)	
	)	
Ortho-McNeil-Janssen Pharmaceuticals, Inc., f/k/a Janssen Pharmaceutica, Inc., And/or Janssen, L.P., And Johnson & Johnson, Inc., Defendants.	)	

VERDICT AS TO JOHNSON & JOHNSON, INC.

1. As to the question of whether or not the above Defendant engaged in unfair or deceptive acts or practices in the conduct of any trade or commerce in the "dear doctor" letter of November 10, 2003, we the jury unanimously find for:

✓ The Defendant

_____ The Plaintiff

(If you found for the Plaintiff on Question #1 then you must answer question 1A.)

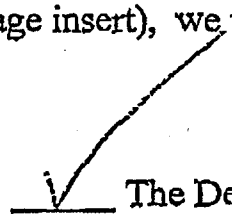
1A. Were the violations of the Unfair Trade Practices Act, by the Defendant, willful?

MAY. 11. 2011 11:08AM 123 NO. 272 P. 4

___ Yes

___ No

2. As to the question of whether or not the above Defendant engaged in unfair or deceptive acts or practices in the conduct of any trade or commerce in its label (package insert), we the jury unanimously find for:



___ The Defendant

_____ The Plaintiff

(If you found for the Plaintiff on Question #2 then you must answer question 2A.)

2A. Were the violations of the Unfair Trade Practices Act, by the Defendant, willful?

___ Yes

___ No

The above verdicts are the unanimous verdict of the jury, this 22 day of March, 2011.

Robert Ellison

FOREPERSON

MAY. 11. 2011 11:08AM 123 NO. 272 P. 5

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R. 3034

RISPERDAL Business Plan 2004

Risperdal®
tablets and oral solution 1 mg/mL RISPERIDONE
Helping Turn Lives Around

EXHIBIT
Smith 22
1-15-09
PENGAD 800-631-6989

Subject to Legal/Regulatory Review

The Mood Evolution: Helping Turn Lives Around

JJRE 00242409
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Today's Agenda

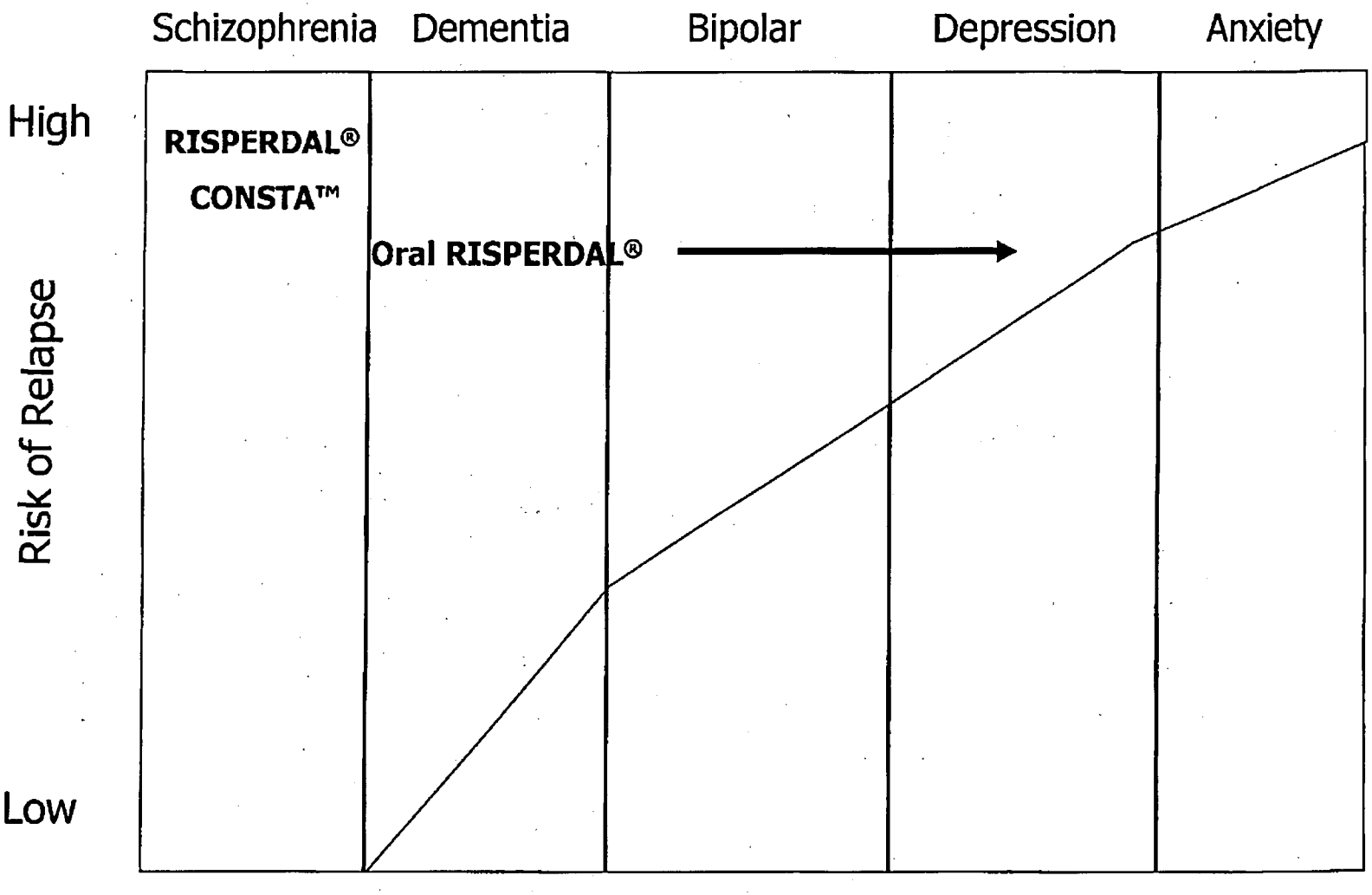
- Introduction
- Market overview
- 2003 review
- Internal assessment
- 2004 strategies
- Forecast/budget

R. 3036

JJRE 00242410
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Subject to Legal/Regulatory Review

Strategic Franchise Direction



Subject to Legal/Regulatory Review

R. 3037

JJRE 00242411
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Themes for 2004

- Grow RISPERDAL in mood & anxiety segment via symptoms of acute mania associated with bipolar disorder
  - Capitalize on the growing PCP opportunity
- Stop Seroquel
- Ensure first mover position in autism
- Address LTC segment challenges

R. 3038

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Subject to Legal/Regulatory Review

Market Overview

- Mood & anxiety is driving market growth
- Market is being further defined by safety and tolerability
- Seroquel is number 1 growth product
- Share impact of Abilify launch and CAE labeling
- C&A is an important growth segment

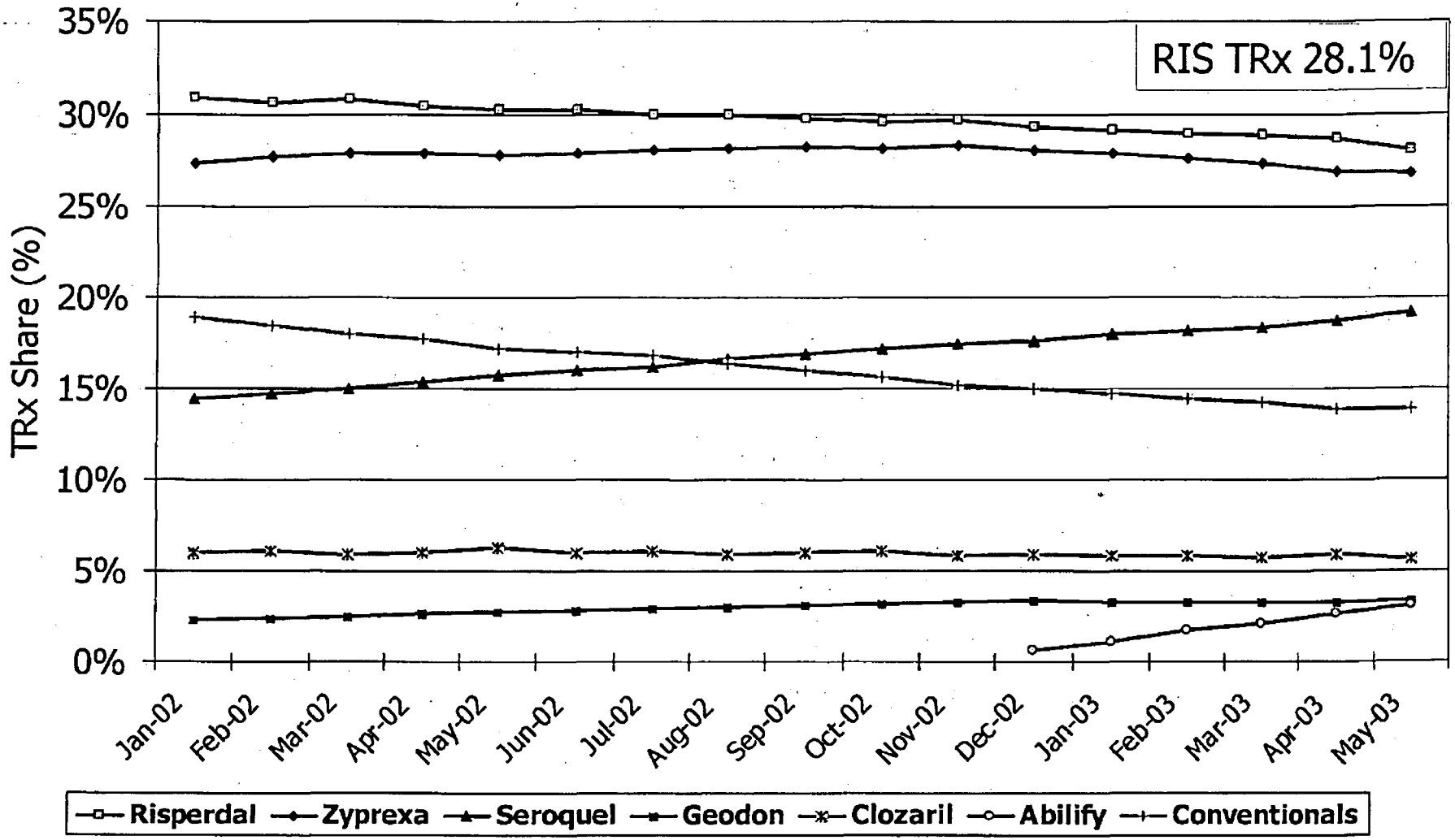
(Mood & Anxiety: Depression, Anxiety, Bipolar)

Subject to Legal/Regulatory Review

R. 3039

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Risperdal is market leader, but numerous competitive threats exist



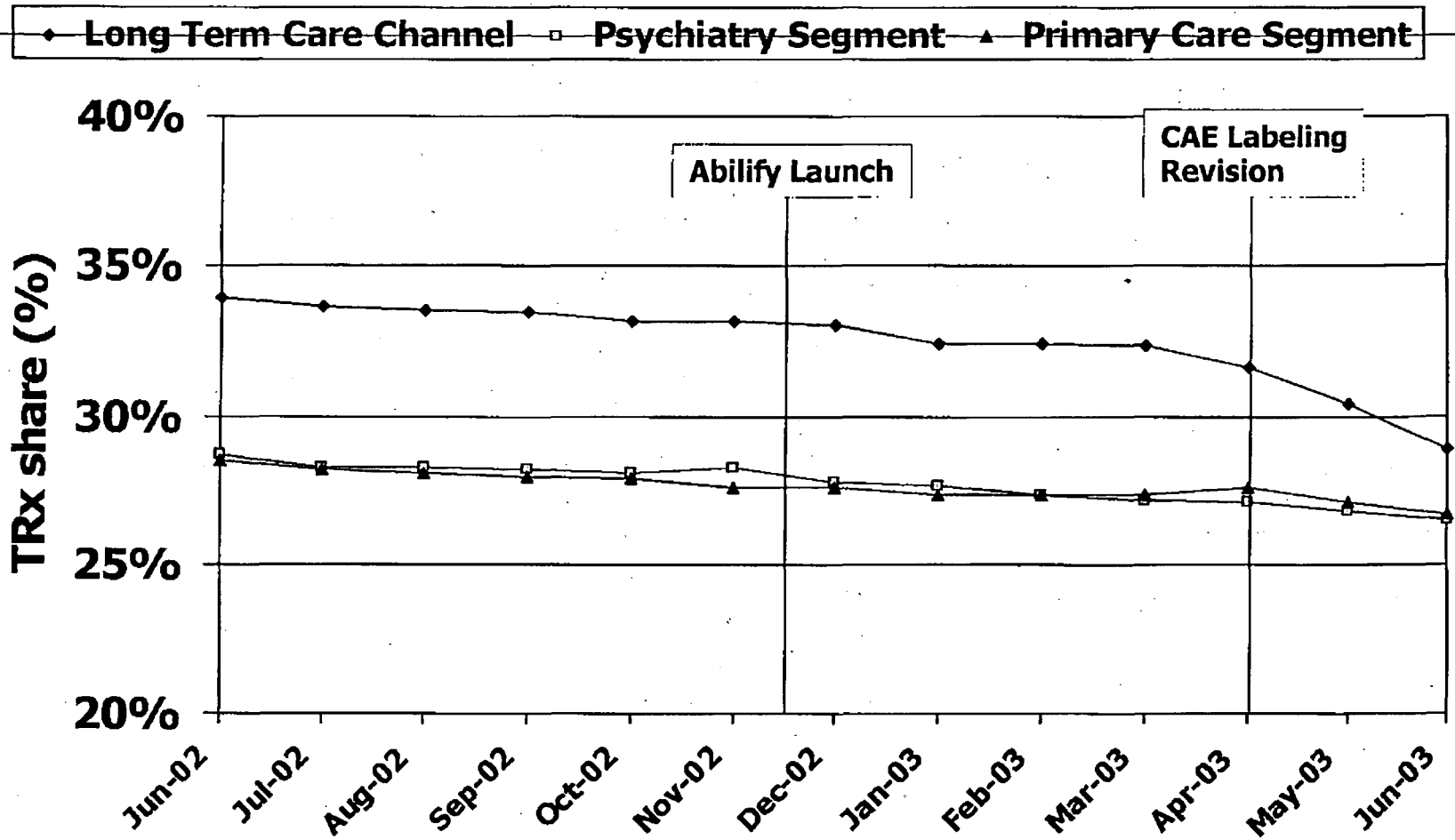
Source: IMS Health, NPA Plus

Subject to Legal/Regulatory Review

R. 3040

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Risperdal TRx share trends



Caveat: TRx trends sourced from separate IMS audits. Long Term Care data sourced from NPA Channel audit, Psych & PCP data sourced from NPA Specialty audit

Source: IMS Health, NPA Plus, June 2003

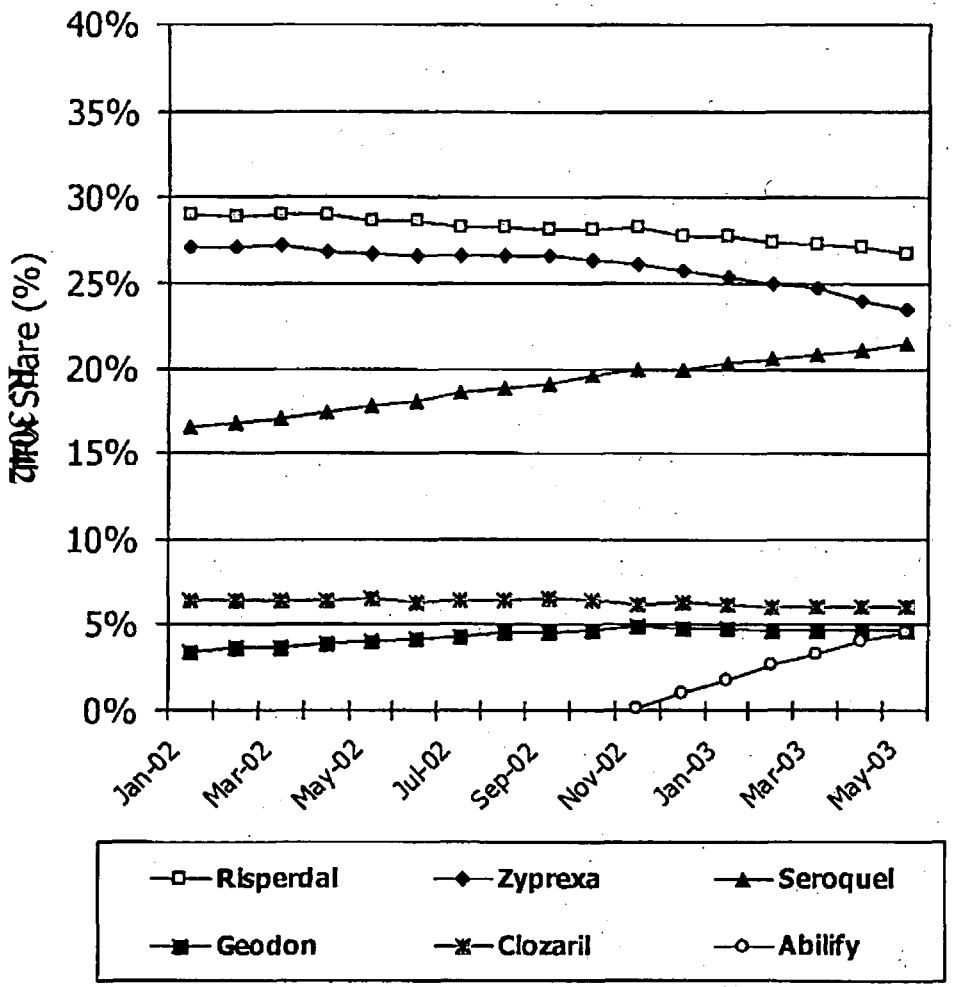
Subject to Legal/Regulatory Review

R. 3041

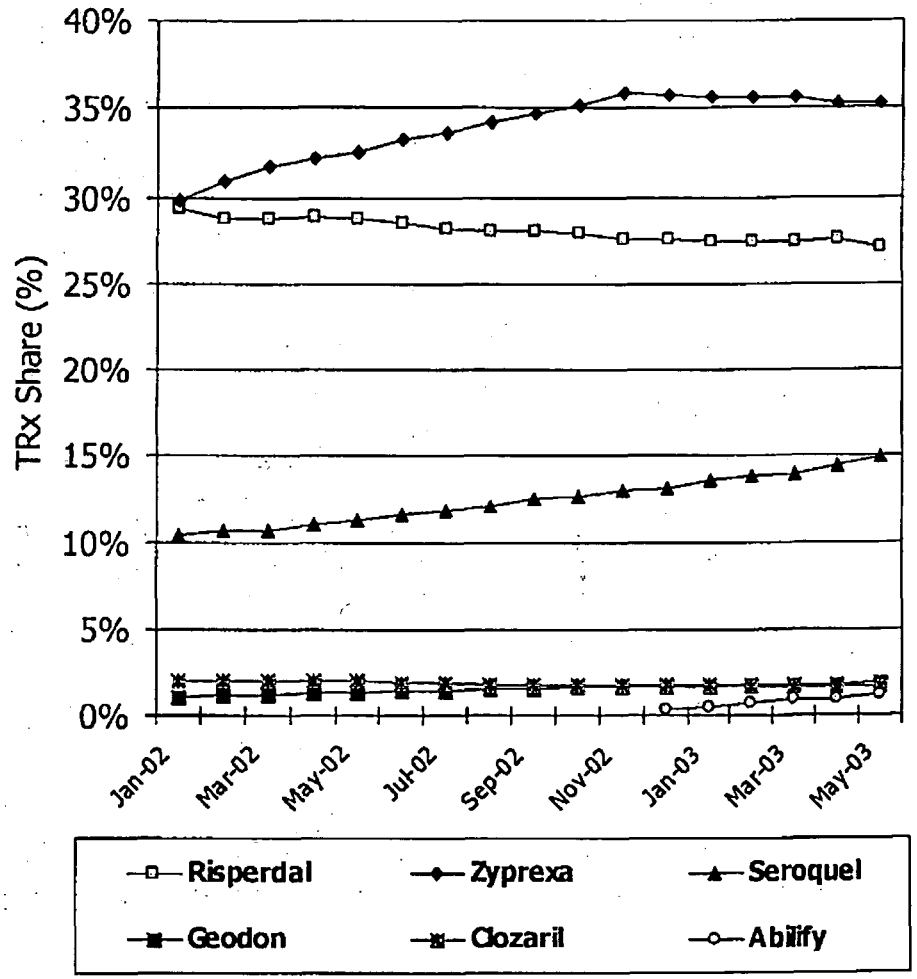
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One market with two distinct segments

PSYCH (+13% growth)



PCP (+27% growth)



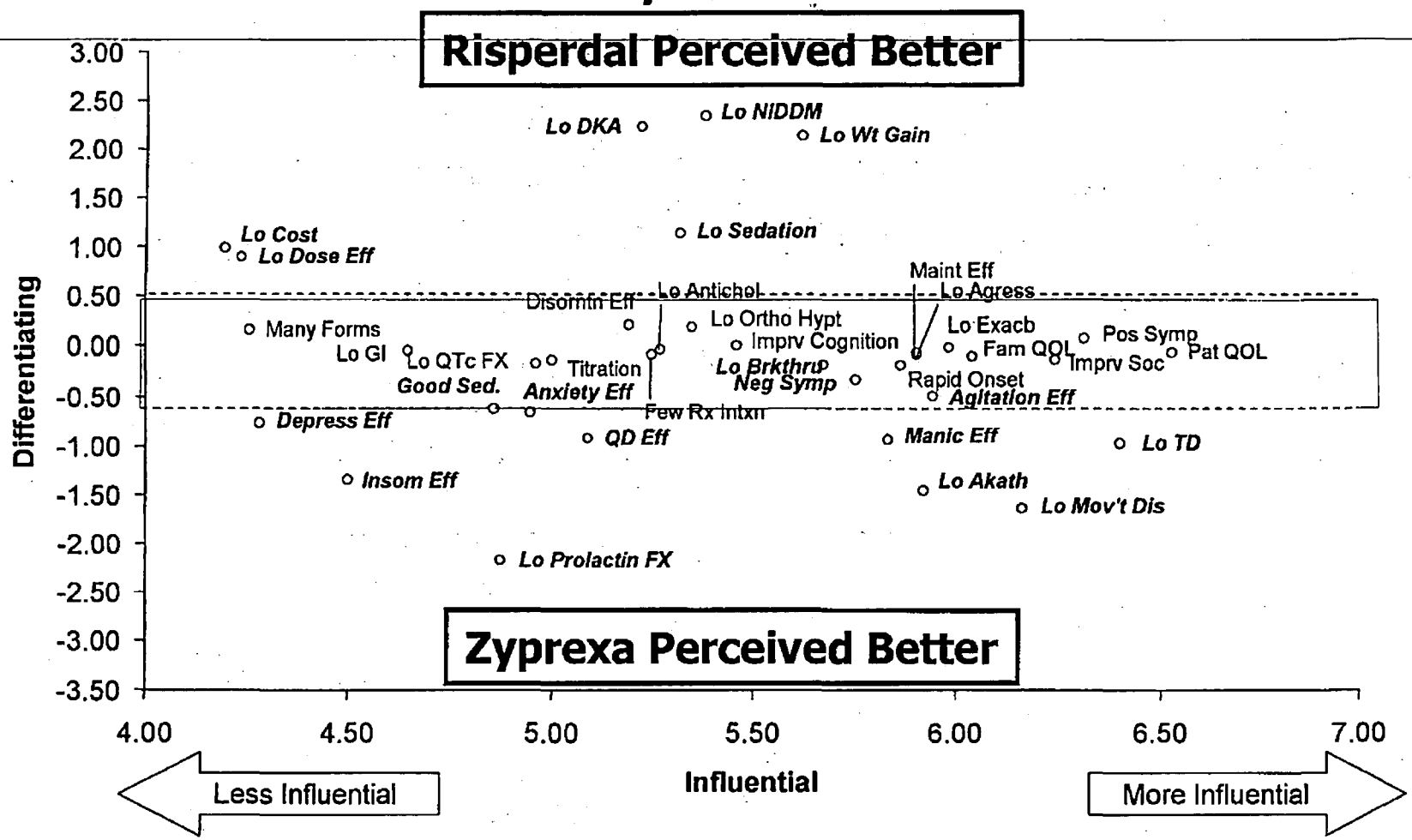
Source: IMS Health, NPA Plus

Subject to Legal/Regulatory Review

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Risperdal v Zyprexa

-Psychiatrists-



□ **Efficacy/Symptom control** □ **Safety/Side effects** □ **Dosing/Administration** □ **QOL**

Q12, 13

* Attribute is bolded and italicized if significant difference between drugs

Base: Psychiatrists; n=251

Source: Annual Tracking Study 2003

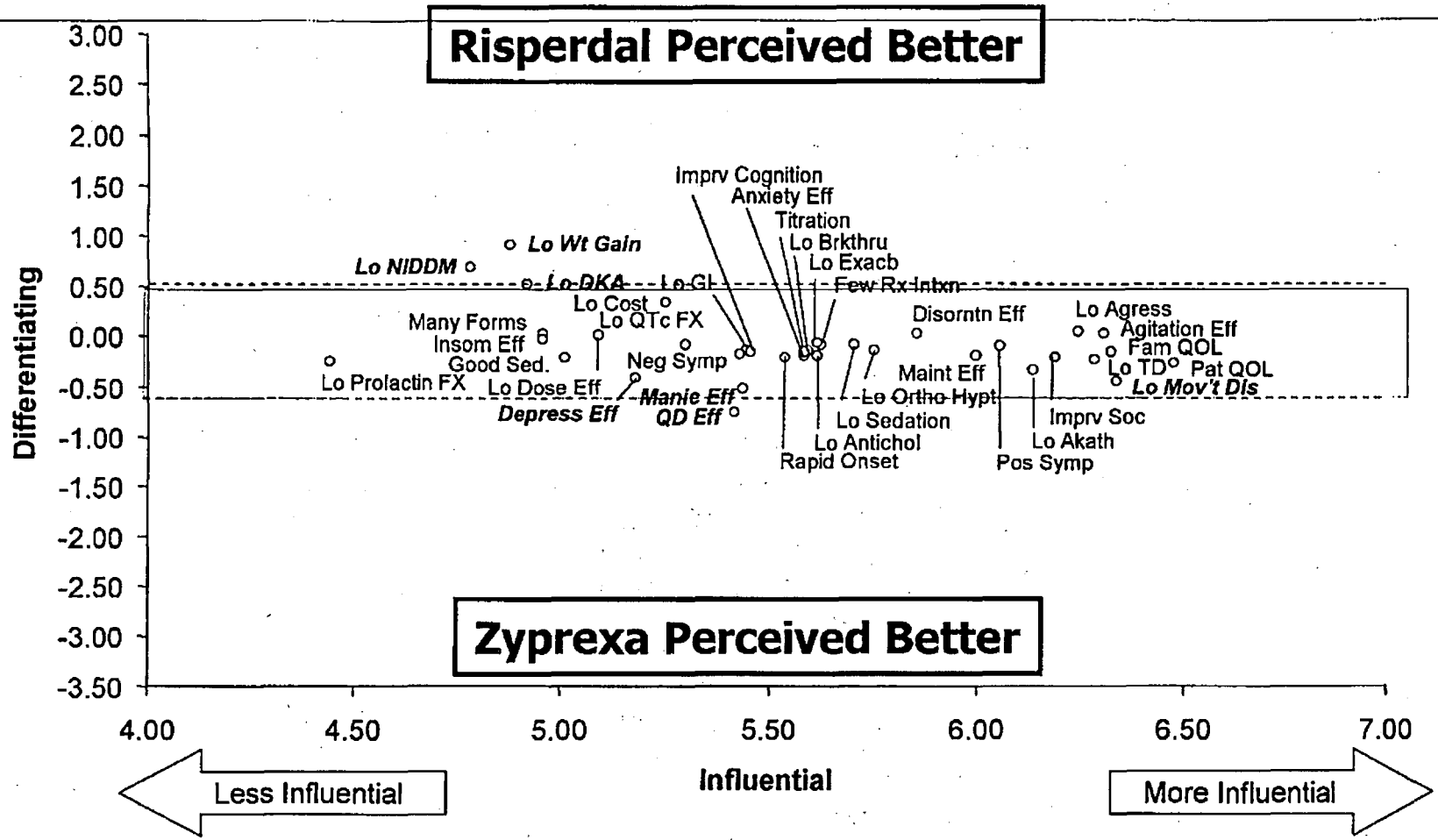
Subject to Legal/Regulatory Review

R. 3043

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Risperdal v Zyprexa

-PCP-



Q12, 13; n=108

* Attribute is bolded and italicized if significant difference between drugs

Source: Annual Tracking Study 2003

Base: PCPs

Subject to Legal/Regulatory Review

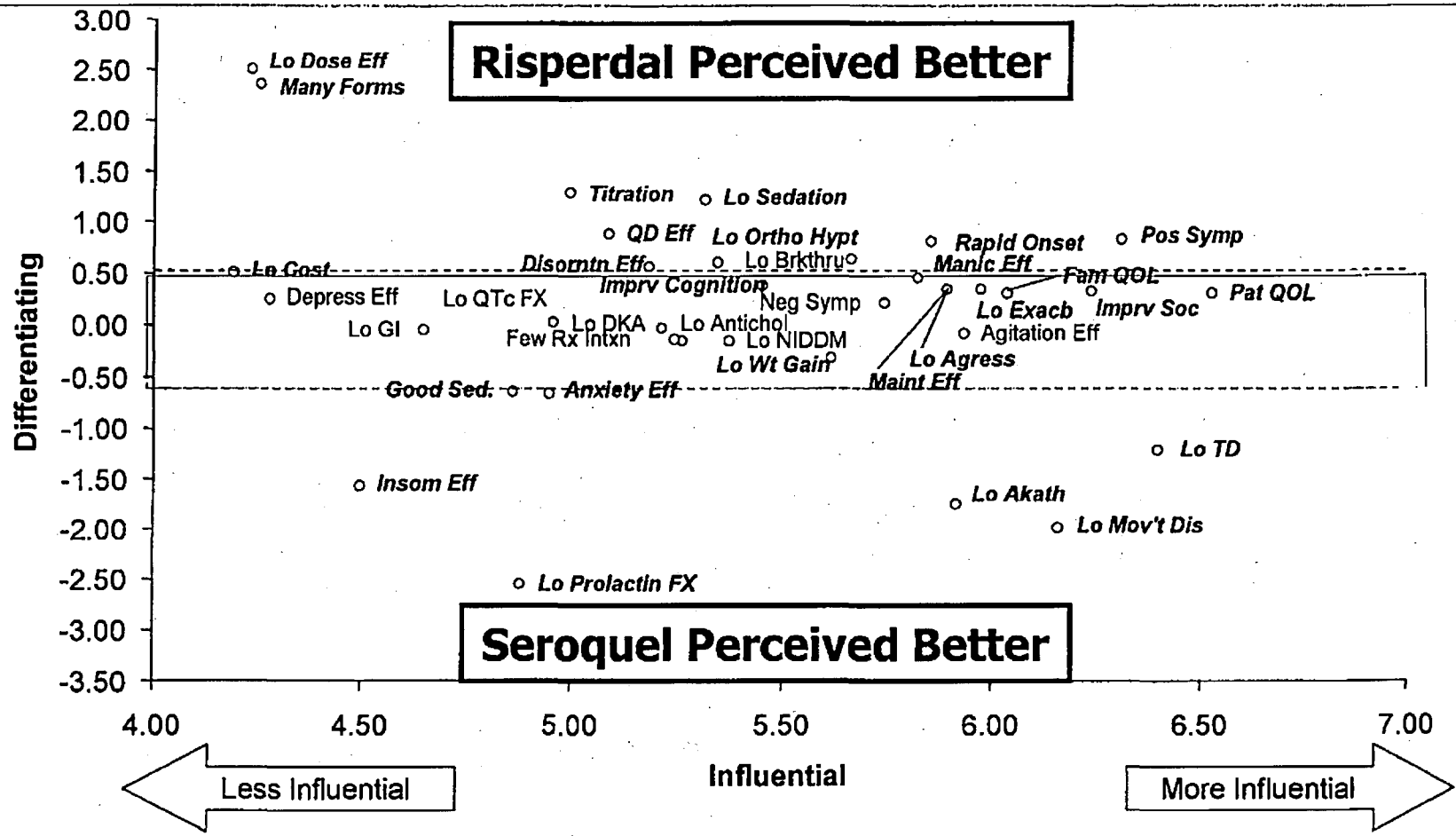
R. 3044

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Risperdal v Seroquel

-Psychiatrists-



☐ Efficacy/Symptom control ☐ Safety/Side effects ☐ Dosing/Administration ☐ QOL

Q12, 13; n=251

* Attribute is bolded and italicized if significant difference between drugs

Source: Annual Tracking Study 2003

Base: Psychiatrists

Subject to Legal/Regulatory Review

R. 3045

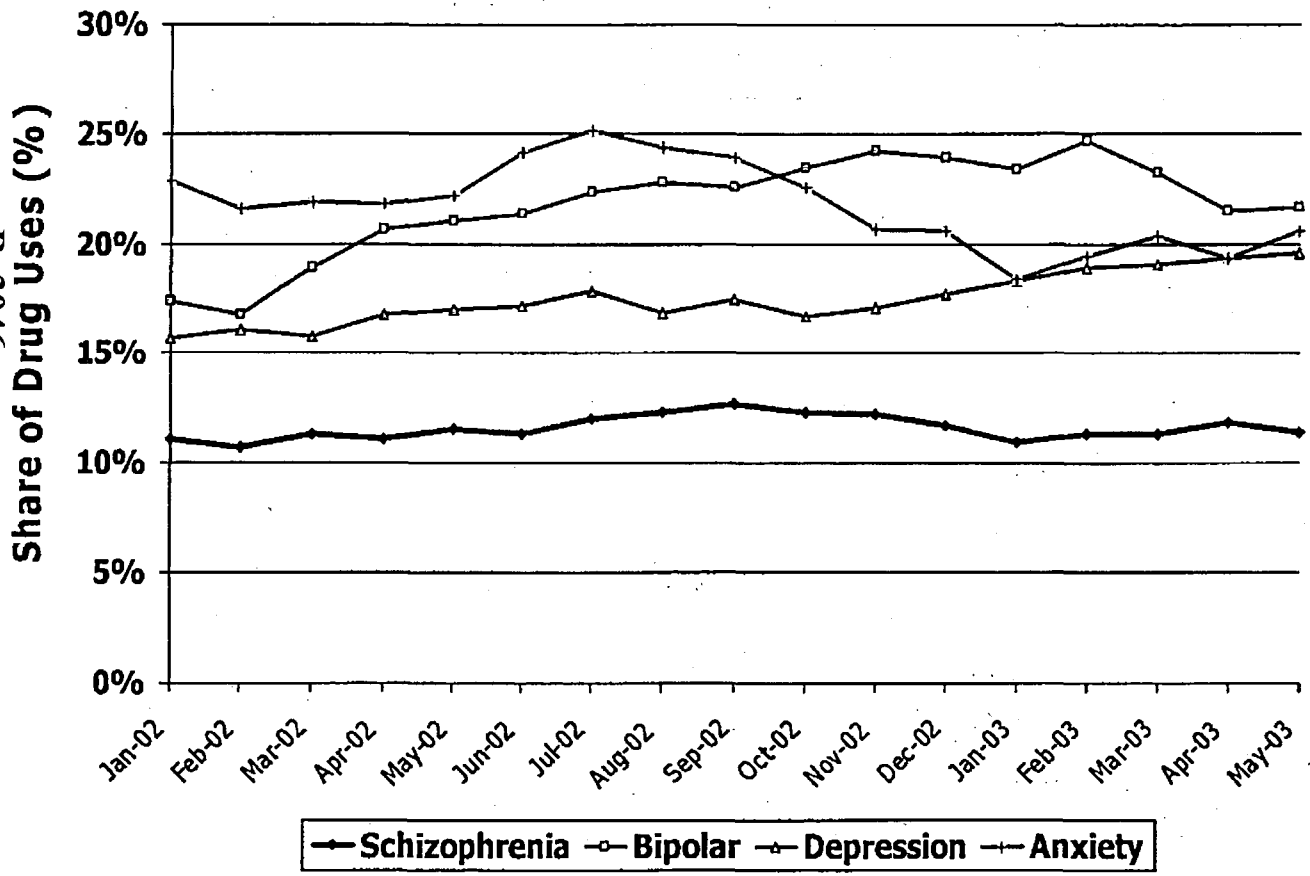
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Seroquel product profile fosters growth across mood & anxiety disease states

JJRE 00242420
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R. 3046

Seroquel Share of Drug Uses Across Diagnoses



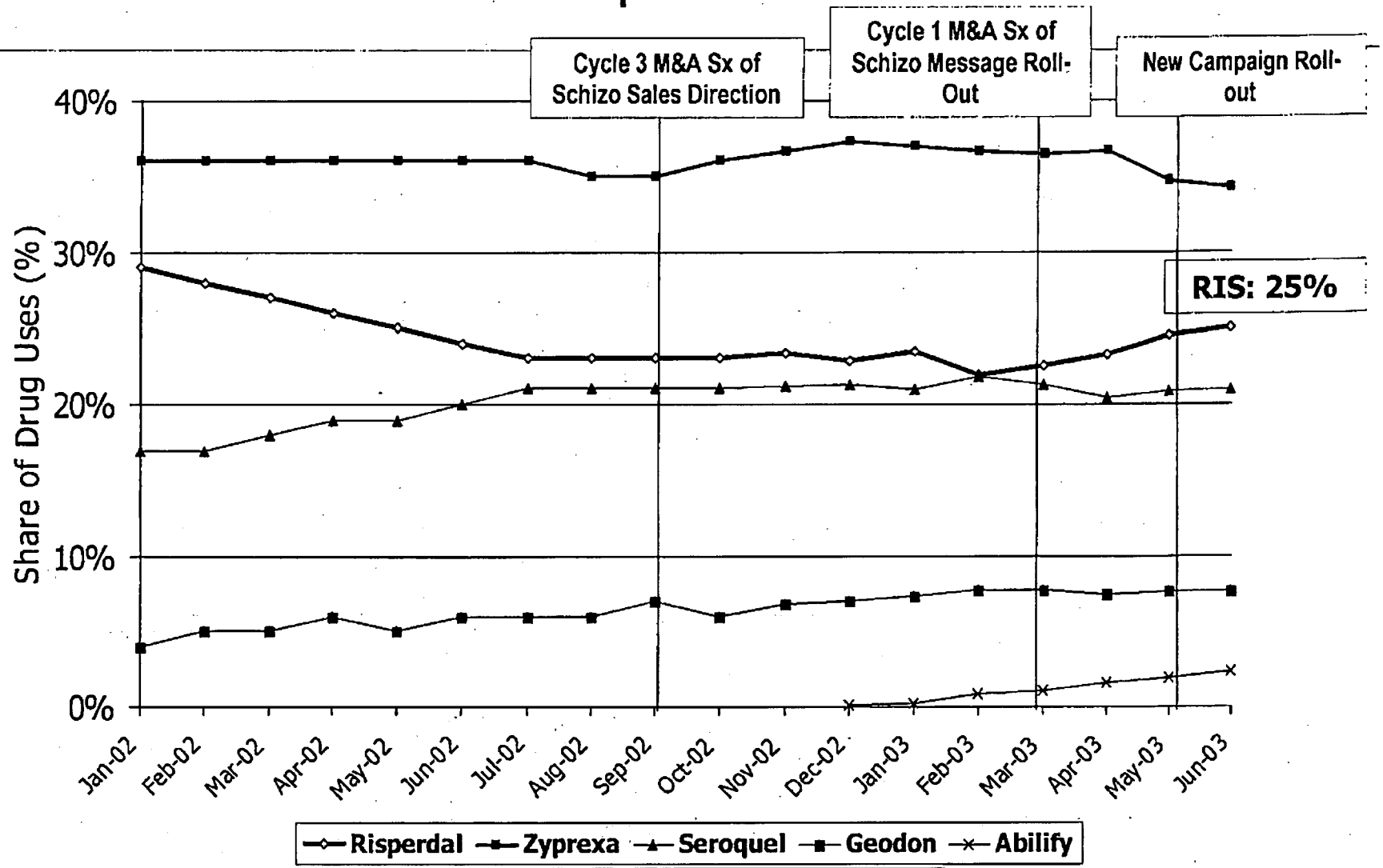
Source: IMS Health, NDTI

Key MR Findings

- **Safety/tolerabilty is critical selling feature**
- **Used for anxiety and sedative properties**
- **AZ is asking prescribers to push dose**

Subject to Legal/Regulatory Review

RISPERDAL is growing within mood & anxiety disorders over the past three months



Mood & Anxiety: Bipolar, Depression, Anxiety

Source: IMS Health, NDTI MAT

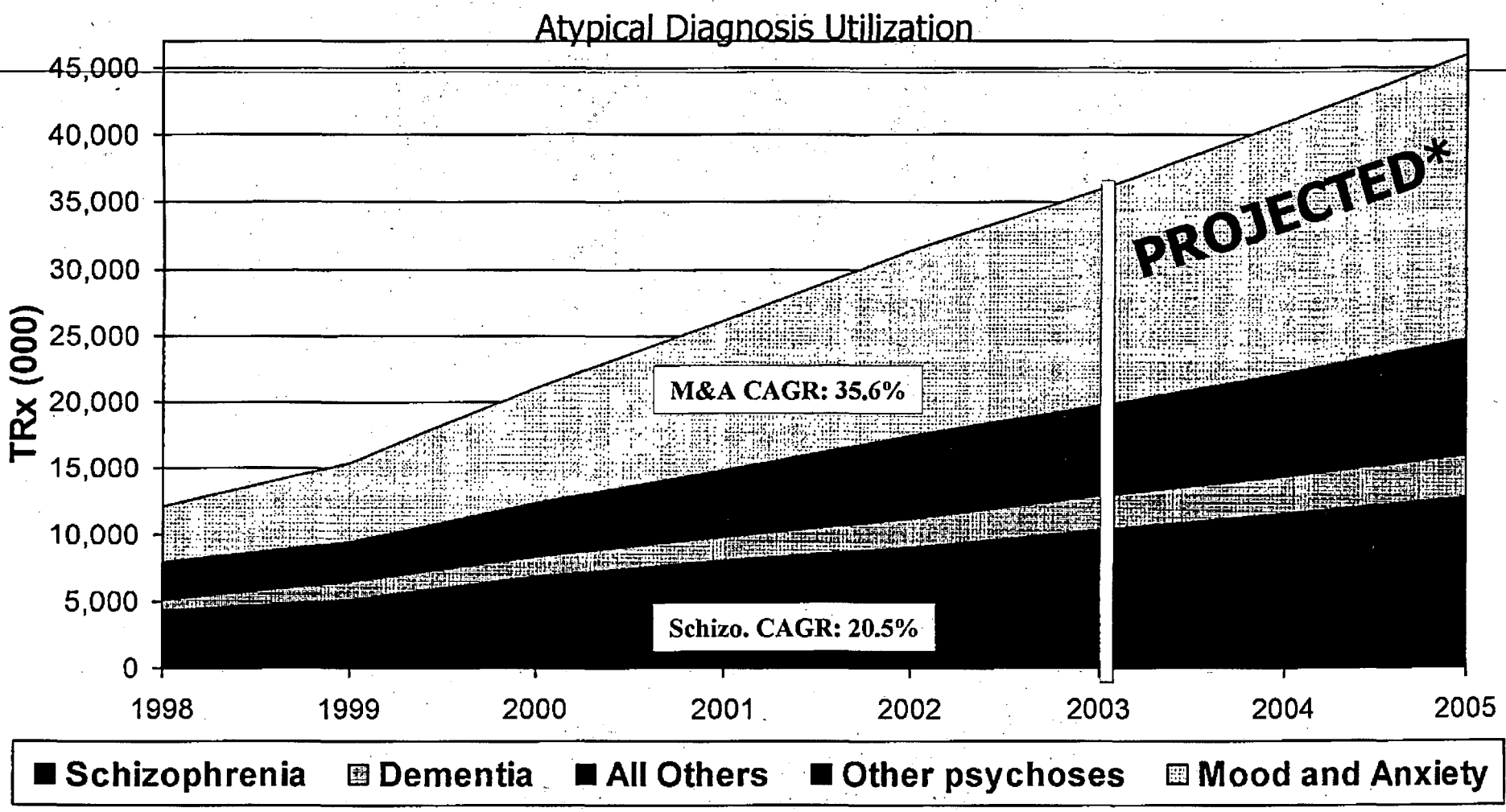
Introduction | Mkt overview | 2003 review | Internal assessment | 2004 strategies | Forecast/budget

Subject to Legal/Regulatory Review

R. 3047

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Mood & anxiety is a growing segment of the atypical market



* Projected data reflects straight linear regression, not accounting for change in market events.

Atypical Market: RIS, ZYP, SER, GEO, ABL, CLZ
Mood & Anxiety: Bipolar, Depression, Anxiety

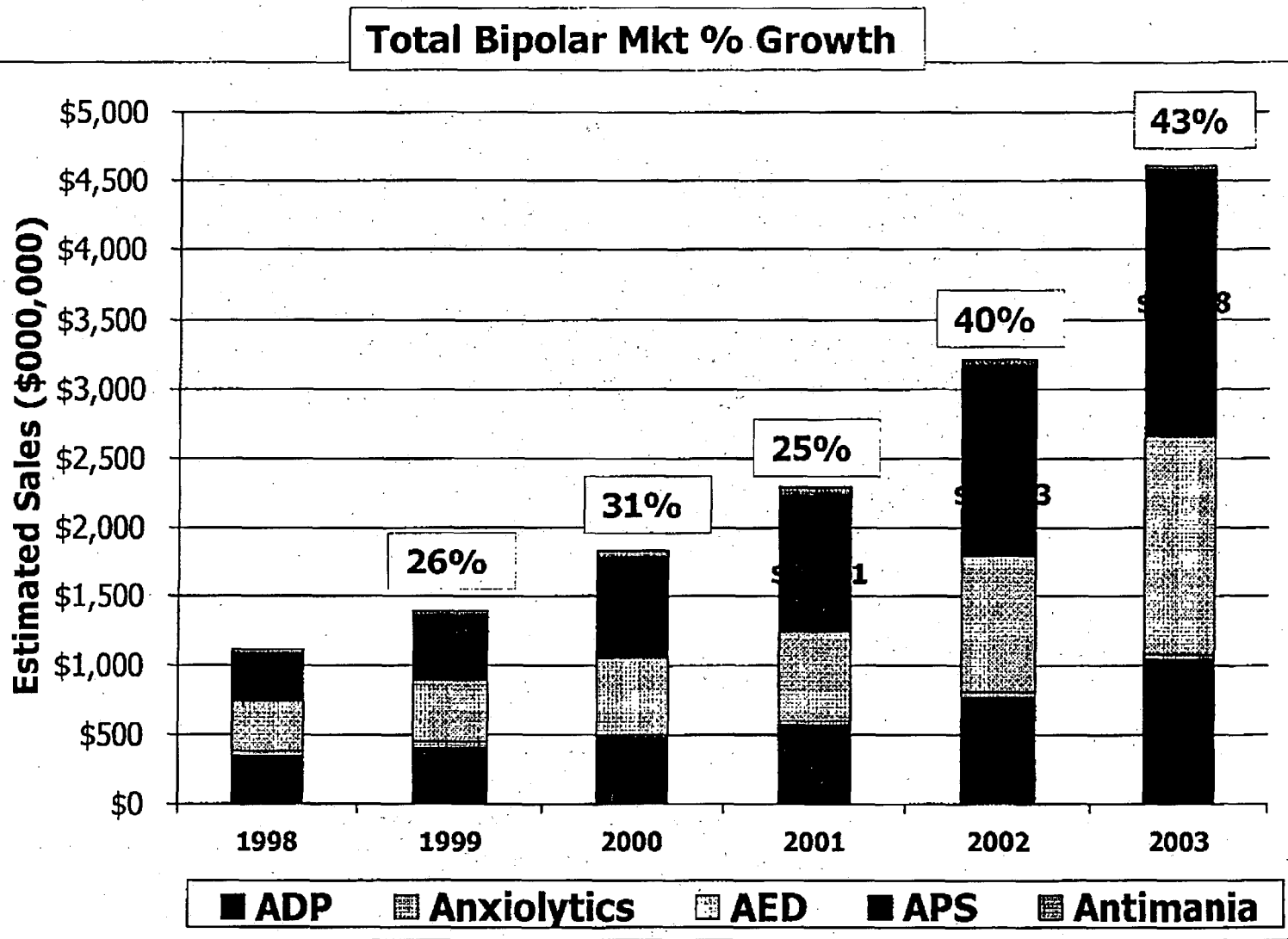
Source: IMS Health, NPA factored by NDTI

Subject to Legal/Regulatory Review

R. 3048

JJRE 00242422
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Bipolar represents a large opportunity



Source: IMS Health, NDTI applied to RPP

*YTD 6/03 reflects actual data with total sales at $2.0 billion and a 43% growth rate; the remaining 6 months are projected at the 43% growth rate

Subject to Legal/Regulatory Review

R. 3049

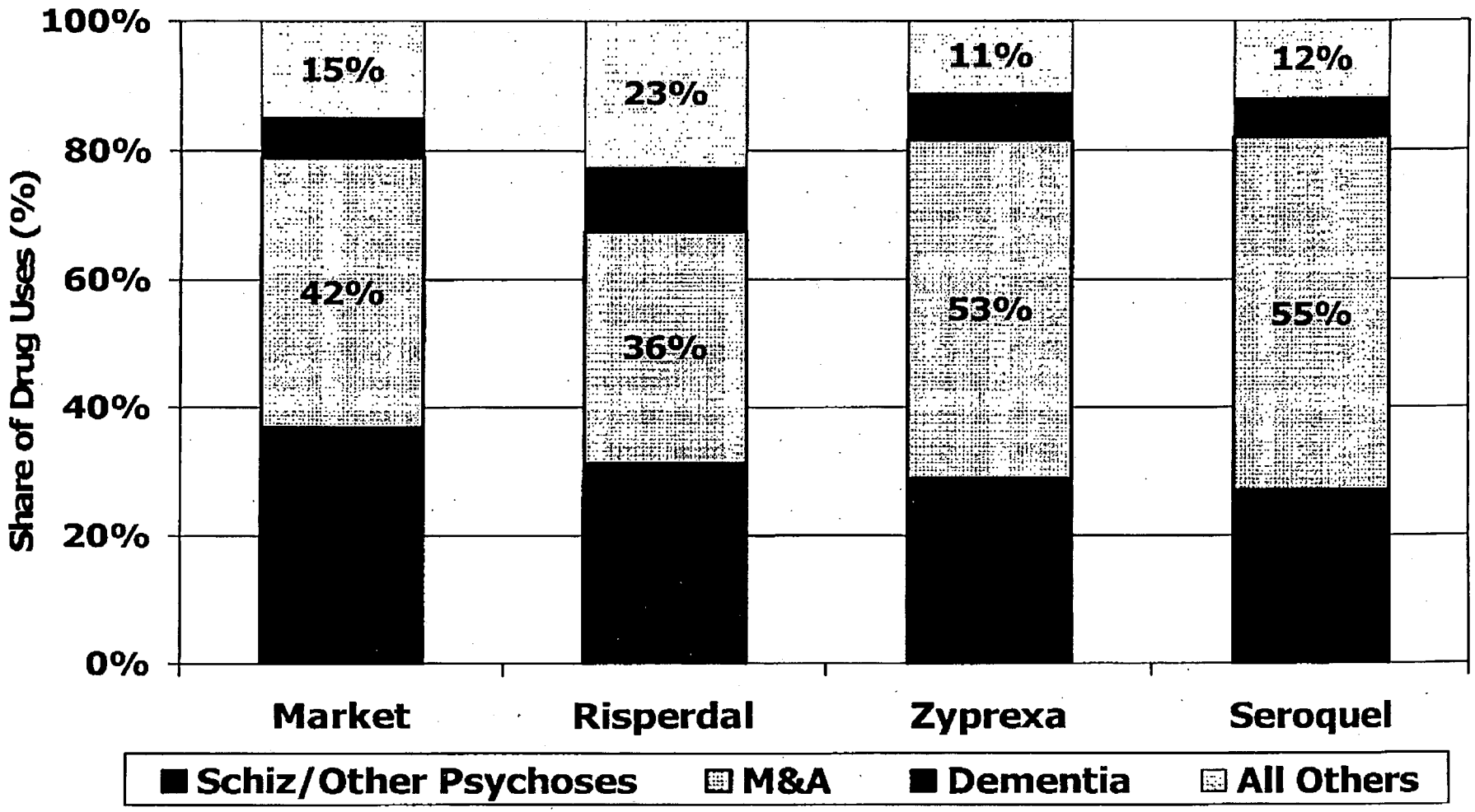
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Mood & anxiety disorders account for 36% of RIS usage, while they account for over half of ZYP and SER

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R. 3050

Distribution by Diagnosis



Source: IMS Health, NDTI MAT 4/03

Mood & Anxiety: Bipolar, Depression, Anxiety

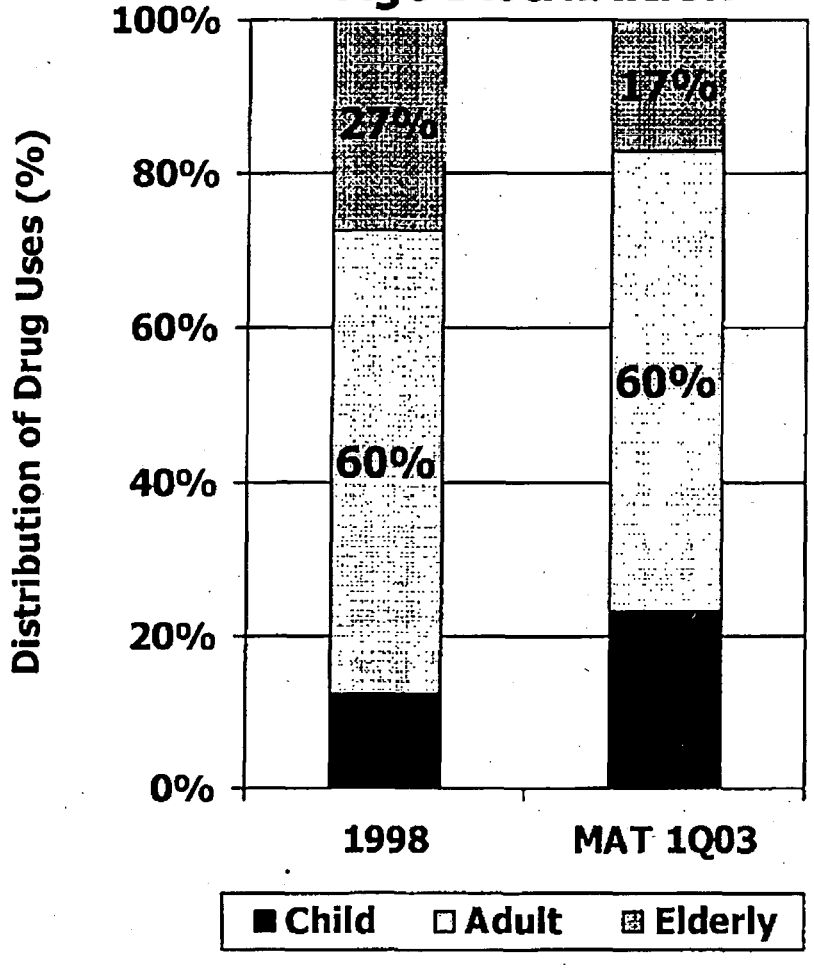
Subject to Legal/Regulatory Review

C&A segment is a significant percent of Risperdal usage

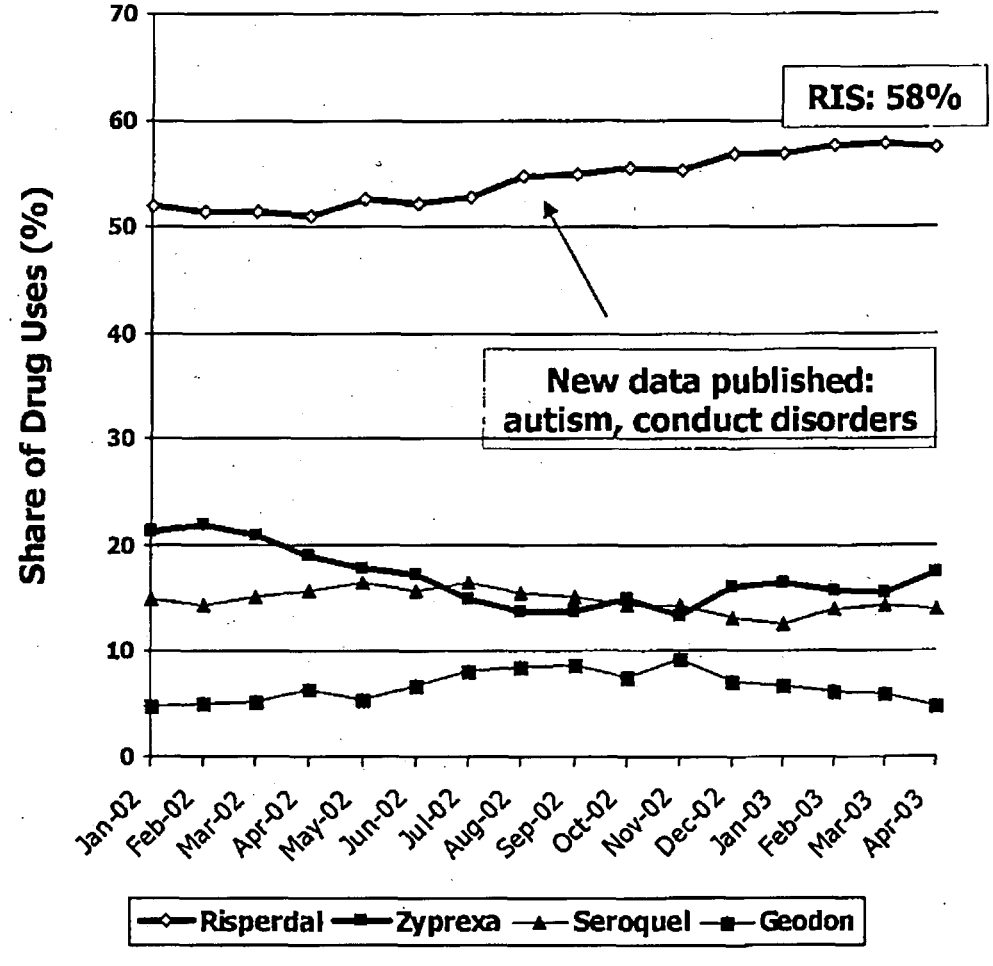
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R. 3051

RISPERDAL Age Distribution



Share of Drug Uses In C&A Patients



Child and adolescent defined as ages 0-17

Source: IMS Health, NDTI MAT

Subject to Legal/Regulatory Review

Competitive Analysis

Competitive APS Pipeline

	Launch	≤ 2002	2003	2004	2005
Risperdal	1994	• Oral Sol.	• M-Tab (Q3) • RIS Consta (Q4) • Acute Mania (Q4)	• Autism/Ped. (Q3) • TRD Data Published (Q2)	• Dementia?
Zyprexa	1996	• Acute Mania • Zydis	• Bipolar Maint. (Q4) • Symbyax Bipolar Depression (Q4)	• Acute IM Form for agitation in dem. (Q1)	
Seroquel	1997		• Acute Mania (Q4)		• Ped. Schiz.
Geodon	2000	• Acute IM Form	• Oral Sol. (Q4)		• Acute Mania
Abilify	2003			• Acute Mania (Q3)	• Dementia (?)

R. 3052

Subject to Legal/Regulatory Review

JJRE 00242426
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Symbyax Overview

- Lilly's fixed combination of fluoxetine (Prozac) and olanzapine (Zyprexa)
- Approval expected by end of 2003
- Indication: bipolar depression
- Initial market research findings:
  - Psych – low interest, activation and fixed dose are liabilities
  - PCP – more interested due to comfort with "shot gun" therapy
  - May have significant positive influence on bipolar market growth
  - Potential to increase PCP comfort level with APS initiation earlier in treatment

R. 3053

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Subject to Legal/Regulatory Review

Key Customer Segments

Key Dynamics/Unmet Needs

Prescribers

- **PCPs will play a more important role in APS market**
- **Increased focus on safety/liability issues facilitates increased use of Seroquel**
- Need for patient outcomes (functioning/remission) data

Payors

- **State/County (Medicaid) budget constraints leading to PDLs & supplemental rebates**
- Increased importance of managed care in light of M&A positioning/pending acute mania associated with bipolar indication
- Potential Medicaid scenarios

Influencers

- LTC PPs / SNFs - focus on safety/liability
- **Increasing prominence of medical/legal liability**
- Patients/caregivers more active in treatment decisions
- Increasing regulatory scrutiny

Subject to Legal/Regulatory Review

R. 3054

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2003 Review

- Move to mood & anxiety symptoms of schizophrenia
- Seroquel growth continues
- Abilify blunting
- CAE label change

R. 3055

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Subject to Legal/Regulatory Review

Move to Mood & Anxiety Symptoms of Schizophrenia Campaign

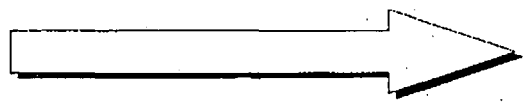
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R. 3056

RISPERDAL Today

The "typical" atypical
"Big gun"
Strength
Positive symptoms

Heritage in Schizophrenia



RISPERDAL Tomorrow

The "Approachable"
broad utility atypical
Behavioral, psychotic,
mood & anxiety
symptoms

Higher Functioning Patients

Subject to Legal/Regulatory Review

Move to Mood: Lessons Learned

- Campaign instilled renewed passion and focus among entire sales & marketing team
- Sets stage to differentiate from RISPERDAL CONSTA
- Physicians see Risperdal differently
- We are a fast follower vs. innovator

R. 3057

JJRE 00242431
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Subject to Legal/Regulatory Review

Seroquel Initiatives

- Market research
- Game theory application
- Flashcard I
- Sales training workshops
- Move to mood (in progress)
- Flashcard II
- Head to head study (initiated)
- Davis reprint
- Cycle 3 sales training resources

R. 3058

JJRE 00242432
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Subject to Legal/Regulatory Review

Seroquel Lessons Learned

- No silver bullet
  - Market research shows a patient functioning "story" is needed
  - Atypicals to-date have not competed directly against Seroquel
- Lilly and Janssen initiatives (diabetes, EPS) have fueled safety concerns of market
- Head to head results needed for promotion
  - Sales force confidence

R. 3059

JJRE 00242433
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Subject to Legal/Regulatory Review

Abilify Blunting

- SWAT team & game theory application to determine message
- Backgrounder/sales force trained prior to approval
- Abilify flashcard
- Target list of early adopters
- Medical Affairs (white paper, clinical reply)

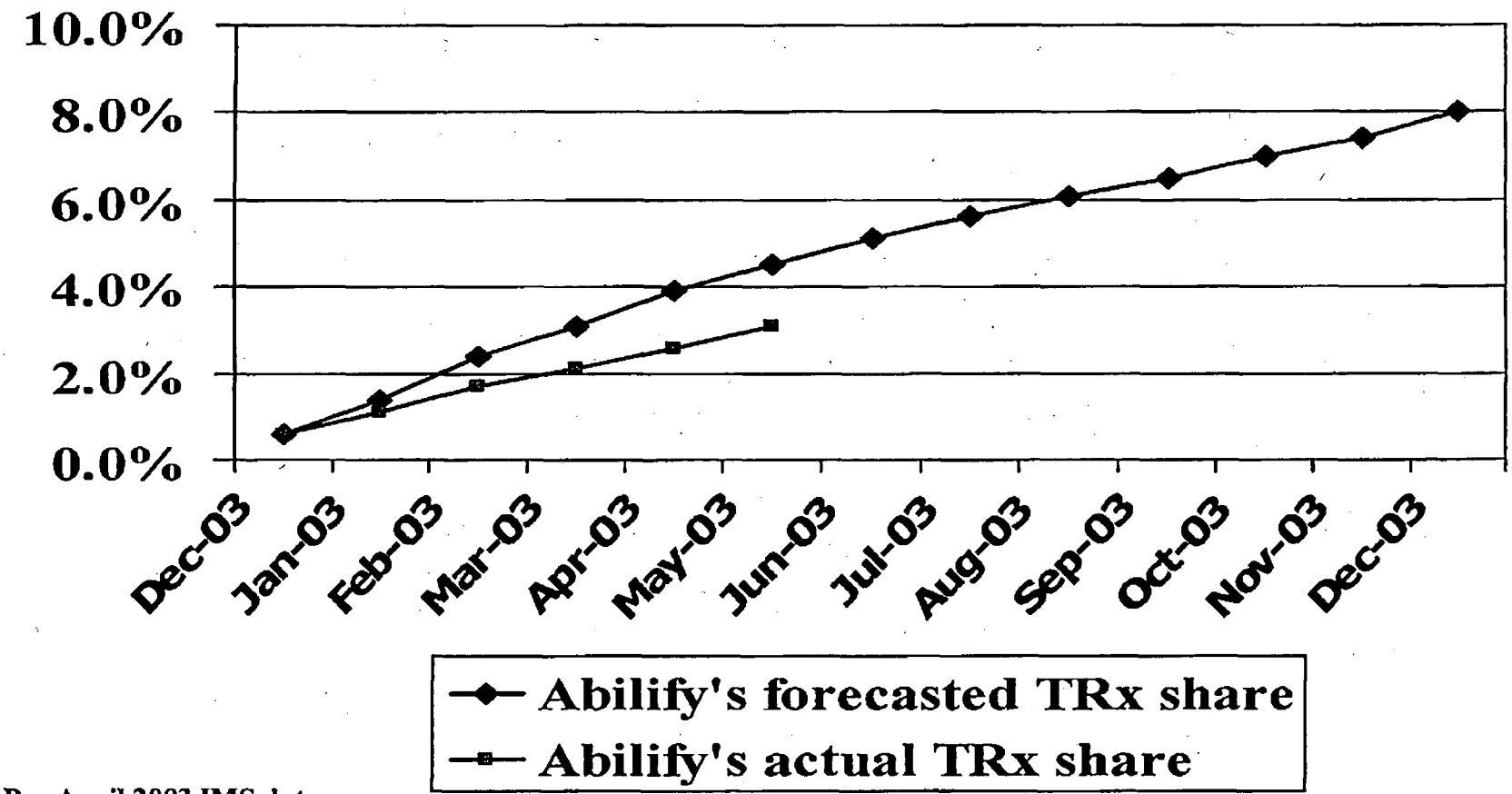
R. 3060

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Abilify Uptake

Since Abilify's launch, Risperdal has lost 0.7%NRx share points, Zyprexa has lost 1.8%NRx share points*



* - Per April 2003 IMS data

R. 3061

JJRE 00242435
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Abilify Blunting: Lessons Learned

- Address competitive threats as early as possible to preposition competition
- Giving early tools helped instill sales representative confidence

R. 3062

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CAE Labeling Change Overview

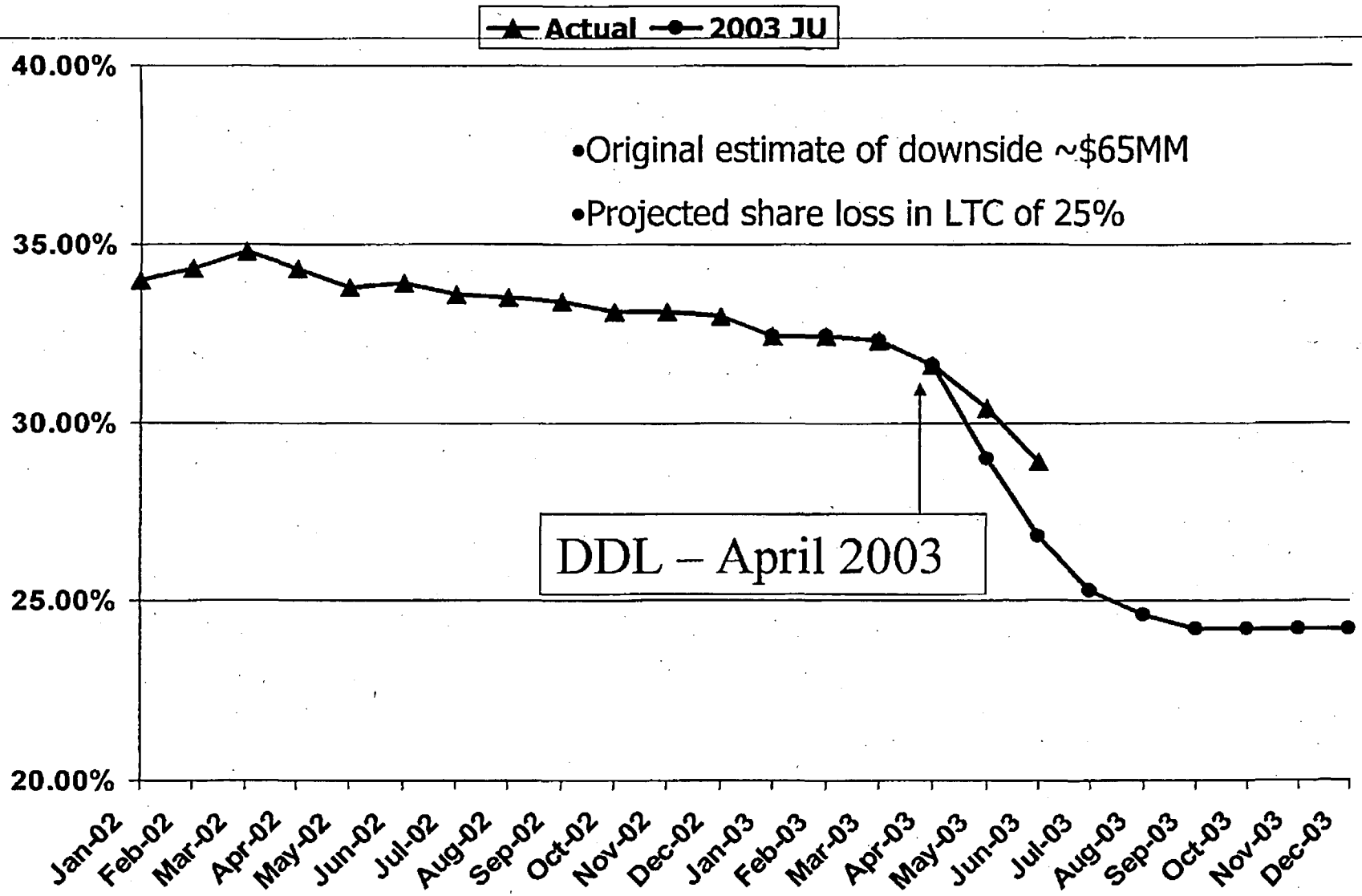
- Predicted major impact
- Developed early plan
- Organizational commitment and alignment
- Executed plan – proactively communicated
- Medical/legal questions of labeling continue

R. 3063

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Risperdal
CAE – LTC TRx Share



Introduction | Mkt overview | 2003 review | Internal assessment | 2004 strategies | Forecast/budget

Subject to Legal/Regulatory Review

R. 3064

JJRE 00242438

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CAE Lessons Learned

- Develop SWAT team early and enroll key partners to address significant issues
- Never underestimate the impact of a DDL
- Test how competitors will spin data/information
- Fear of medical/legal issues can outweigh evidence based medicine (prescribers and non-prescribers)
- Investor relations focus on category

R. 3065

JJRE 00242439
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Subject to Legal/Regulatory Review

JJRE 00242440
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R. 3066

Internal Assessment

Subject to Legal/Regulatory Review

JJRE 00242441
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R. 3067

Lessons Learned	Implications
• Mood & Anxiety disorders are the driver of the market growth	• **Optimize acute mania associated with bipoar indication** • Maximize mood & anxiety data dissemination post acute mania approval
• Perceived efficacy differences now eroding: market becoming increasingly differentiated on safety	• **Need to redefine the value of efficacy** • Accelerated Seroquel growth & opportunity for Abilify (perceived as safer products)
• Greater PCP component as market shifts to other disorders	• **Targeted focus in PCP (sales resources)**
• C&A market is unsatisfied and underserved	• Appropriate resource allocation and partnerships
• Changing Medicaid environment	• Eroding gross-to-net • Potentially improved access vs. competition

Subject to Legal/Regulatory Review

Internal Assessment

SWOT Analysis & Issue Identification

Strengths	Weaknesses
• ***Data***	• ***CAE labeling***
• Theorized unique mechanism of action	• ***Narrow labeled Indications***
• Strong pharmacoeconomic profile	***–Acute mania assoc w/bipolar***
• Broad utility across patient and disease spectrum only in schizophrenia	***–Behavioral Sx assoc w/autism***
• Most dosage formulations	• ***"Typical" atypical perception (movement disorders/prolactin)***
• Leadership in C&A / LTC	• Patent expiration interfering with lifecycle investment
	• Low product emphasis in primary care sales force
	• Lack of .25mg M-TAB dose
	• Unable to use low dose data in promotion
	• Fragmented institutional coverage
Opportunities	**Threats**
• ***Acute mania indication allows promotion within M&A***	• ***Safety becomes the main decision point for treatment***
• ***First mover advantage in unique indications (autism)***	• ***Increasing medical/legal concerns***
• **Differentiating on patient functionality**	• ***Combination AD/APS product redefines treatment paradigm***
• **Exploitation of Ris Consta halo**	• **Increasing budget constraints of payors (medicaid/managed care/LTC/state controls)**
• Safety halo of autism	• Competitive SOV increase in PCP
• APS prescribing by PCPs fastest growing customer segment	• Competitive responses from new sources
• Growing utilization of APS in niche markets (DOC,MRDD,Acute)	• Zyprexa IM allows Lilly to actively promote for dementia
• Formulary preferences	
• J&J CNS portfolio	

Key Issues

- **Multiple internal and external launches**
- **Market being defined around safety and tolerability**
- **Seroquel Growth**
- **Increasing level of payor influence**

R. 3068

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Results Required — *Strategic Objectives*

Quantitative

- Achieve $1.505 billion NTS in 2004
- 2004 annualized TRx share of 24.5%
- Launch acute mania by Q1, 2004
- Launch autism by Q3, 2004
- Publish positive TRD data by Q4, 2004

Qualitative

- Gain physician perception of broad utility of Risperdal to improve patient functioning (shift in perceptual maps)
- Increase awareness of theorized receptor binding profile at lower doses
- Leverage data/indications to help improve safety perceptions

R. 3069

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Strategy Formulation

R. 3070

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JJRE 00242445
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R. 3071

Multiple internal and external launches

Market being defined around safety and tolerability

Seroquel Growth

Increasing level of payor influence

3 – 5 Core Strategies

- **Launch acute mania associated with bipolar disorder to solidify M&A position**
- **Leverage autism to drive first mover advantage**
- **Redefine efficacy: differentiate RISPERDAL on functional outcomes**
- **Target Seroquel through competitive differentiation**
- **Leverage clinical, safety and economic message to drive business in targeted accounts**

Subject to Legal/Regulatory Review

Strategy Formation

CNS — OPS

Multiple internal and external launches	Market being defined around safety and tolerability	Seroquel Growth	Increasing level of payor Influence

Launch Acute Mania associated with bipolar to solidify M&A position

- Sales aid
- Bipolar Summit
- Single-sponsor Bipolar Digest Reanalysis and publication of Risperdal datasets
- Slide kits
- **Greater PDE/Comp emphasis on PCP**
- Virtual pt simulations
- Bipolar symphony
- Educational programs

Leverage autism to drive First mover advantage

- **Autism promotional campaign**
- **McNeil co-promotion**
- Launch public relations campaign
- Symposia
- FDAMA distribution of RUPP reprint
- National C&A Summit
- Educational programs

Target Seroquel through competitive differentiation

- Bipolar promotional campaign
- Pilot interactive sales aid on field tablet computers
- Direct Mail
- Low-dose premiums
- Sales training
- In-service video
- E-detailing pilot
- Review article on receptor binding
- Educational programs

Redefine efficacy: differentiate Risperdal on functional outcomes

- Sales aid
- Holistic patient education tool
- Audioconferences
- Sales training
- Reprints
- Consensus guidelines on treatment goals
- Mood Tracker disease management model
- Educational programs

Leverage clinical, safety, economic message to drive business in targeted accounts

- EBM and educational programs for dementia and MRDD
- Comprehensive multi-channel pull-through
- Programs to address polypharmacy and transitioning
- Appropriate use acute mania associated with bipolar education
- Focused account presentations
- MCO segmentation plan

Introduction → Mkt overview → 2003review → Internal assessment → 2004 strategies → Forecast/budget

R. 3072

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Brand Innovation

Strategy: Maximize Bipolar Launch	Total Budget:: $2.0 million

Program Title: The Bipolar Symphony

Description: Bipolar disorder has long been linked to many persons excelling in the arts including: Vincent Van Gogh, Edgar Allen Poe and Mozart. Externally these people were geniuses; internally, this disease handcuffed their ability to function within society.

The Bipolar Symphony is:

- A series of ten event marketing programs to be held across the country
- Combines art and medicine to describe the economic and emotional burden of bipolar disorder
- Presents newly available treatment options to help bipolar patients lead happier, more productive lives

Timing: 1Q 2004 – 3Q 2004

Measurement:

1.) 150 attendees per program
2.) 2% market share growth of attendees – using early view
3.) Greater than 4 out of 5 evaluation on content and delivery effectiveness

R. 3073

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Risperdal Autism Indication

Key Issue	Strategy	Strategic Initiative	Tactics
• Multiple launches – new formulations (RISPERDAL Consta) and indications (Acute Mania, Autism, Dementia)	• Optimize launch of Pediatric Autism Indication	• Ensure successful launch through focused and efficient execution and collaboration with other J&J operating companies	• Co-promotion with McNeil CNS sales force • Promotional program development and implementation • Public relations program • Medical education programs

R. 3074

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Janssen/McNeil Partnership
Autism Indication

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R. 3075

Psychiatry

- McNeil CNS calls on 11,000 psychiatrists (general and child) that are ADHD 20-90 – potential targets for RISPERDAL Autism
- Janssen CNS calls on many, but not all, of these targets
  - 40% 40x/year (APS 40-90)
  - 42% 20x/year (APS 20-30)
  - 18% not called on

Pediatrics

- Potential market development opportunity – currently being market researched
- Approximately 5000 pediatricians have written at least 12 APS Rxs in last 12 months
- Need to determine nature of McNeil coverage

Potential Investment

- $4.2 million

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Strategic Objective — Ensure successful launch of pediatric Autism indication

Core Strategy — Launch Autism to drive first mover advantage

Strategic Initiatives	Expected Results	Success Predictors	Key Milestones
Ensure successful launch through focused and efficient execution and collaboration with other J&J operating companies	Incremental sales of $42 MM in 2004	High awareness (>90%) of new indication among targeted customers	FDA approval of Autism indication 6/04

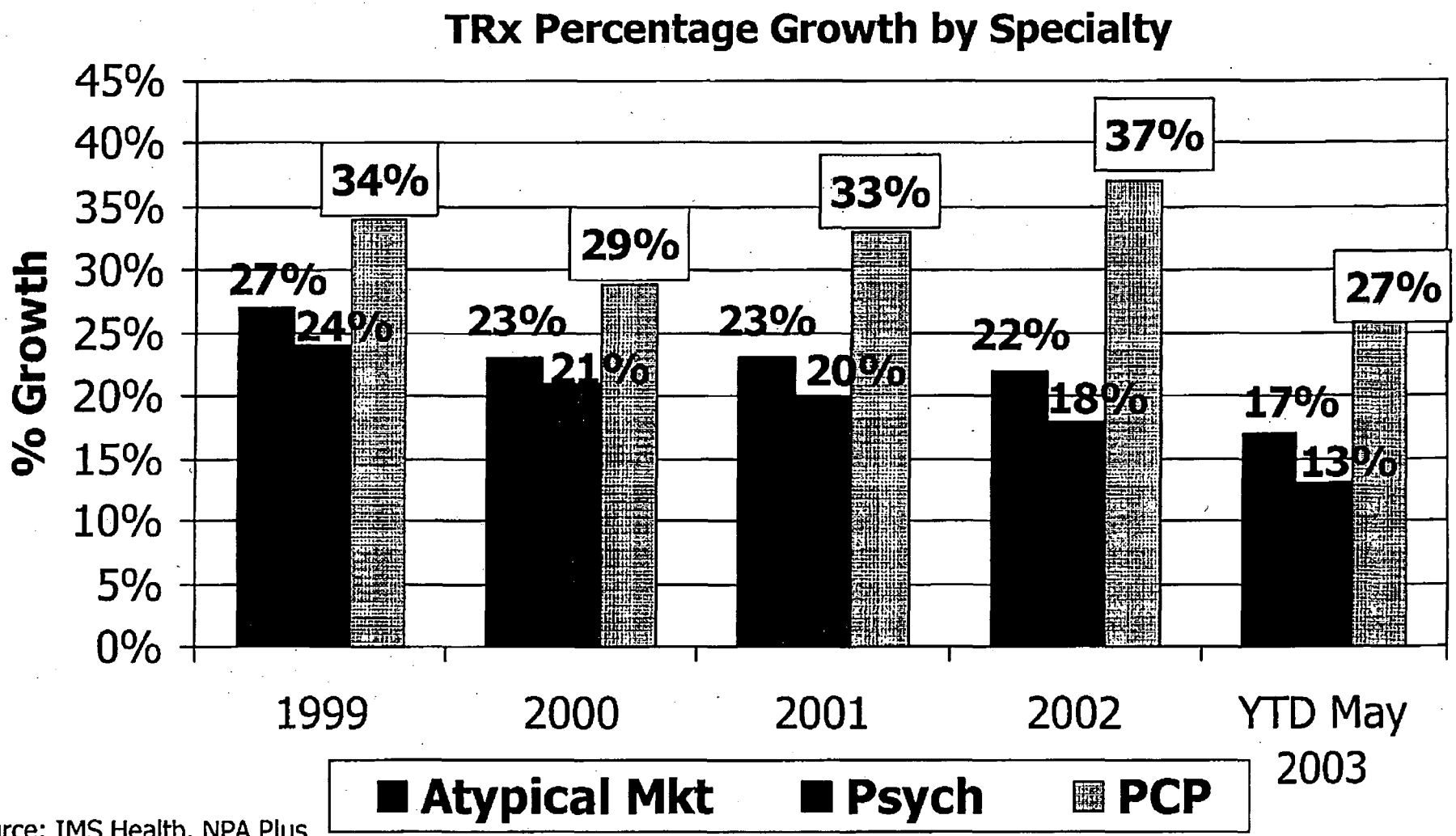
R. 3076

Base Case	2003	2004	2005	2006	2007	2008	TOTAL
Incremental Sales ($MM)	$7	$42	$132	$155	$174	$124	$634

NPV = $243

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PCP Opportunity



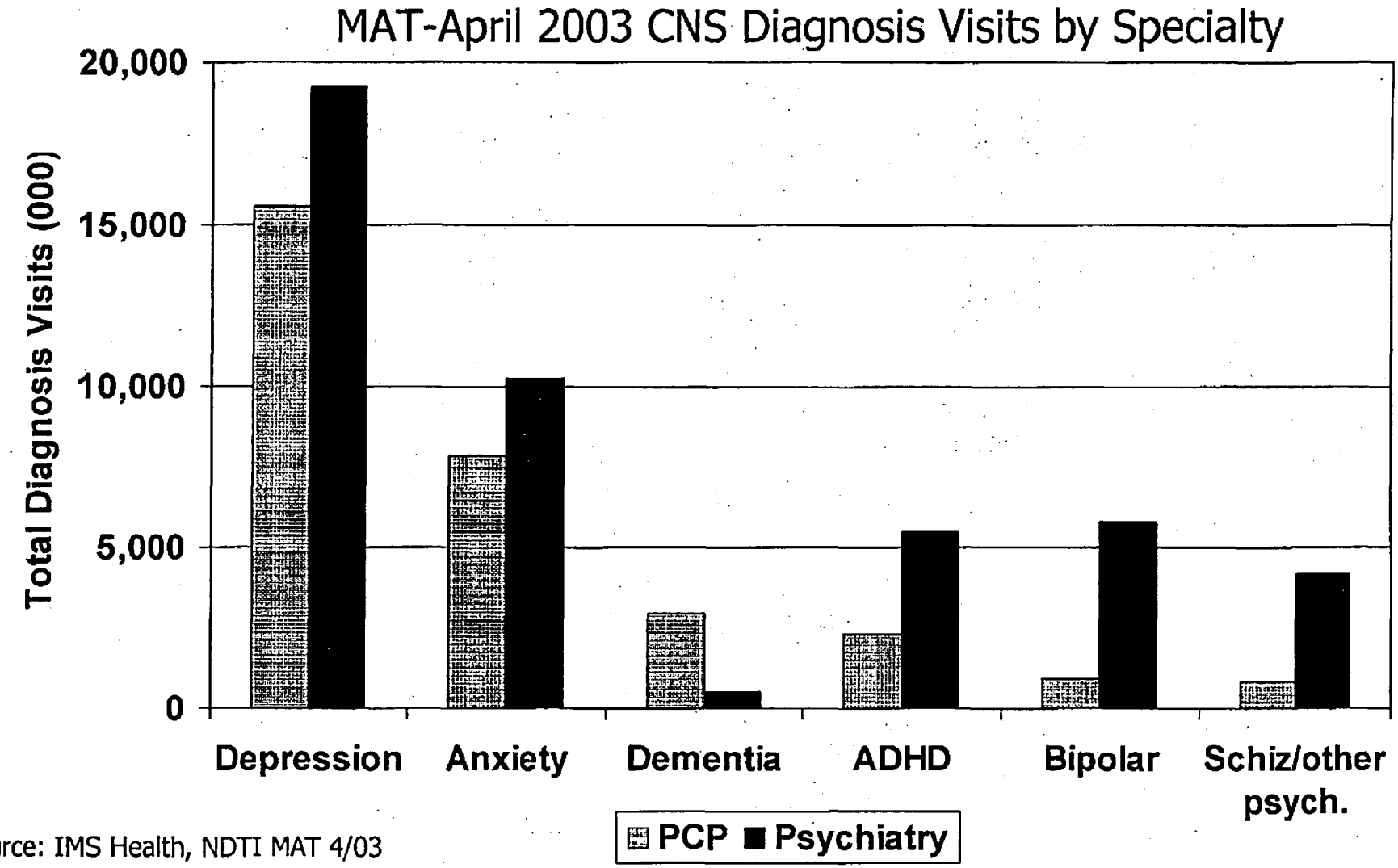
Source: IMS Health, NPA Plus Trend Break Jan 2002

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R. 3077

JJRE 00242451
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PCP Opportunity



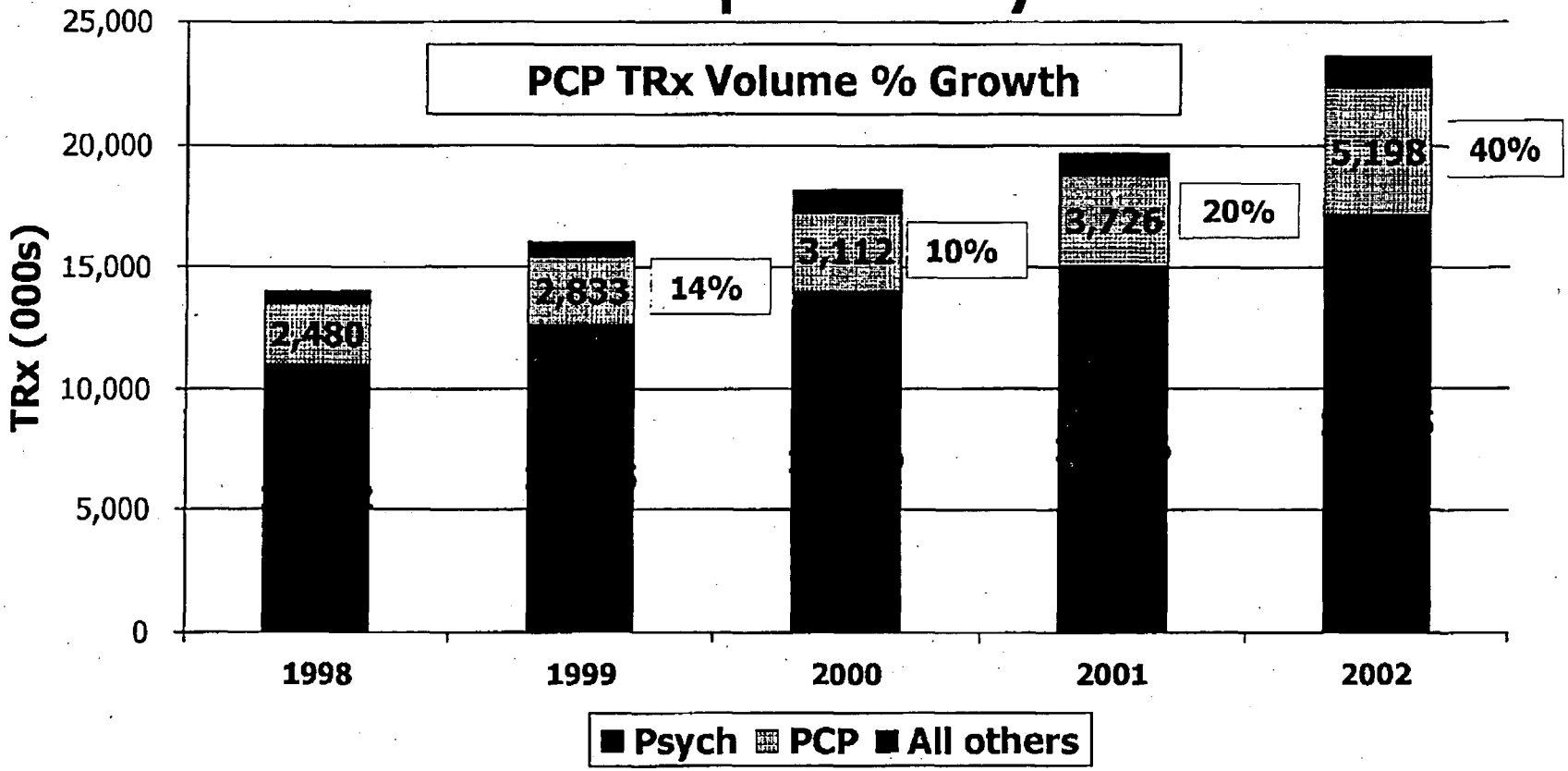
Source: IMS Health, NDTI MAT 4/03

Subject to Legal/Regulatory Review

R. 3078

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Bipolar Disorder Market Estimated TRx Volume By Specialty



Bipolar Market: USC 64300, 64100, 20200, 64600, 64400

Source: IMS Health, NDTI applied to NPA Plus

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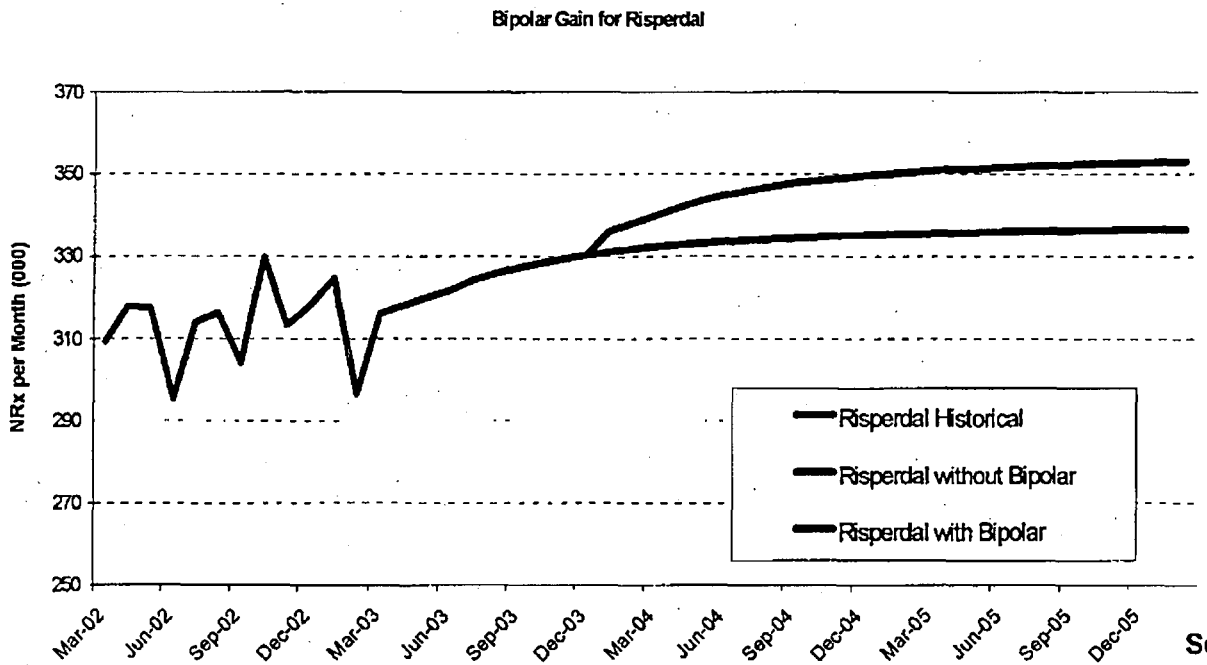
R. 3079

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RISPERDAL Model with Bipolar Gain

For RISPERDAL®, half of the gain observed for Zyprexa was modeled from Jan 2004.

- The net effect is that PC/Others are modeled to grow by 1.07% per month and Psychs by 0.15% per month MORE than they would have without the Bipolar indication.



Source: Market Rx

Subject to Legal/Regulatory Review

R. 3080

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Risperdal PCP Opportunity

- Increased number of primary presentations needed in PC
- Increased number of total PDEs needed in PC
- Increase weighting of Risperdal in PC incentive plan
- Focused resources to maximize opportunity

R. 3081

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Controls & Monitoring

R. 3082

Subject to Legal/Regulatory Review

Anticipated PME Spending (2003 vs. 2004)

Controls and Monitoring — Risperdal Brand

Description	2003 PME ($K)	Proposed 2004 PME ($K)	2004 PME (%)	Leveraged w/Ris Consta
Advertising	2,100	2,000	3.1%	
Agency Fees	2,500	2,300	3.6%	
Sales Aids/Promo Lit.	6,442	5,500	8.7%	
Regional PMEs	11,259	7,000	10.9%	4,300
Medical Education/Publications	19,919	16,100	25.2%	1,000
Speaker Programs	12,711	8,000	12.5%	2,000
Premiums	2,156	1,000	1.6%	1,200
Samples	3,914	4,000	6.3%	
National Exhibits	2,836	2,200	3.4%	1,000
Advisory Boards	13,912	7,000	11.1%	
Public Relations	950	1,400	2.2%	
Grants/Charitable Contributions	6,172	3,000	4.7%	500
Direct to Patient Initiatives	0	1,500	2.3%	
E Business	100	1,000	1.5%	
SCM	2,000	2,000	3.1%	1,000
Acute mania assoc. with Bipolar Launch Meeting	0	0	0%	1,000
Other	2,687	0	0%	
Total PME	**89,658**	**64,000**	**100%**	**12,000**
Less 2002 Pre Spend (finance to provide)				

R. 3083

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2004 PBP Forecasts

RISPERDAL® Net Sales Forecast ($MM)

Downside $1,433.0	Base Case $1,505.0	Upside $1,575.0
Assumptions	**Assumptions**	**Assumptions**
• Market growth = 10.0% • Annual Market Share = 23.6% • Exit Market Share = 21.7% • GTN = 68.25% • No Change to wording of CAE label • Seroquel Acute Mania Launch has greater than forecasted impact	• Market Growth = 11.0% • Annual Market Share = 24.5% • Exit Market Share = 23.5% • GTN = 68.25% (Increased Medicaid Utilization) • PCP 3 x 500 sales force expansion complete • Price Increases of 3.9% in July 2004 • Risperdal TRD Publication 2Q 04 • Seroquel Acute Mania Launch 1Q 04 • Symbyax Launch Q1 04 • Zyprexa Bipolar Maintenance Launch 1Q 04 • Geodon Acute Mania Launch 4Q 04 • AZ sales force focus shift from Seroquel to new product launches • Change in wording of CAE Label	• Market growth = 12.5% • Annual Market Share = 25.2% • Exit Market Share = 24.9% • GTN = 68.25% • Acute Mania Launch 1Q 04 • Increase in C&A share due to Rupp publication (3Q 03) and Autism Indication (3Q 04) • Increased Zyprexa diabetes awareness/potential label change • Greater impact of Change in wording of CAE Label

R. 3084

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2004 Risperdal
Critical Success Factors

- Flawless execution of Bipolar launch to leverage entry into M&A disorders
  - Capitalize on PCP Opportunities
- Stop Seroquel Growth
- Successfully Launch Autism
- Stabilize LTC Share

R. 3085

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BACK-UP

JJRE 00242460
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 1 2000

NDA 20-272
NDA 20-588

Janssen Research Foundation
Attention: Victoria Wagner-Weber
1125 Trenton-Harbourton Road
POB 200
Titusville, NJ 08560

Exhibit
Grogg – 21
03.24.09

Dear Ms. Wagner-Weber:

Please refer to your new drug applications (NDA) for Risperdal (risperidone).

We have recently examined postmarketing surveillance data from the FDA Adverse Event Reporting System for Risperdal as well as for other atypical antipsychotics with respect to spontaneous reports of new onset diabetes mellitus, non-ketotic hyperosmolar coma, and diabetic ketoacidosis. This examination has revealed a number of these adverse experiences in association with risperidone treatment.

To assist us in fully evaluating the possibility that atypical antipsychotics may produce disturbances in glucose metabolism, we are requesting that sponsors of these agents provide us with more extensive safety information. Accordingly, we ask that you submit the following for our consideration:

1) A comprehensive review of all preclinical data pertaining to hyperglycemia. We are particularly interested in any evidence of islet cell pathology observed in animal studies.
2) A thorough assessment of all Phase 1, 2, and 3 studies in the risperidone NDA and any subsequent supplements for evidence of new-onset diabetes mellitus, hyperosmolar coma, diabetic ketoacidosis, weight gain, and hyperglycemia. This should include the frequency of deaths, serious adverse events, total adverse events, and dropouts due to events related to abnormalities of glucose metabolism listed above, data regarding mean changes from baseline in plasma glucose level, and the percentage of patients meeting criteria for a markedly abnormal plasma glucose concentration from an appropriate pool of placebo-controlled Phase 2/3 studies. Any deaths, dropouts, or serious adverse events should have an accompanying detailed narrative summary.
3) A review of spontaneous postmarketing reports for new-onset diabetes mellitus, hyperosmolar coma, diabetic ketoacidosis, weight gain, and hyperglycemia.
4) An estimate of patient exposure.
5) Copies of any correspondence with foreign regulatory agencies related to these events in association with risperidone.

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Plaintiff Ex. 164

R. 3087

In addition, we ask that you investigate the possibility of collaborating with organizations having large pools of treated patients (e.g., HMO or VA databases) that might be examined for evidence of hyperglycemia or new-onset diabetes mellitus associated with risperidone.

Please compile this information and submit it to us within 3 months.

If you have any questions, call Steve Hardeman, R.Ph., Regulatory Project Manager, at (301) 594-5533.

Sincerely,

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

JJRP 00379874
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Exhibit
Grogg – 22
03.24.09

From: Dodd, Sheri [JANUS]
Sent: Thursday, July 20, 2000 4:15 PM
To: Mahmoud, Ramy [JANUS]; Farup, Christina [JANUS]; Markowitz, Jeff [JANUS Non J&J]; Grogg, Amy [JANUS]
Cc: Durkin, Mike [JANUS]
Subject: RE: Atypicals and Diabetes

Sensitivity: Confidential

ERI is running the analysis now and we won't have the report until 7/20 but in time for the inclusion in the FDA response. It is looking at crude incidence of diabetes among the use of atypicals (each atypical analyzed individually - not mixed groups), conventionals, and no exposure to antipsycotics. I am hopefully that the analysis will have 2 crude incidence runs: one for exposure to antipsychotics (no dx requirement) and the other with exposure plus ICD-9 schizophrenia dx. Time is a factor is trying to get both sets of crude incidence. Priority is the exposure/no dx.

Sheri

-----Original Message-----
From: Mahmoud, Ramy [JANUS]
Sent: Thursday, July 20, 2000 10:08 AM
To: Farup, Christina [JANUS]; Markowitz, Jeff [JANUS Non J&J]; Dodd, Sheri [JANUS]; Grogg, Amy [JANUS]
Cc: Durkin, Mike [JANUS]
Subject: RE: Atypicals and Diabetes
Sensitivity: Confidential

What do we have that is on ERI or MediCal or on the pair of states' BC/BS plans that we got with Frank (GPRD may be of future value, but in the present....)? Very close to a report I can look at for potential inclusion in our FDA response?
-Ramy

-----Original Message-----
From: Farup, Christina [JANUS]
Sent: Tuesday, July 18, 2000 9:16 AM
To: Markowitz, Jeff [JANUS Non J&J]; Dodd, Sheri [JANUS]; Grogg, Amy [JANUS]
Cc: Mahmoud, Ramy [JANUS]; Durkin, Mike [JANUS]
Subject: RE: Atypicals and Diabetes
Sensitivity: Confidential

Sheri

You raise some very good points--clearly lumping the atypicals in view of Jeff's findings is not appropriate. As far as who should take the lead on the analysis of the GPRD dataset--it should probably be Dan Fife. He is a drug safety epidemiologist--Koen, Andrew, and Guy are not. Amy, I would recommend having a discussion with Dan as he was on the original e-mail distribution and I imagine is quite involved with this task force.

Christina

-----Original Message-----
From: Markowitz, Jeff [JANUS Non J&J]
Sent: Tuesday, July 18, 2000 8:52 AM
To: Dodd, Sheri [JANUS]; Grogg, Amy [JANUS]
Cc: Farup, Christina [JANUS]; Mahmoud, Ramy [JANUS]; Durkin, Mike [JANUS]
Subject: RE: Atypicals and Diabetes
Sensitivity: Confidential

Sherri:
There's a very clear pattern of results within the re-analyzed HECON data of a protective effect of Risperdal relative to the other anti-psychotics. In pairwise comparisons, the odds ratios are typically in the 2.0 range indicating a

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Plaintiff Ex. 165
R. 3089

two-fold increased risk of diabetes in patients treated with anti-psychotics other than Risperidal. Moreover, the risk of diabetes among Risperidal subjects is about the same as our untreated sample. These analyses control for pre-existing diabetes within a restricted range of time -- usually 4 months. We're still running some final multivariate analyses, and the results are continuing to hold up under closer scrutiny. A manuscript could definitely be written based on this study; other avenues could also be explored to get this out as quickly as possible.

Regards, Jeff

-----Original Message-----
From: Dodd, Sheri [JANUS]
Sent: Monday, July 17, 2000 6:58 PM
To: Grogg, Amy [JANUS]
Cc: Farup, Christina [JANUS]; Mahmoud, Ramy [JANUS]; Durkin, Mike [JANUS]; Markowitz, Jeff [JANUS Non J&J]
Subject: RE: Atypicals and Diabetes
Importance: High
Sensitivity: Confidential

Amy,
I really think that Janssen has a critical opportunity to do some counter-analysis work in light of the study mentioned in the previous emails. I understand your point about getting our ducks together but I think that with such a positive study (see the numbers below) a more proactive approach would be for us to rerun this analysis in the GPRD with the appropriate break out of the atypical (OLZ+CLOZ vs all other atypicals). Again, this study is highly positive and is the only positive control study that I am aware of and it will stick in inquiring minds. With the risk of a class effect, I think that further work on this study design, in the same GPRD database, with the appropriate atypical breakout is do-able and quite necessary as an appropriate measure in anticipation of this upcoming publication.

I would recommend sending this info on to Koen and Guy in Beerse. Guy has a lot of expertise in the GPRD database and could provide much support from an analysis standpoint. You might also want to inform Andrew Eggleston as well as we know he is quite active in the diabetes work with the atypicals.

I know I looked at the GPRD database as a potential to run the study like we are running at ERI and their were few OLZ patients. Although we don't know the mix of OLZ vs other atypicals in their Atypical group, it might still be worth the effort.

I have ran the following rough numbers to see the significance level and as you can see, it is highly significant.

	Cases	Controls	Totals
Atypical	8	???	???
Not Atypical	416	???	???
Total	424	1522	1946

Impossible to interpret without more data, however for the OR to be higher for atypicals, the ratio for Controls (atypical/not typical) must be less than 8/416. So there are limited range of permutations: e.g.

29 : 1493 (equality) or = 1
23 : 1499 or = 1.25
17: 1505 or = 1.7
12: 1511 or = 2.42
8 :1515 or = 3.64 (p=0.007 uncorrected, 0.017 continuity adjusted)
7 : 1516 or = 4.16 * this is close to overall (3 to 6)
6 : 1517 or = 4.86 (p=0.001, p=0.004)
5 : 1518 or = 5.84 (p=0.0005, p=0.0016)
2 : 1521 or = 14.625

*

	Cases	Controls	Totals
Atypical	8	7	15
Not Atypical	416	1516	1932
Total	424	1522	(1947)

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R. 3090

1946
p=0.003 (uncorrected)
p=0.008 (corrected)

Amy, I know you were only the forwarder of the FYI but given the importance of differentiating RIS from the other atypical and our charge to retrospectively examine the risk of diabetes in populations I think some thought should be given to this potential analysis.

Let me know if you have any questions. Looking forward to hearing input.

Sheri

p.s. I ran the Stats on a program called StatSac.

-----Original Message-----
From: Grogg, Amy [JANUS]
Sent: Monday, July 17, 2000 11:45 AM
To: Dodd, Sheri [JANUS]; Markowitz, Jeff [JANUS Non J&J]
Subject: RE: Atypicals and Diabetes
Sensitivity: Confidential

This was just an FYI for what else others are doing out there. I think the best we can do is to get our "ducks in a row" with our analyses and get them published (if positive) as posters as soon as possible.

Amy

-----Original Message-----
From: Dodd, Sheri [JANUS]
Sent: Monday, July 17, 2000 1:36 PM
To: Markowitz, Jeff [JANUS Non J&J]; Grogg, Amy [JANUS]
Subject: RE: Atypicals and Diabetes
Sensitivity: Confidential

Fully agree Jeff. With the other case reports out there that are differentiating between the atypicals, this research in not really in line with current thinking. To lump is very misleading and with the small n=8 is there anything to be said that is meaningful - even if they were all OLZ?
This is dangerous information that leans towards a class effect for the atypical class. Anything we can do?

-----Original Message-----
From: Markowitz, Jeff [JANUS Non J&J]
Sent: Monday, July 17, 2000 11:32 AM
To: Dodd, Sheri [JANUS]
Subject: RE: Atypicals and Diabetes
Sensitivity: Confidential

Sherri:

Good point. Here's my response to Amy's note:
Amy:

Several comments on the summary of the study you forwarded --- I don't think that it's appropriate to lump together all atypicals in an analysis. For example, our preliminary results indicate that Olanzapine users have a higher risk of diabetes relative to Risperdal. The information summarizing the study results below are sketchy. However, there are far too few diabetes cases on atypicals in the analysis (n=8) to say anything that's meaningful with respect to the different atypicals. I wouldn't want to combine the atypicals into a single grouping variable if the rates differed by treatment. Suppose that all of the diabetes cases are on Olanzapine; to then conclude that atypicals have higher rates would be very misleading.

Thanks, Jeff

-----Original Message----

JJRE 02282697
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R. 3091

From: Dodd, Sheri [JANUS]
Sent: Monday, July 17, 2000 1:28 PM
To: Grogg, Amy [JANUS]; Markowitz, Jeff [JANUS Non J&J]
Subject: RE: Atypicals and Diabetes
Sensitivity: Confidential

Amy,
A few questions/thoughts
1) N=8 atypical users and they show a relative risk vs controls? What were the controls? Unexposed?
2) If the Diabetes is thought to be reversible after ceasing atypical medication, then how could the cases be classified as more severe vs less severe?

Sheri
-----Original Message-----
From: Grogg, Amy [JANUS]
Sent: Monday, July 17, 2000 8:12 AM
To: Dodd, Sheri [JANUS]; Markowitz, Jeff [JANUS Non J&J]
Subject: FW: Atypicals and Diabetes
Sensitivity: Confidential

Sheri and Jeff,

Please see below.

Amy

-----Original Message-----
From: Mahmoud, Ramy [JANUS]
Sent: Monday, July 17, 2000 8:28 AM
To: Grogg, Amy [JANUS]; Sadik, Kay [JANUS]; Farup, Christina [JANUS]
Subject: FW: Atypicals and Diabetes
Sensitivity: Confidential

FYI,
-Ramy

-----Original Message-----
From: Van Tittelboom, Tony [JanBe]
Sent: Monday, July 17, 2000 3:33 AM
To: De Smedt, Goedele [JanBe]; Bruynseels, Jan [JanBe]; Caers, Ivo [JanBe]; Griffiths, Jane [JACGB]; McIntyre, Todd [JANUS]; Mahmoud, Ramy [JANUS]; Hantson, Ludwig [JANUS]
Subject: FW: Atypicals and Diabetes
Sensitivity: Confidential

FYI

Tony

tel ext. : 5037
fax ext.: 3331

-----Original Message-----
From: De Locht, Patrick [JanBe]
Sent: Monday, 17 July 2000 8:56
To: Van Tittelboom, Tony [JanBe]
Subject: FW: Atypicals and Diabetes
Sensitivity: Confidential

FYI,
Mvg,
Patrick

JJRE 02282698
Confidential/Produced in Litigation Pursuant to Protective Order
R. 3092

-----Original Message-----
From: Lewi, Tine [JanBe]
Sent: Friday, 14 July 2000 19:25
To: Fernandez, Antonio [JJC]; Mcguinness, Pam [JanBe Extern]
Cc: Van Ginckel, Leo [JanBe]; Richardson, Craig [JanBe]; Fife, Daniel [JANUS]; Atsma, Willem Jan [JanBe]; De Locht, Patrick [JanBe]
Subject: Atypicals and Diabetes
Sensitivity: Confidential

Dear,

Leo asked me to forward the following message to you:

Catherine Vasilakis (researcher at Boston Collaborative Drug Surveillance Program) presented a case study on anti-psychotics and Diabetes. The details below are based on notes taken during her presentation at a workshop on post-marketing surveillance. A publication is to appear soon and I'll forward it to you once published.

Conclusion of the study:
Use of atypicals is associated with a higher relative risk of Diabetes. If Diabetes occured, a trend towards more severe cases of Diabetes was identified with the atypical users (more insulin dependent cases).

Due to the strict inclusion and exclusion criteria, a product comparison among atypicals was not yet feasible.

Summary of the study:
* based on GPRD data
* Inclusion criteria: incidence of Diabetes during time period 1/94 to 12/98 after anti-psychotic usage. Age 18-64. Information recorded during one year
* Exposure to antipsychotics stratified in three groups:
- Current exposure: up to 6 months prior to Diabetes
- recent exposure: between 6 months and 1 year prior to Diabetes
- unexposed

* Results:
- Cases: 424 cases were identified, 1522 selected controls. Among the 424 cases were 8 users of atypicals
- Comorbidities: Hypertension & Myocardial Infarction / Angina Pectoris were more prevalent in cases (27 versus 12 & 12 versus 5)

* Incidence of Diabetes:
Atypicals
Users, who had 1-4 prescriptions (3 cases), had a relative risk of Diabetes of 6.0 compared to controls. Users with more than 10 Rxs (4 cases) had a relative riks of 3.1.
Typicals
The relative risk increased slightly with longer drug exposure: 1-4 RXs - 1.2; 5 to 9 RXs - 1.5; more than 10 RXs - 1.6

Remark: small number of cases. But, as promised, I'll send you the article with more details as soon as published.

Kind regards,

Tine

JJRE 02282699
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R. 3093

Exhibit
Grogg – 23
03.24.09

From: Grogg, Amy [JANUS]
Sent: Tuesday, August 01, 2000 7:23 AM
To: Vandenbossche, Joris [JanBe]; Rosenberg, Joanne [JANUS]
Cc: Caers, Ivo [JanBe]; Derivan, Albert [JANUS]; Vergis, Janet [JANUS]; Hantson, Ludwig [JANUS]; Farup, Christina [JANUS]; Mahmoud, Ramy [JANUS]; Dodd, Sheri [JANUS]; Markowitz, Jeff [JANUS Non J&J]; Fife, Daniel [JANUS]
Subject: Antipsychotics and Diabetes - Reports and Project Status

Importance: High



Risperdal and Diabetes 7-31-00...

Dear all,

The following reports are attached here and in subsequent e-mails (due to size limitations):

* Risperdal and diabetes project status report from Janssen U.S. Medical Affairs Outcomes Research - INTERNAL USE ONLY
* Full report and tables from HECON analysis
* ERI interim report and tables - DO NOT INCLUDE IN RESPONSE TO FDA

The most complete picture within the HECON analysis is seen in tables 11-13, the logistic regression results. Risperdal is the only antipsychotic which does not have a significant effect on the incidence of diabetes. This analysis correctly includes confounding variables which can affect the differences between agents. As this is a claims database analysis, limitations include:
- retrospective comparisons available only
- clinical endpoints, such as weight gain and other symptoms, are unavailable
- timeframe available 1/1/96 through 12/31/97
- previous use of drugs which may have an affect on diabetes (either antipsychotics or others)
However, the limitations are discussed in the report and do not significantly detract from the results. Most limitations would be true for all groups and therefore not change the differences seen between agents. The report gives a fairly accurate picture of antipsychotics and their diabetic effects in an employed population.

As the ERI report is only a crude analysis of new-onset diabetes and does not control for confounding variables which might affect the results, I would not suggest inclusion in the submission to the FDA. These potential confounding variables include but are not limited to: prior antipsychotic use, concurrent antipsychotic use, age, race, and gender. I have included the interim results from this analysis for internal review and comments only.

Please refer to the project status report for next steps with all projects and reports.

Feel free to contact me with any questions or comments.

Amy Grogg, Pharm.D.
Associate Director, CNS Outcomes Research
Janssen Pharmaceutica
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200
609-730-3153 phone
609-730-3125 fax
agrogg1@janus.jnj.com

JJRE 02280519
Plaintiff Ex. 166
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R. 3094

Exhibit
Grogg – 24
03.24.09

From: Grogg, Amy [JANUS]
Sent: Tuesday, August 01, 2000 7:25 AM
To: Vandenbossche, Joris [JanBe]; Rosenberg, Joanne [JANUS]
Cc: Caers, Ivo [JanBe]; Vergis, Janet [JANUS]; Hantson, Ludwig [JANUS]; Derivan, Albert [JANUS]; Mahmoud, Ramy [JANUS]; Farup, Christina [JANUS]; Dodd, Sheri [JANUS]; Markowitz, Jeff [JANUS Non J&J]; Fife, Daniel [JANUS]
Subject: ERI report and tables - DO NOT INCLUDE IN FDA SUBMISSION

Importance: High

Dear all,

See below as referenced in previous e-mail.

ERI diabetes 7-28-00.doc (29 K...

ERI diabetes results 7-28-00.x...

Amy Grogg, Pharm.D.
Associate Director, CNS Outcomes Research
Janssen Pharmaceutica
1125 Trenton-Harbourton Road
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609-730-3153 phone
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Plaintiff Ex. 167
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R. 3095

ERI – Antipsychotics and Diabetes

Brief description of work:

Seven thousand twenty eight (7,028) patients were identified from the New England Insurer (NEI) database, having at least one dispensing of risperidone, olanzapine, clozapine, quetiapine, or haloperidol between 4/1/95 and 12/31/98. Their earliest dispensing during this time period, which was preceded by at least 90 days of full health coverage in the health plan, was identified as the index dispensing. Patients were categorized into one of the five drug groups, based on the drug dispensed on the index date. Four hundred seventy five (475) patients were dropped since they did not have any dispensings meeting this criterion. (NOTE: The index dispensing is not necessarily the patient's first dispensing of the antipsychotic study drug, since they may have received dispensings before becoming a member of the health plan, or they may have received dispensings during their first 90 days of enrollment.)

An additional 359 patients were excluded due to evidence of prevalent diabetes preceding their index dispensing date, leaving 6,194 patients in our study group. Evidence of diabetes was defined as the presence in the claims records of at least one dispensing of a diabetes related medication or at least one doctor visit or inpatient stay associated with diabetes (i.e. ICD-9 250 was listed on the claim record) during the 90 days preceding the index date or on the index date itself.

Patients were followed as long as they were continuously exposed to the drug, plus a defined time window. Continuous exposure was defined as "dispensing date + days supply + 30 days". As long as there was another dispensing of the same medication before the end of that period, the exposure period was considered to be continuous.

We defined two different follow-up periods for identification of onset of diabetes. The first follow-up period ended at the end of the defined exposure period. The second follow-up period, referred to as the 30 day extension, ended 30 days after the end of the exposure period.

The rate of diabetes was also computed separately for those with evidence of schizophrenia and those without evidence of schizophrenia. Patients were categorized into the schizophrenia group if they had at least one doctor visit or inpatient stay associated with a diagnosis of schizophrenia (ICD-9 295xx) at any time during the follow-up period. There were a total of 519 patients in the schizophrenia group.

Table 1 gives the age and sex distribution of the 6,194 patients meeting the eligibility requirements. The risperidone group is the largest, with just over 3,000 patients. The olanzapine and haloperidol groups each had about half that many patients. There were relatively few patients in the clozapine or quetiapine groups.

Table 2 gives the incidence rate of new onset diabetes for each of the 5 drug groups, and for each of the two defined follow-up periods.

This brief analysis did not look in detail at switching from one antipsychotic to another. However, we did compute the number of patients who were exposed to another one of the four anti-psychotics during exposure to

their index drug. The number of patients with such overlapping drug dispensings is shown in Table 3.

Table 4 gives the incidence rate of new onset diabetes for each of the 5 drug groups, stratified by schizophrenia. These rates are also reported for each of the two defined follow-up periods. Interestingly, the incidence rate of new onset diabetes is lower in the non-schizophrenia groups, regardless of the drug category.

Medications Used for Diabetes:

Acarbose
Acetohexamide
Chlorpropamide
Glimepiride
Glipizide
Glyburide
Metformin hydrochloride
Miglitol
Repaglinide
Tolazamide
Tolbutamide
Troglitazone
Insulin

Table 1. Age and Sex Distribution by First Qualifying Anti-psychotic Dispensed During the Study Period
April 1, 1995 - December 31, 1998

		Risperidone		Olanzapine		Clozapine		Quetiapin		Haloperidol		Total	
Sex and Age*		N	%	N	%	N	%	N	%	N	%	N	%
Males													
	0-9	106	8.08	17	2.64	0	0.00	2	6.67	17	2.62	142	5.28
	10-19	362	27.59	125	19.41	2	3.64	0	0.00	74	11.40	563	20.93
	20-29	137	10.44	95	14.75	17	30.91	5	16.67	57	8.78	311	11.56
	30-39	228	17.38	133	20.65	10	18.18	4	13.33	97	14.95	472	17.55
	40-49	211	16.08	145	22.52	11	20.00	5	16.67	108	16.64	480	17.84
	50-64	169	12.88	105	16.30	11	20.00	10	33.33	142	21.88	437	16.25
	65+	99	7.55	24	3.73	4	7.27	4	13.33	154	23.73	285	10.59
Total (males)		1,312	100.00	644	100.00	55	100.00	30	100.00	649	100.00	2,690	100.00
Females													
	0-9	23	1.33	5	0.58	0	0.00	0	0.00	5	0.65	33	0.94
	10-19	198	11.43	100	11.70	3	3.53	5	7.35	28	3.66	334	9.53
	20-29	154	8.89	80	9.36	12	14.12	6	8.82	38	4.97	290	8.28
	30-39	368	21.25	208	24.33	19	22.35	17	25.00	117	15.31	729	20.80
	40-49	460	26.56	211	24.68	29	34.12	15	22.06	169	22.12	884	25.23
	50-64	331	19.11	185	21.64	20	23.53	18	26.47	165	21.60	719	20.52
	65+	198	11.43	66	7.72	2	2.35	7	10.29	242	31.68	515	14.70
Total (females)		1,732	100.00	855	100.00	85	100.00	68	100.00	764	100.00	3,504	100.00
Total		3,044	49.14	1,499	24.20	140	2.26	98	1.58	1,413	22.81	6,194	100.00

*Age as of the first qualifying dispensing date (the index date) of risperidone, olanzapine, clozapine, quetiapine, or haloperidol.

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Table 2. Incidence Rate of New Onset Diabetes*

Index Exposure	Number of Patients	Person Years of Exposure	# New onset Diabetes Thru Exposure Period	Incidence Rate Per 100,000 Person Years, Thru Exposure Period	Person Years for 30 day Extension	# New onset Diabetes Thru 30 Day Extension	Incidence Rate Per 100,000 Person-Years, Thru 30 Day Extension
Risperidone	3,044	1,264.55	35	2,767.78	1,468.24	40	2,724.34
Olanzapine	1,499	561.97	13	2,313.31	662.61	13	1,961.94
Clozapine	140	161.02	6	3,726.34	168.54	6	3,560.00
Quetiapine	98	27.75	0	0.00	34.10	0	0.00
Haloperidol	1,413	569.59	21	3,686.86	665.69	26	3,905.73

*During the first continuous exposure interval for a given study drug.

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Table 3. Overlap of Drug Use*

Index Exposure	Number of Patients	Person Years for 30 day Extension	Number of Patients with Risperidone Dispensings	Number of Patients with Olanzapine Dispensings	Number of Patients with Clozapine Dispensings	Number of Patients with Quetiapine Dispensings	Number of Patients with Haloperidol Dispensings
Risperidone	3,044	1,468.24	3,044	217	14	22	58
Olanzapine	1,499	662.61	102	1,499	7	37	31
Clozapine	140	168.54	9	21	140	1	2
Quetiapine	98	34.10	3	1	1	98	2
Haloperidol	1,413	665.69	138	84	4	4	1,413

* Defined as the number of patients who were also exposed to another study antipsychotic at any point during the exposure

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Table 4. Incidence Rate of New Onset Diabetes by Evidence of Schizophrenia*

Index Exposure and Evidence of Schizophrenia	Number of Patients	Person Years of Exposure	# New onset Diabetes Thru Exposure Period	Incidence Rate Per 100,000 Person Years, Thru Exposure Period	Person Years for 30 day Extension	# New onset Diabetes Thru 30 Day Extension	Incidence Rate Per 100,000 Person-Years, Thru 30 Day Extension
Risperidone							
Schizophrenics	210	160.59	3	1,868.16	174.11	3	1,723.07
Non-Schiz.	2,834	1,103.97	32	2,898.64	1,294.14	37	2,859.05
Olanzapine							
Schizophrenics	116	68.75	0	0.00	76.30	0	0.00
Non-Schiz.	1,383	493.22	13	2,635.76	586.31	13	2,217.27
Clozapine							
Schizophrenics	66	94.34	2	2,119.97	98.02	2	2,040.33
Non-Schiz.	74	66.67	4	5,999.26	70.52	4	5,672.46
Quetiapine							
Schizophrenics	7	3.04	0	0.00	3.55	0	0.00
Non-Schiz.	91	24.70	0	0.00	30.55	0	0.00
Haloperidol							
Schizophrenics	120	78.40	1	1,275.45	86.71	1	1,153.26
Non-Schiz.	1,293	491.19	20	4,071.77	578.98	25	4,317.95

*During the first continuous exposure interval for a given study drug we searched for new onset diabetes and for visits associated with

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DEPARTMENT OF HEALTH & HUMAN SERVICES

FOI

Food and Drug Administration
Rockville MD 20857

JAN 5 1999

TRANSMITTED VIA FACSIMILE

Todd McIntyre, Ph.D.
Director, Regulatory Affairs
Janssen Research Foundation
1125 Trenton-Harbourton Rd.
Titusville, NJ 08560-0200

RE: NDA #20-272, 20-588
Risperdal (risperidone) Tablets
Risperdal (risperidone) Oral Solution
MACMIS #6908

Dear Dr. McIntyre:

This letter concerns Janssen Research Foundation's (Janssen) promotional materials and activities for the marketing of Risperdal (risperidone) Tablets that have been reviewed by the Division of Drug Marketing, Advertising and Communications (DDMAC) as part of its monitoring and surveillance program. In particular, DDMAC is concerned with a campaign that markets Risperdal for geriatric patients. These materials include, but are not limited to sales aids (ID# RS-420, RS-422, RS-473, RS-494), journal ads (ID# RS-470-1, RS-470-1-C, RS-470-1RB, RS-470-2, RS-470-2RB), a display panel (ID# RS-468), brochures (ID# RS-459, RS-469), and a letter (ID #RS-308). Other recent materials include journal ads (ID # RS-450-2, RS-451-2, RS-451-2A, RS-451-C, RS-470-1R, RS-470-2R), letters (ID # RS-462S, RS-477-1, RS-477-1R), a flashcard (ID # RS-518), a calendar (ID #RS-474), and a computer program (ID #RS-463). DDMAC has concluded that these materials are false, misleading, and/or lacking in fair balance, and in violation of the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder.

Specifically, DDMAC has the following objections:

Geriatric Campaign

1. Janssen is disseminating materials that state or imply that Risperdal has been determined to be safe and effective for the elderly population in particular. There is limited data on the use of Risperdal in the elderly, and the elderly population was not specifically studied in the clinical trials for Risperdal. Thus, presentations that focus on this population are

Exhibit
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misleading in that they imply that the drug has been found to be specifically effective in the elderly population.

Also, according to the approved product labeling (PI), there are safety considerations for Risperdal in the elderly population. In healthy elderly subjects, the clearance of both risperidone and its active metabolite was decreased, and the elimination half-lives were prolonged. Hepatic impairment would further increase the mean free fraction of plasma risperidone. Risperdal should be used cautiously in healthy elderly individuals because of the potential for decreased clearance of drug, potential drug interactions, hepatic and renal dysfunction, and cardiovascular sensitivity. The safety of Risperdal in "fragile" individuals or individuals with concomitant illnesses has not been evaluated in adequate and well-controlled studies.

2. Risperdal is indicated for the management of the manifestations of psychotic disorders. However, Janssen is disseminating materials that imply, without adequate substantiation, that Risperdal is safe and effective in specifically treating hostility in the elderly.

Efficacy

Materials that claim that Risperdal is indicated "for psychotic symptoms associated with a broad range of disorders," including schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder, and elderly psychosis, are false or misleading because the adequate and well-controlled clinical studies for Risperdal were not designed to examine the efficacy of Risperdal in this broad range of disorders.

Fair Balance

1. Janssen is disseminating materials that are lacking in fair balance because the risk information appears in pale and tiny font at the bottom or back of a journal ad or other presentation, or after the closing of a letter. Thus, the risk information is not presented with a prominence and readability that is reasonably comparable to the presentation of efficacy information.

2. Janssen is disseminating materials that are lacking in fair balance because they emphasize that Risperdal has a low incidence of certain side effects while minimizing or ignoring important risk information for Risperdal. For example, the sales aid ID# RS-420 has bolded headlines that state that Risperdal has a "low incidence of excessive sedation" and "low incidence of anticholinergic side effects," but the precaution concerning orthostatic hypertension is located in plain text in the "Dosing/Formulations" section, the ninth page of the ten-page piece. Further, the warning regarding tardive dyskinesia is minimized and the common adverse events, which occurred up to 34% of the time, have been reduced to a small paragraph with no quantification beneath a half-page table of common events associated with discontinuation (showing discontinuations were infrequent). Treatment-emergent extrapyramidal symptoms occurred 17-34% of patients on Risperdal (16% placebo). The dose-relationship of extrapyramidal symptoms is important risk information that is not included in many of the materials including this sales aid.

3. Materials that state or imply that Risperdal has a low incidence of movement disorders are false or misleading. According to the PI for Risperdal, adverse events that would cause movement disorders were common in the clinical studies for Risperdal and were often dose-related, as in the treatment-emergent extrapyramidal symptoms.

4. Materials that state or imply Risperdal has a low incidence of excessive sedation are false or misleading. According to the PI, the incidence of somnolence was 3% for 10 mg/day and 8% for 16 mg/day Risperdal (placebo = 1%). Sleepiness, increased duration of sleep, accommodation disturbances, asthenia, lassitude, and increased fatigability were all dose-related adverse events.

5. Materials that state or imply that Risperdal has a low incidence of anticholinergic effects are false or misleading. According to the PI, the incidence of constipation was 7% for the 10 mg/day and 13% for the 16 mg/day dose of Risperdal (placebo = 3%), and cognitive impairment (Precautions section of the PI) and reduced salivation are frequent adverse events. Furthermore, this claim is lacking in fair balance because there is no similar emphasis on adverse events that do occur with Risperdal.

6. Claims of low incidence of adverse events coupled with presentations of adverse events associated with discontinuation are false or misleading

because it implies that the events associated with discontinuation were the extent of the adverse events experienced with Risperdal.

Comparative Claims

1. Materials that state or imply that Risperdal has superior safety or efficacy to other antipsychotics due to its receptor antagonist profile are false or misleading because the mechanism of action of Risperdal is unknown, as is the correlation of the specific receptor antagonism to the clinical effectiveness and safety of the drug.

2. Presentations that compare the efficacy or safety of Risperdal to an active control make false and misleading superiority claims in the absence of substantiation from adequate and well-controlled comparative data (see for example, sales aid #RS-422).

Quality of Life Claims

1. Materials that claim that Risperdal can "enhance daily living" or that it offers "quality control of symptoms for daily living" are considered to be false or misleading in the absence of adequate and well-controlled studies using validated instruments to determine benefit to health-related quality of life.

2. The tagline "Quality control" is false or misleading because it is used out of context and can be interpreted to mean, without adequate substantiation, that Risperdal can control health-related quality of life.

The materials and promotional messages Janssen has disseminated contain false and/or misleading information about the safety and effectiveness of Risperdal. The violations discussed above do not necessarily constitute an exhaustive list. Accordingly, Janssen should immediately discontinue the use of all materials that state, suggest, or imply false, misleading, or unbalanced claims of the type discussed in this letter. Janssen should provide a written response to DDMAC stating its intent to comply with this request. The letter should also include a complete listing of the materials that Janssen will discontinue as a result of this letter, including the dates that the materials were discontinued, as well as a list of those materials that will remain in use.

Janssen's response should be received no later than January 19, 1999. If Janssen has any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, rm.17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS 6908 in addition to the NDA number.

Sincerely,

Lisa L. Stockbridge, Ph.D.
Regulatory Reviewer
Division of Drug Marketing,
Advertising and Communications

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Exhibit
Mahmoud – 12
04.21.09

TRANSMITTED BY FACSIMILE

Ajit Shetty, M.D.
CEO
Janssen Pharmaceutica, Inc.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Re: NDA #s 20-272 and 20-588
Risperdal® (risperidone)
MACMIS # 12195

WARNING LETTER

Dear Dr. Shetty:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a "Dear Healthcare Provider" (DHCP) Letter for Risperdal® (risperidone) disseminated by Janssen Pharmaceutica, Inc. on November 10, 2003. DDMAC has concluded that the DHCP letter is false or misleading in violation of Sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. 352(a) and 321(n)) because it fails to disclose the addition of information relating to hyperglycemia and diabetes mellitus to the approved product labeling (PI), minimizes the risk of hyperglycemia-related adverse events, which in extreme cases is associated with serious adverse events including ketoacidosis, hyperosmolar coma, and death, fails to recommend regular glucose control monitoring to identify diabetes mellitus as soon as possible, and misleadingly claims that Risperdal is safer than other atypical antipsychotics. The healthcare community relies on DHCP letters for accurate and timely information regarding serious risks and associated changes in labeling and the dissemination of this letter at a time critical to educating healthcare providers is a serious public health issue.

Background

According to the approved product labeling (PI), Risperdal is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. Risperdal is indicated for the treatment of schizophrenia and for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder. Risperdal is also indicated in combination with lithium or valproate for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

Previously, information concerning the risks of hyperglycemia and diabetes appeared in the Adverse Reactions section of the PI under the subheading "Other Events Observed During the Premarketing Evaluation of RISPERDAL®." This section identified diabetes mellitus as an infrequent event (occurring in 1/100 to 1/1000 patients) and polyuria/polydipsia as a frequent event (occurring in at least 1/100 patients). In addition, the Adverse Reactions section of the PI

had a subheading titled "Postintroduction reports" and described hyperglycemia and diabetes mellitus aggravated, including diabetic ketoacidosis, as temporally (but not necessarily causally) related to Risperdal.

In response to post-marketing reports of diabetes mellitus, including some cases that resulted in hospitalization and/or death, FDA evaluated the risk of the development of diabetes mellitus in patients treated with atypical antipsychotics. This evaluation included a thorough review from a number of sources, including clinical trial data, spontaneous post-marketing reports, epidemiological studies, published case series, published clinical pharmacology studies, published preclinical studies, and unpublished studies for clozapine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole. Based on this review, and given the severity of the events reported and the potential to identify those events at an earlier stage with additional monitoring, FDA determined to require the addition of language to the Warnings section of the PI for all atypical antipsychotics regarding the risk of hyperglycemia and diabetes. By letter dated September 11, 2003, FDA notified Janssen (through Johnson & Johnson Pharmaceutical Research & Development, L.L.C.) of the new warning requirement. On November 6, 2003, Janssen submitted supplemental NDAs covering addition of the following information to the Warnings section of the PI for Risperdal:

> Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiologic studies suggest an increased risk of treatment emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.
>
> Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

FDA subsequently approved these supplements, and requested that Janssen issue a DHCP letter communicating the important new risk information. FDA also asked Janssen to submit a copy of the letter to the NDA and to the MedWatch program, and reminded Janssen of its reporting requirements under 21 CFR 314.80 and 314.81.

Omission of Material Information

The DHCP letter fails to communicate the fact that information regarding the potential consequences of hyperglycemia and the recommendation of regular glucose control monitoring was added to the PI for Risperdal. Instead, as discussed below, the letter minimizes risks associated with Risperdal and claims that Risperdal is safer than other atypical antipsychotics, when this has not been demonstrated by substantial evidence or substantial clinical experience.

Minimization of Risks/Misleading Comparative Claim

The DHCP letter states:

> Hyperglycemia-related adverse events have infrequently been reported in patients receiving RISPERDAL. Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research[1,2,3,4,5,6,7,8] suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

This statement suggests that Risperdal does not increase the risk of diabetes, contradicting the Warning in the revised PI and minimizing the risks associated with the drug including hyperglycemia-related adverse events such as ketoacidosis, hyperosmolar coma, and death, and minimizing the importance of blood glucose control monitoring.

The references cited in the letter do not represent the weight of the pertinent scientific evidence. That evidence, as explained above, indicates an increased risk of hyperglycemia-related adverse events and diabetes with Risperdal. In addition, this statement does not accurately describe the results of the cited studies. Two of the studies[1,8] actually show an increased risk of diabetes and hyperglycemia with Risperdal. In the first study, investigators found that the risk for diabetes in the risperidone cohort was higher than in the haloperidol cohort (HR 1.23, 95% 1.01 - 1.5). In

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[1] Buse JB, Cavazonni P, Hornbuckle K et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiology* 2003;56:164-170.

[2] Caro JJ, Ward A, Levinton C and Robinson K. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry* 2002;63:1135-1139.

[3] Fuller MA, Shermock KM, Secic M and Grogg AL. Comparative study of the development of diabetes mellitus in patients taking risperidone and olanzapine. *Pharmacotherapy* 2003;23(8):1037-1043.

[4] Gianfrancesco F, White R, Wang RH and Nasrallah HA. Antipsychotic-induced type 2 diabetes: evidence from a large health plan database. *J Clin Psychopharmacol* 2003;23(4):328-335.

[5] Gianfrancesco F, Grogg A, Mahmoud R et al. Differential effects of antipsychotic agents on the risk of development of type 2 diabetes mellitus in patients with mood disorders. *Clin Therapeutics* 2003;25(4):1150-1171.

[6] Gianfrancesco FD, Grogg AL, Mahmoud RA et al. Differential effects of risperidone, olanzapine, clozapine and conventional antipsychotics on type II diabetes: findings from a large health plan database. *J Clin Psychiatry* 2002;63:920-930.

[7] Koro CE, Fedder DO, L'Italien GJ et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 2002;325:243-245.

[8] Sernyak MJ, Leslie DL, Alarcon RD et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry* 2002;159:561-566.

the second study, for patients less than forty years old, olanzapine, clozapine, quetiapine and risperidone were all associated with a statistically significant increase in risk for diabetes. Thus, the cited studies as well as the complete "body of evidence" supporting the labeling change are misrepresented in the DHCP letter.

FDA is not aware of substantial evidence or substantial clinical experience to support Janssen's claim that "Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics." If you have data to support this claim, please submit them to FDA for review. FDA is unable to conclude, based on unpublished and published studies, whether the differences in results represent true differences in risk for diabetes mellitus among drugs or are due to limitations in the study designs or in some cases, the limited sample sizes examined. FDA's conclusion regarding the lack of evidence to support a ranking of risk among the atypical antipsychotics is reflected in the following statement from the Warnings section of the PI for Risperdal: "Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available."

Failure to Submit Post-Marketing Reports

The DHCP letter was not submitted to FDA on Form FDA 2253 at the time of initial dissemination, as required by the post-marketing reporting requirements (21 CFR 314.81 (b)(3)(i)).

Conclusions and Requested Actions

The DHCP letter misleadingly omits material information about Risperdal, minimizes potentially fatal risks associated with the drug, and claims superior safety to other drugs in its class without adequate substantiation, in violation of Sections 502(a) and 201(n) of the Act (21 U.S.C. §§ 352(a) and 321(n)).

DDMAC requests that Janssen immediately cease the dissemination of promotional materials for Risperdal that contain claims the same as or similar to those described above and provide a plan of action to disseminate accurate and complete information to the audience(s) that received the violative promotional materials. Please submit a written response to this letter on or before May 3, 2004, describing your intent to comply with this request, listing all promotional materials for Risperdal that contain claims the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 12195 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for Risperdal, and may determine that additional measures will be necessary to fully correct the false or misleading messages resulting from your violative conduct. It is your responsibility to ensure that your promotional materials for Risperdal comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising and Communications

Cc: William C. Weldon
CEO
Johnson & Johnson Pharmaceutical
Research & Development, L.L.C.

From: Mahmoud, Ramy [JANUS]
Sent: Tuesday, October 10, 2000 10:20 PM
To: Dac, Nadia [JANUS]; Berry, Sally [JANUS]; Clark, Elizabeth [JANUS]
Cc: Watson, Debi [JANUS]; Benton, Lynda [JANUS]
Subject: RE: Meyer Hyperlipidemia Publication

I suggest that Sally speak with Myers - I agree with the view that she expressed below. If it is not too pushy, his data better support the course of action Sally outlines than what appears to have been implemented. As long as we are low-key about this it shouldn't be a hard conversation, especially since our fall-back position would be as Nadia outlines (i.e., just review your own data after X time and adjust accordingly...). Beth, do you think that contacting Dan Casey would be a better/alternative idea here?
-Ramy

----Original Message----
From: Dac, Nadia [JANUS]
Sent: Tuesday, October 10, 2000 10:00 AM
To: Berry, Sally [JANUS]; Clark, Elizabeth [JANUS]
Cc: Watson, Debi [JANUS]; Benton, Lynda [JANUS]; Amatniek, Joan [JANUS]; Danyluk, Alexander [JANUS]; Grogg, Amy [JANUS]; Mahmoud, Ramy [JANUS]; Martinez, Rick [JANUS]; Sachak, Sohel [JANUS]; Schubert, Lauren [JANUS]; Vangala, Surya [JANUS]
Subject: RE: Meyer Hyperlipidemia Publication

Sally-

I know Dr. Meyer has a more favorable impression of RIS over the other atyps, based on his lectures from this year. If he is insisting on screening all atyps, let's ask him to keep track of what he finds so that we have more data on RIS' safety.

Thank you,
Nadia

----Original Message----
From: Berry, Sally [JANUS]
Sent: Thursday, October 05, 2000 11:16 AM
To: Clark, Elizabeth [JANUS]
Cc: Watson, Debi [JANUS]; Benton, Lynda [JANUS]; Dac, Nadia [JANUS]; Amatniek, Joan; Berry, Sally; Danyluk, Alexander; Grogg, Amy; Mahmoud, Ramy; Martinez, Rick; Sachak, Sohel; Schubert, Lauren; Vangala, Surya
Subject: RE: Meyer Hyperlipidemia Publication

Beth,

Thank you for this valuable information.

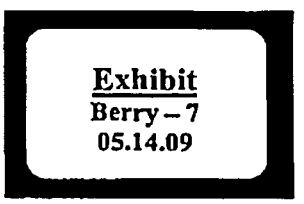
All,

This is what we need to prevent happening! That is, we do not want to be lumped in to the atypical class for diabetes. I think we need to work hard on a strategy to avoid risperdal being thought of as a diabetes-inducing medication. Instead, when worried about diabetes, we want doctors to prescribe risperdal. This will become even more important in the future when other atypicals are introduced to the market that, like RIS, do not have problems with diabetes.

With respect to Dr. Meyers' work, I would feel better if he screened patients with schizophrenia for diabetes, not just those on atypicals, or those considering a switch to atypicals.

Sally

-----Original Message-----
From: Clark, Elizabeth [JANUS]



JJRE 02296123
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Sent: Wednesday, October 04, 2000 5:49 PM
To: Berry, Sally [JANUS]
Subject: RE: Meyer Hyperlipidemia Publication

Hi Sally,
My understanding is that Dr. Meyer does recommend all patients being started on atypicals be screened including risperidone patients. May be as more data becomes available he will feel more comfortable not screening risperidone patients. He has actually established an atypical panel with his lab service.

We will be certain you have a chance for a 1:1 when he does his HOV. (PS I will not be able to attend ACNP due to limited industry registration.)

I look forward to meeting you next week.
Kind regards,
Beth

----Original Message----
From: Berry, Sally [JANUS]
Sent: Wednesday, October 04, 2000 6:43 AM
To: Mahmoud, Ramy [JANUS]; Schubert, Lauren [JANUS]; Myers, Joyce [JANUS]; Vangala, Surya [JANUS]; Martinez, Rick [JANUS]; Grogg, Amy [JANUS]; Danyluk, Alexander [JANUS]; Sachak, Sohel [JANUS]; Watson, Debi [JANUS]
Cc: Clark, Elizabeth [JANUS]
Subject: RE: Meyer Hyperlipidemia Publication

Lauren.

I agree with Ramy's comments. Dr. Meyer did a nice job with this study. I was interested in his last comment wherein he essentially suggests that patients on atypicals be screened for glucose, weight and lipid problems. Does he suggest this for ris patients as well?

If he visits the home office, I would like to schedule a 1:1 meeting with him. Otherwise, perhaps you or Beth could introduce me to him at ACNP or ICOSR. Do you know where he plans to submit this paper?

Sally
Sally Berry, MD, PhD
Associate Director, CNS Medical Affairs
Janssen Pharmaceutica
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200
609-730-3374 phone
609-730-3125 fax
sberry@janus.jnj.com

----Original Message----
From: Mahmoud, Ramy [JANUS]
Sent: Tuesday, October 03, 2000 7:19 AM
To: Schubert, Lauren [JANUS]; Myers, Joyce [JANUS]; Berry, Sally [JANUS]; Vangala, Surya [JANUS]; Martinez, Rick [JANUS]; Grogg, Amy [JANUS]; Danyluk, Alexander [JANUS]; Sachak, Sohel [JANUS]; Watson, Debi [JANUS]
Cc: Clark, Elizabeth [JANUS]
Subject: RE: Meyer Hyperlipidemia Publication

May want to point out to Jonathan (he just touches on it), that insulin acts at the liver to suppress synthesis of serum lipids and that varying degrees of putative insulin resistance secondary to dibenzothiazepine treatment may produce hyperlipidemias by that mechanism. Also, I think it is a stretch to call weight gain of 12lbs "modest" -- this is certainly nothing like the measurement-error difference in HA1C from 4.9 to 5.0 that is also referred to as "modest". And it would be very nice if he could be asked to include something to the effect of "but not risperidone" after referring to problems with the class generally in multiple spots (especially the abstract). His paper would be better if it had something about the risk and importance of acute pancreatitis - including mortality I believe? risk of type 1 DM? hospital stays? etc. - (rather than just mentioning it as a side effect of extreme TG elevations). Additionally, he notes that TC=HDL+LDL+TG/5, but as I recall this procedure doesn't work in the lab when there are these kinds of severe TG

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R. 3113

elevations (this serum would actually look "milky"), and you have to send off the sample for a different type of direct assay of the TG levels. He may want to look into this before publishing this part as is. Please communicate with him on this soonest (prior to submission!).
-Ramy

-----Original Message-----
From: Schubert, Lauren [JANUS]
Sent: Monday, October 02, 2000 8:36 PM
To: Mahmoud, Ramy [JANUS]; Myers, Joyce [JANUS]; Berry, Sally [JANUS]; Vangala, Surya [JANUS]; Martinez, Rick [JANUS]; Grogg, Amy [JANUS]; Danyluk, Alexander [JANUS]; Sachak, Sohel [JANUS]
Cc: Clark, Elizabeth [JANUS]
Subject: FW: Meyer Hyperlipidemia Publication

Hello All,

Below is a paper from Jonathan Meyer on Severe Hyperlipidemia. When this was mentioned in our weekly report, the Risperdal Brand was interested in a home visit.

I would like to get some responses from our team on the interest level with this visit....and I will plan this visit to meet the schedules of those who would like to meet with Dr. Meyer.

After I get our interest level, I will work with brand to schedule as appropriate .

Thanks,

Lauren
Lauren Schubert
Director West MSL Program
Phone: (573) 486-4474
Fax: (573) 486-3074
Aspen: 7524
E-Mail: lschube1@janus.jnj.com
1265 Highway H
Hermann, Missouri 65041

-----Original Message-----
From: Clark, Elizabeth [JANUS]
Sent: Wednesday, September 27, 2000 8:51 AM
To: Schubert, Lauren [JANUS]
Subject: Meyer Hyperlipidemia Publication

Hi Lauren,
Here is Jonathan Meyer's Atypical Antipsychotic Associated Severe Hyperlipidemia paper.
<< File: Atyp Hyperlipidemia.doc >>
As we discussed could you please forward this to anyone who may be interested in meeting with Dr. Meyer.
Best regards,
Beth

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R. 3114

Exhibit
Pandina – 5
05.21.09

RISPERDAL®
(risperidone)

7503238
(0908)
01RS2013

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RISPERDAL® safely and effectively. See full prescribing information for RISPERDAL®.

RISPERDAL® (risperidone) tablets, RISPERDAL® (risperidone) oral solution, RISPERDAL® M-TAB® (risperidone) orally disintegrating tablets

Initial U.S. Approval: 1993

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. RISPERDAL® is not approved for use in patients with dementia-related psychosis. (5.1)

RECENT MAJOR CHANGES

Boxed Warning	08/2008
Warnings and Precautions (5.1)	08/2008

INDICATIONS AND USAGE

RISPERDAL® is an atypical antipsychotic agent indicated for:

- Treatment of schizophrenia in adults and adolescents aged 13-17 years (1.1)
- Alone, or in combination with lithium or valproate, for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults, and alone in children and adolescents aged 10-17 years (1.2)
- Treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years (1.3)

DOSAGE AND ADMINISTRATION

	Initial Dose	Titration	Target Dose	Effective Dose Range
Schizophrenia–adults (2.1)	2 mg/day	1-2 mg daily	4-8 mg daily	4-16 mg/day
Schizophrenia–adolescents(2.1)	0.5 mg/day	0.5-1 mg daily	3 mg/day	1-6 mg/day
Bipolar mania–adults (2.2)	2-3 mg/day	1 mg daily	1-6 mg/day	1-6 mg/day
Bipolar mania in children/adolescents (2.2)	0.5 mg/day	0.5-1 mg daily	2.5 mg/day	0.5-6 mg/day
Irritability associated with autistic disorder (2.3)	0.25 mg/day (<20 kg) 0.5 mg/day (≥20 kg)	0.25-0.5 mg at ≥2 weeks	0.5 mg/day (<20 kg) 1 mg/day (≥20 kg)	0.5-3 mg/day

DOSAGE FORMS AND STRENGTHS

- Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg (3)
- Oral solution: 1 mg/mL (3)
- Orally disintegrating tablets: 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to the product (4)

WARNINGS AND PRECAUTIONS

- Cerebrovascular events, including stroke, in elderly patients with dementia-related psychosis. RISPERDAL® is not approved for use in patients with dementia-related psychosis (5.2)
- Neuroleptic Malignant Syndrome (5.3)
- Tardive dyskinesia (5.4)
- Hyperglycemia and diabetes mellitus (5.5)
- Hyperprolactinemia (5.6)
- Orthostatic hypotension (5.7)
- Potential for cognitive and motor impairment (5.8)
- Seizures (5.9)
- Dysphagia (5.10)
- Priapism (5.11)
- Thrombotic Thrombocytopenic Purpura (TTP) (5.12)
- Disruption of body temperature regulation (5.13)
- Antiemetic Effect (5.14)
- Suicide (5.15)
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies (5.16)
- Diseases or conditions that could affect metabolism or hemodynamic responses (5.16)

ADVERSE REACTIONS

The most common adverse reactions in clinical trials (≥10%) were somnolence, appetite increased, fatigue, rhinitis, upper respiratory tract infection, vomiting, coughing, urinary incontinence, saliva increased, constipation, fever, Parkinsonism, dystonia, abdominal pain, anxiety, nausea, dizziness, dry mouth, tremor, rash, akathisia, and dyspepsia. (6)

The most common adverse reactions that were associated with discontinuation from clinical trials were somnolence, nausea, abdominal pain, dizziness, vomiting, agitation, and akathisia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen, L.P. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Due to CNS effects, use caution when administering with other centrally-acting drugs. Avoid alcohol. (7.1)
- Due to hypotensive effects, hypotensive effects of other drugs with this potential may be enhanced. (7.2)
- Effects of levodopa and dopamine agonists may be antagonized. (7.3)
- Cimetidine and ranitidine increase the bioavailability of risperidone. (7.5)
- Clozapine may decrease clearance of risperidone. (7.6)
- Fluoxetine and paroxetine increase plasma concentrations of risperidone. (7.10)
- Carbamazepine and other enzyme inducers decrease plasma concentrations of risperidone. (7.11)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: should not breast feed. (8.3)
- Pediatric Use: safety and effectiveness not established for schizophrenia less than 13 years of age, for bipolar mania less than 10 years of age, and for autistic disorder less than 5 years of age. (8.4)
- Elderly or debilitated; severe renal or hepatic impairment; predisposition to hypotension or for whom hypotension poses a risk: Lower initial dose (0.5 mg twice daily), followed by increases in dose in increments of no more than 0.5 mg twice daily. Increases to dosages above 1.5 mg twice daily should occur at intervals of at least 1 week. (8.5, 2.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 08/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNINGS – INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

1 INDICATIONS AND USAGE
- 1.1 Schizophrenia
- 1.2 Bipolar Mania
- 1.3 Irritability Associated with Autistic Disorder

2 DOSAGE AND ADMINISTRATION
- 2.1 Schizophrenia
- 2.2 Bipolar Mania
- 2.3 Irritability Associated with Autistic Disorder – Pediatrics (Children and Adolescents)
- 2.4 Dosage in Special Populations
- 2.5 Co-Administration of RISPERDAL® with Certain Other Medications
- 2.6 Administration of RISPERDAL® Oral Solution
- 2.7 Directions for Use of RISPERDAL® M-TAB® Orally Disintegrating Tablets

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- 5.2 Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis
- 5.3 Neuroleptic Malignant Syndrome (NMS)
- 5.4 Tardive Dyskinesia
- 5.5 Hyperglycemia and Diabetes Mellitus
- 5.6 Hyperprolactinemia
- 5.7 Orthostatic Hypotension
- 5.8 Potential for Cognitive and Motor Impairment
- 5.9 Seizures
- 5.10 Dysphagia
- 5.11 Priapism
- 5.12 Thrombotic Thrombocytopenic Purpura (TTP)
- 5.13 Body Temperature Regulation
- 5.14 Antiemetic Effect
- 5.15 Suicide
- 5.16 Use in Patients with Concomitant Illness
- 5.17 Monitoring: Laboratory Tests

6 ADVERSE REACTIONS
- 6.1 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials - Schizophrenia
- 6.2 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Bipolar Mania
- 6.3 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials - Autistic Disorder
- 6.4 Other Adverse Reactions Observed During the Premarketing Evaluation of RISPERDAL®
- 6.5 Discontinuations Due to Adverse Reactions
- 6.6 Dose Dependency of Adverse Reactions in Clinical Trials
- 6.7 Changes in Body Weight
- 6.8 Changes in ECG
- 6.9 Postmarketing Experience

Plaintiff Ex. 280

7 DRUG INTERACTIONS
7.1 Centrally-Acting Drugs and Alcohol
7.2 Drugs with Hypotensive Effects
7.3 Levodopa and Dopamine Agonists
7.4 Amitriptyline
7.5 Cimetidine and Ranitidine
7.6 Clozapine
7.7 Lithium
7.8 Valproate
7.9 Digoxin
7.10 Drugs That Inhibit CYP 2D6 and Other CYP Isozymes
7.11 Carbamazepine and Other Enzyme Inducers
7.12 Drugs Metabolized by CYP 2D6
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
10.1 Human Experience
10.2 Management of Overdosage
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Schizophrenia
14.2 Bipolar Mania - Monotherapy
14.3 Bipolar Mania – Combination Therapy
14.4 Irritability Associated with Autistic Disorder
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Orthostatic Hypotension
17.2 Interference with Cognitive and Motor Performance
17.3 Pregnancy
17.4 Nursing
17.5 Concomitant Medication
17.6 Alcohol
17.7 Phenylketonurics

*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. RISPERDAL® (risperidone) is not approved for the treatment of patients with dementia-related psychosis. *[See Warnings and Precautions (5.1)]*

1 INDICATIONS AND USAGE

1.1 Schizophrenia

Adults

RISPERDAL® (risperidone) is indicated for the acute and maintenance treatment of schizophrenia *[see Clinical Studies (14.1)]*.

Adolescents

RISPERDAL® is indicated for the treatment of schizophrenia in adolescents aged 13–17 years *[see Clinical Studies (14.1)]*.

1.2 Bipolar Mania

Monotherapy - Adults and Pediatrics

RISPERDAL® is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults and in children and adolescents aged 10-17 years *[see Clinical Studies (14.2)]*.

Combination Therapy – Adults

The combination of RISPERDAL® with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder *[see Clinical Studies (14.3)]*.

1.3 Irritability Associated with Autistic Disorder

Pediatrics

RISPERDAL® is indicated for the treatment of irritability associated with autistic disorder in children and adolescents aged 5–16 years, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods *[see Clinical Studies (14.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

Usual Initial Dose

RISPERDAL® can be administered once or twice daily. Initial dosing is generally 2 mg/day. Dose increases should then occur at intervals not less than 24 hours, in increments of 1-2 mg/day, as tolerated, to a recommended dose of 4-8 mg/day. In some patients, slower titration may be appropriate. Efficacy has been demonstrated in a range of 4-16 mg/day *[see Clinical Studies (14.1)]*. However, doses above 6 mg/day for twice daily dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are generally not recommended. In a single study supporting once-daily dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy

While it is unknown how long a patient with schizophrenia should remain on RISPERDAL®, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years *[see Clinical Studies (14.1)]*. Patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Adolescents

The dosage of RISPERDAL® should be initiated at 0.5 mg once daily, administered as a single-daily dose in either the morning or evening. Dosage adjustments, if indicated, should occur at intervals not less than 24 hours, in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 3 mg/day. Although efficacy has been demonstrated in studies of adolescent patients with schizophrenia at doses between 1 and 6 mg/day, no additional benefit was seen above 3 mg/day, and higher doses were associated with more adverse events. Doses higher than 6 mg/day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

There are no controlled data to support the longer term use of RISPERDAL® beyond 8 weeks in adolescents with schizophrenia. The physician who elects to use RISPERDAL® for extended periods in adolescents with schizophrenia should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that after an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching From Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or treating patients with concomitant antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. The period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

2.2 Bipolar Mania

Usual Dose

Adults

RISPERDAL® should be administered on a once-daily schedule, starting with 2 mg to 3 mg per day. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments/decrements of 1 mg per day, as studied in the short-term, placebo-controlled trials. In these trials, short-term (3 week) anti-manic efficacy was demonstrated in a flexible dosage range of 1-6 mg per day *[see Clinical Studies (14.2, 14.3)]*. RISPERDAL® doses higher than 6 mg per day were not studied.

Pediatrics

The dosage of RISPERDAL® should be initiated at 0.5 mg once daily, administered as a single-daily dose in either the morning or evening. Dosage adjustments, if indicated, should occur at intervals not less than 24 hours, in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 2.5 mg/day. Although efficacy has been demonstrated in studies of pediatric patients with bipolar mania at doses between 0.5 and 6 mg/day, no additional benefit was seen above 2.5 mg/day, and higher doses were associated with more adverse events. Doses higher than 6 mg/day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

Maintenance Therapy

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with RISPERDAL®. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of RISPERDAL® in such longer-term treatment (i.e., beyond 3 weeks). The physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

2.3 Irritability Associated with Autistic Disorder – Pediatrics (Children and Adolescents)

The safety and effectiveness of RISPERDAL® in pediatric patients with autistic disorder less than 5 years of age have not been established.

The dosage of RISPERDAL® should be individualized according to the response and tolerability of the patient. The total daily dose of RISPERDAL® can be administered once daily, or half the total daily dose can be administered twice daily.

Dosing should be initiated at 0.25 mg per day for patients < 20 kg and 0.5 mg per day for patients ≥ 20 kg. After a minimum of four days from treatment initiation, the dose may be increased to the recommended dose of 0.5 mg per day for patients < 20 kg and 1 mg per day for patients ≥ 20 kg. This dose should be maintained for a minimum of 14 days. In patients not achieving sufficient clinical response, dose increases may be considered at ≥2-week intervals in increments of 0.25 mg per day for patients < 20 kg or 0.5 mg per day for patients ≥ 20 kg. Caution should be exercised with dosage for smaller children who weigh less than 15 kg.

In clinical trials, 90% of patients who showed a response (based on at least 25% improvement on ABC-I, *[see Clinical Studies (14.4)]*) received doses of RISPERDAL® between 0.5 mg and 2.5 mg per day. The maximum daily dose of RISPERDAL® in one of the pivotal trials, when the therapeutic effect reached plateau, was 1 mg in patients < 20 kg, 2.5 mg in patients ≥ 20 kg, or 3 mg in patients > 45 kg. No dosing data is available for children who weighed less than 15 kg.

Once sufficient clinical response has been achieved and maintained, consideration should be given to gradually lowering the dose to achieve the optimal balance of efficacy and safety. The physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Patients experiencing persistent somnolence may benefit from a once-daily dose administered at bedtime or administering half the daily dose twice daily, or a reduction of the dose.

2.4 Dosage in Special Populations

The recommended initial dose is 0.5 mg twice daily in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg twice daily. Increases to dosages above 1.5 mg twice daily should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect *[see Clinical Pharmacology (12.3)]*. Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored *[see Warnings and Precautions (5.2, 5.7, 5.16)]*. If a once-daily dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-daily regimen for 2-3 days at the target dose. Subsequent switches to a once-daily dosing regimen can be done thereafter.

2.5 Co-Administration of RISPERDAL® with Certain Other Medications

Co-administration of carbamazepine and other enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with RISPERDAL® would be expected to cause decreases in the plasma concentrations of the sum of risperidone and 9-hydroxyrisperidone combined, which could lead to decreased efficacy of RISPERDAL® treatment. The dose of RISPERDAL® needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers *[see Drug Interactions (7.11)]*.

Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold, respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. The dose of RISPERDAL® needs to be titrated accordingly when fluoxetine or paroxetine is co-administered *[see Drug Interactions (7.10)]*.

2.6 Administration of RISPERDAL® Oral Solution

RISPERDAL® Oral Solution can be administered directly from the calibrated pipette, or can be mixed with a beverage prior to administration. RISPERDAL® Oral Solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea.

2.7 Directions for Use of RISPERDAL® M-TAB® Orally Disintegrating Tablets

Tablet Accessing

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are supplied in blister packs of 4 tablets each.

Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg are supplied in a child-resistant pouch containing a blister with 1 tablet each.

The child-resistant pouch should be torn open at the notch to access the blister. Do not open the blister until ready to administer. Peel back foil from the side to expose the tablet. DO NOT push the tablet through the foil, because this could damage the tablet.

Tablet Administration

Using dry hands, remove the tablet from the blister unit and immediately place the entire RISPERDAL® M-TAB® Orally Disintegrating Tablet on the tongue. The RISPERDAL® M-TAB® Orally Disintegrating Tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. RISPERDAL® M-TAB® Orally Disintegrating Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to split or to chew the tablet.

3 DOSAGE FORMS AND STRENGTHS

RISPERDAL® Tablets are available in the following strengths and colors: 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green). All are capsule shaped, and imprinted with "JANSSEN" on one side and either "Ris 0.25", "Ris 0.5", "R1", "R2", "R3", or "R4" on the other side according to their respective strengths.

RISPERDAL® Oral Solution is available in a 1 mg/mL strength.

RISPERDAL® M-TAB® Orally Disintegrating Tablets are available in the following strengths, colors, and shapes: 0.5 mg (light coral, round), 1 mg (light coral, square), 2 mg (coral, square), 3 mg (coral, round), and 4 mg (coral, round). All are biconvex and etched on one side with "R0.5", "R1", "R2", "R3", or "R4" according to their respective strengths.

4 CONTRAINDICATIONS

Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone. Therefore, RISPERDAL® is contraindicated in patients with a known hypersensitivity to the product.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. RISPERDAL® (risperidone) is not approved for the treatment of dementia-related psychosis *[see Boxed Warning]*.

5.2 Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. *[See also Boxed Warnings and Warnings and Precautions (5.1)]*

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.4 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that: (1) is known

to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

5.5 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

5.6 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, RISPERDAL® elevates prolactin levels and the elevation persists during chronic administration. RISPERDAL® is associated with higher levels of prolactin elevation than other antipsychotic agents.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. An increase in pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Non-Clinical Toxicology (13.1)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

5.7 Orthostatic Hypotension

RISPERDAL® may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2 and 3 studies in adults with schizophrenia. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either once daily or 1 mg twice daily) in normal adults and 0.5 mg twice daily in the elderly and patients with renal or hepatic impairment *[see Dosage and Administration (2.1, 2.4)]*. Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

5.8 Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high-dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

5.9 Seizures

During premarketing testing in adult patients with schizophrenia, seizures occurred in 0.3% (9/2607) of RISPERDAL®-treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

5.10 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. *[See also Boxed Warning and Warnings and Precautions (5.1)]*

5.11 Priapism

Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

5.12 Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28 year-old female patient receiving oral RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

5.13 Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

5.14 Antiemetic Effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

5.15 Suicide

The possibility of a suicide attempt is inherent in patients with schizophrenia and bipolar mania, including children and adolescent patients, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

5.16 Use in Patients with Concomitant Illness

Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL®, are reported to have an increased sensitivity to antipsychotic medications. Manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2), and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients *[see Dosage and Administration (2.4)]*.

5.17 Monitoring: Laboratory Tests

No specific laboratory tests are recommended.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions (5.2)]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions (5.3)]*
- Tardive dyskinesia *[see Warnings and Precautions (5.4)]*
- Hyperglycemia and diabetes mellitus *[see Warnings and Precautions (5.5)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.6)]*
- Orthostatic hypotension *[see Warnings and Precautions (5.7)]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions (5.8)]*
- Seizures *[see Warnings and Precautions (5.9)]*
- Dysphagia *[see Warnings and Precautions (5.10)]*
- Priapism *[see Warnings and Precautions (5.11)]*
- Thrombotic Thrombocytopenic Purpura (TTP) *[see Warnings and Precautions (5.12)]*
- Disruption of body temperature regulation *[see Warnings and Precautions (5.13)]*
- Antiemetic effect *[see Warnings and Precautions (5.14)]*
- Suicide *[see Warnings and Precautions (5.15)]*
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies *[see Warnings and Precautions (5.16)]*
- Diseases or conditions that could affect metabolism or hemodynamic responses *[see Warnings and Precautions (5.16)]*

The most common adverse reactions in clinical trials (≥ 10%) were somnolence, appetite increased, fatigue, rhinitis, upper respiratory tract infection, vomiting, coughing, urinary incontinence, saliva increased, constipation, fever, Parkinsonism, dystonia, abdominal pain, anxiety, nausea, dizziness, dry mouth, tremor, rash, akathisia, and dyspepsia.

The most common adverse reactions that were associated with discontinuation from clinical trials (causing discontinuation in >1% of adults and/or >2% of pediatrics) were somnolence, nausea, abdominal pain, dizziness, vomiting, agitation, and akathisia *[see Adverse Reactions (6.5)]*.

The data described in this section are derived from a clinical trial database consisting of 9712 adult and pediatric patients exposed to one or more doses of RISPERDAL® for the treatment of schizophrenia, bipolar mania, autistic disorder, and other psychiatric disorders

in pediatrics and elderly patients with dementia. Of these 9712 patients, 2626 were patients who received RISPERDAL® while participating in double-blind, placebo-controlled trials. The conditions and duration of treatment with RISPERDAL® varied greatly and included (in overlapping categories) double-blind, fixed- and flexible-dose, placebo- or active-controlled studies and open-label phases of studies, inpatients and outpatients, and short-term (up to 12 weeks) and longer-term (up to 3 years) exposures. Safety was assessed by collecting adverse events and performing physical examinations, vital signs, body weights, laboratory analyses, and ECGs.

Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using WHOART terminology.

Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of RISPERDAL® (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for RISPERDAL® often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The majority of all adverse reactions were mild to moderate in severity.

6.1 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials - Schizophrenia

Adult Patients with Schizophrenia

Table 1 lists the adverse reactions reported in 1% or more of RISPERDAL®-treated adult patients with schizophrenia in three 4- to 8-week, double-blind, placebo-controlled trials.

Table 1. Adverse Reactions in ≥ 1% of RISPERDAL®-Treated Adult Patients with Schizophrenia in Double-Blind, Placebo-Controlled Trials

Body System Adverse Reaction	Percentage of Patients Reporting Event RISPERDAL® 2-8 mg per day (N=366)	>8-16 mg per day (N=198)	Placebo (N=225)
Body as a whole - general disorders			
Back pain	3	2	<1
Fatigue	3	1	0
Chest pain	3	1	2
Fever	2	1	1
Asthenia	1	1	<1
Syncope	<1	1	<1
Edema	<1	1	0
Cardiovascular disorders, general			
Hypotension postural	2	<1	0
Hypotension	<1	1	0
Central and peripheral nervous system disorders			
Parkinsonism*	12	17	6
Dizziness	10	4	2
Dystonia*	5	5	2
Akathisia*	5	5	2
Dyskinesia	1	1	<1
Gastrointestinal system disorders			
Dyspepsia	10	7	6
Nausea	9	4	4
Constipation	8	9	7
Abdominal pain	4	3	0
Mouth dry	4	<1	<1
Saliva increased	3	1	<1
Diarrhea	2	<1	1
Hearing and vestibular disorders			
Earache	1	1	0
Heart rate and rhythm disorders			
Tachycardia	2	5	0
Arrhythmia	0	1	0
Metabolic and nutritional disorders			
Weight increase	1	<1	0
Creatine phosphokinase increased	<1	2	<1
Musculoskeletal system disorders			
Arthralgia	2	3	<1
Myalgia	1	0	0
Platelet, bleeding and clotting disorders			
Epistaxis	<1	2	0
Psychiatric disorders			
Anxiety	16	12	11
Somnolence	14	5	4
Anorexia	2	0	<1
Red blood cell disorders			
Anemia	<1	1	0
Reproductive disorders, male			
Ejaculation failure	<1	1	0
Respiratory system disorders			
Rhinitis	7	11	6
Coughing	3	3	3
Upper respiratory tract infection	2	3	<1
Dyspnea	2	2	0
Skin and appendages disorders			
Rash	2	4	2
Seborrhea	<1	2	0
Urinary system disorders			
Urinary tract infection	<1	3	0
Vision disorders			
Vision abnormal	3	1	<1

* Parkinsonism includes extrapyramidal disorder, hypokinesia, and bradycardia. Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Akathisia includes hyperkinesia and akathisia.

Pediatric Patients with Schizophrenia

Table 2 lists the adverse reactions reported in 5% or more of RISPERDAL®-treated pediatric patients with schizophrenia in a 6-week double-blind, placebo-controlled trial.

Table 2. Adverse Reactions in ≥ 5% of RISPERDAL®-Treated Pediatric Patients with Schizophrenia in a Double-Blind Trial

Body System Adverse Reaction	Percentage of Patients Reporting Event RISPERDAL® 1-3 mg per day (N=55)	4-6 mg per day (N=51)	Placebo (N=54)
Central and peripheral nervous system disorders			
Parkinsonism*	13	16	6
Tremor	11	10	6
Dystonia*	9	18	7
Dizziness	7	14	2
Akathisia*	7	10	6
Gastrointestinal system disorders			
Saliva increased	0	10	2
Psychiatric disorders			
Somnolence	24	12	4
Anxiety	7	6	0

* Parkinsonism includes extrapyramidal disorder, hypokinesia, and bradykinesia. Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Akathisia includes hyperkinesia and akathisia.

6.2 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Bipolar Mania

Adult Patients with Bipolar Mania

Table 3 lists the adverse reactions reported in 1% or more of RISPERDAL®-treated adult patients with bipolar mania in four 3-week, double-blind, placebo-controlled monotherapy trials.

Table 3. Adverse Reactions in ≥ 1% of RISPERDAL®-Treated Adult Patients with Bipolar Mania in Double-Blind, Placebo-Controlled Monotherapy Trials

Body System Adverse Reaction	Percentage of Patients Reporting Event RISPERDAL® 1-6 mg per day (N=448)	Placebo (N=424)
Body as a whole - general disorders		
Fatigue	2	<1
Fever	1	<1
Asthenia	1	<1
Edema	1	<1
Central and peripheral nervous system disorders		
Parkinsonism*	20	6
Dystonia*	11	3
Akathisia*	9	3
Tremor	6	4
Dizziness	5	5
Gastrointestinal system disorders		
Nausea	5	2
Dyspepsia	4	2
Saliva increased	3	<1
Diarrhea	3	2
Mouth dry	1	1
Heart rate and rhythm disorders		
Tachycardia	1	<1
Liver and biliary system disorders		
SGOT increased	1	<1
Musculoskeletal disorders		
Myalgia	2	2
Psychiatric disorders		
Somnolence	12	4
Anxiety	2	2
Reproductive disorders, female		
Lactation nonpuerperal	1	0

Table 3. Adverse Reactions in ≥ 1% of RISPERDAL®-Treated Adult Patients with Bipolar Mania in Double-Blind, Placebo-Controlled Monotherapy Trials (continued)

Body System Adverse Reaction	Percentage of Patients Reporting Event RISPERDAL® 1-6 mg per day (N=448)	Placebo (N=424)
Respiratory disorders		
Rhinitis	2	2
Skin and appendages disorders		
Acne	1	0
Vision disorders		
Vision abnormal	2	<1

* Parkinsonism includes extrapyramidal disorder, hypokinesia, and bradycardia. Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Akathisia includes hyperkinesia and akathisia.

Table 4 lists the adverse reactions reported in 2% or more of RISPERDAL®-treated adult patients with bipolar mania in two 3-week, double-blind, placebo-controlled adjuvant therapy trials.

Table 4. Adverse Reactions in ≥2% of RISPERDAL®-Treated Adult Patients with Bipolar Mania in Double-Blind, Placebo-Controlled Adjuvant Therapy Trials

Body System Adverse Reaction	Percentage of Patients Reporting Event RISPERDAL®+ Mood Stabilizer (N=127)	Placebo + Mood Stabilizer (N=126)
Body as a whole – general disorders		
Chest pain	2	2
Fatigue	2	2
Central and peripheral nervous system disorders		
Parkinsonism*	9	4
Dizziness	8	2
Dystonia*	6	3
Akathisia*	6	0
Tremor	5	2
Gastrointestinal system disorders		
Nausea	6	5
Diarrhea	6	4
Saliva increased	4	0
Abdominal pain	2	0
Heart rate and rhythm disorders		
Palpitation	2	0
Metabolic and nutritional disorders		
Weight increase	2	2
Psychiatric disorders		
Somnolence	12	5
Anxiety	4	2
Respiratory disorders		
Pharyngitis	5	2
Coughing	3	1
Skin and appendages disorders		
Rash	2	2
Urinary system disorders		
Urinary incontinence	2	1
Urinary tract infection	2	1

* Parkinsonism includes extrapyramidal disorder, hypokinesia and bradykinesia. Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Akathisia includes hyperkinesia and akathisia.

Pediatric Patients with Bipolar Mania

Table 5 lists the adverse reactions reported in 5% or more of RISPERDAL®-treated pediatric patients with bipolar mania in a 3-week double-blind, placebo-controlled trial.

Table 5. Adverse Reactions in ≥ 5% of RISPERDAL®-Treated Pediatric Patients with Bipolar Mania in Double-Blind, Placebo-Controlled Trials

Body System Adverse Reaction	Percentage of Patients Reporting Event RISPERDAL® 0.5-2.5 mg per day (N=50)	3-6 mg per day (N=61)	Placebo (N=58)
Body as a whole - general disorders			
Fatigue	18	30	3
Central and peripheral nervous system disorders			
Dizziness	16	13	5
Dystonia*	8	13	2
Parkinsonism*	2	7	2
Akathisia*	0	7	2
Gastrointestinal system disorders			
Abdominal pain	18	15	5
Dyspepsia	16	5	3
Nausea	16	13	7
Vomiting	12	10	7
Diarrhea	8	7	2

Table 5. Adverse Reactions in ≥ 5% of RISPERDAL®-Treated Pediatric Patients with Bipolar Mania in Double-Blind, Placebo-Controlled Trials (continued)

Body System Adverse Reaction	Percentage of Patients Reporting Event RISPERDAL® 0.5-2.5 mg per day (N=50)	3-6 mg per day (N=61)	Placebo (N=58)
Heart rate and rhythm disorders			
Tachycardia	0	5	2
Psychiatric disorders			
Somnolence	42	56	19
Appetite increased	4	7	2
Anxiety	0	8	3
Reproductive disorders, female			
Lactation nonpuerperal	2	5	0
Respiratory system disorders			
Rhinitis	14	13	10
Dyspnea	2	5	0
Skin and appendages disorders			
Rash	0	7	2
Urinary system disorders			
Urinary incontinence	0	5	0
Vision disorders			
Vision abnormal	4	7	0

* Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Parkinsonism includes extrapyramidal disorder, hypokinesia, and bradykinesia. Akathisia includes hyperkinesia and akathisia.

6.3 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials - Autistic Disorder

Table 6 lists the adverse reactions reported in 5% or more of RISPERDAL®-treated pediatric patients treated for irritability associated with autistic disorder in two 8-week, double-blind, placebo-controlled trials.

Table 6. Adverse Reactions in ≥ 5% of RISPERDAL®-Treated Pediatric Patients Treated for Irritability Associated with Autistic Disorder in Double-Blind, Placebo-Controlled Trials

Body System Adverse Reaction	Percentage of Patients Reporting Event RISPERDAL® 0.5-4.0 mg per day (N=76)	Placebo (N=80)
Body as a whole - general disorders		
Fatigue	42	13
Fever	20	19
Central and peripheral nervous system disorders		
Dystonia*	12	6
Tremor	12	1
Dizziness	9	3
Parkinsonism*	8	0
Automatism	7	1
Dyskinesia	7	0
Gastrointestinal system disorders		
Vomiting	25	21
Saliva increased	22	6
Constipation	21	8
Mouth dry	13	6
Nausea	8	8
Heart rate and rhythm disorders		
Tachycardia	7	0
Metabolic and nutritional disorders		
Weight increase	5	0
Psychiatric disorders		
Somnolence	67	23
Appetite increased	49	19
Anxiety	16	15
Anorexia	8	8
Confusion	5	0
Respiratory system disorders		
Rhinitis	36	23
Upper respiratory tract infection	34	15
Coughing	24	18
Skin and appendages disorders		
Rash	11	8
Urinary system disorders		
Urinary incontinence	22	20

* Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Parkinsonism includes extrapyramidal disorder, hypokinesia, and bradycardia.

6.4 Other Adverse Reactions Observed During the Premarketing Evaluation of RISPERDAL®

The following adverse reactions occurred in < 1% of the adult patients and in < 5% of the pediatric patients treated with RISPERDAL® in the above double-blind, placebo-controlled clinical trial data sets. In addition, the following also includes adverse reactions

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reported in RISPERDAL®-treated patients who participated in other studies, including double-blind, active-controlled and open-label studies in schizophrenia and bipolar mania studies in pediatric patients with psychiatric disorders other than schizophrenia, bipolar mania, or autistic disorder, and studies in elderly patients with dementia.

Body as a Whole, General Disorders: edema peripheral, pain, influenza-like symptoms, leg pain, malaise, allergy, crying abnormal, allergic reaction, rigors, allergy aggravated, anaphylactoid reaction, hypothermia

Central Nervous System Disorders: gait abnormal, speech disorder, coma, ataxia, dysphonia, stupor, cramps legs, vertigo, hypoesthesia, tardive dyskinesia, neuroleptic malignant syndrome

Endocrine Disorders: hyperprolactinemia, gynecomastia

Gastrointestinal System Disorders: dysphagia, flatulence

Heart Rate and Rhythm Disorders: AV block, bundle branch block

Liver and Biliary Disorders: SGPT increased, hepatic enzymes increased

Metabolic and Nutritional Disorders: thirst, hyperglycemia, xerophthalmia, generalized edema, diabetes mellitus aggravated, diabetic coma

Musculoskeletal Disorders: muscle weakness, rhabdomyolysis

Platelet, Bleeding, and Clotting Disorders: purpura

Psychiatric Disorders: insomnia, agitation, emotional lability, apathy, nervousness, concentration impaired, impotence, decreased libido

Reproductive Disorders, Female: amenorrhea, menstrual disorder, leukorrhea

Reproductive Disorders, Male: ejaculation disorder, abnormal sexual function, priapism

Resistance Mechanism Disorders: otitis media, viral infection

Respiratory Disorders: respiratory disorder

Skin and Appendages Disorders: skin ulceration, skin discoloration, rash erythematous, skin exfoliation, rash maculopapular, erythema multiforme

Urinary Disorders: micturition frequency

Vascular Disorders: cerebrovascular disorder

Vision Disorders: conjunctivitis

White Cell Disorders: leucopenia, granulocytopenia

6.5 Discontinuations Due to Adverse Reactions

Schizophrenia - Adults

Approximately 7% (39/564) of RISPERDAL®-treated patients in double-blind, placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% (10/225) who were receiving placebo. The adverse reactions associated with discontinuation in 2 or more RISPERDAL®-treated patients were:

Table 7. Adverse Reactions Associated With Discontinuation in 2 or More RISPERDAL®-Treated Adult Patients in Schizophrenia Trials

	RISPERDAL®		
Adverse Reaction	2-8 mg/day (N=366)	>8-16 mg/day (N=198)	Placebo (N=225)
Dizziness	1.4%	1.0%	0%
Nausea	1.4%	0%	0%
Agitation	1.1%	1.0%	0%
Parkinsonism	0.8%	0%	0%
Somnolence	0.8%	0.5%	0%
Dystonia	0.5%	0%	0%
Abdominal pain	0.5%	0%	0%
Hypotension postural	0.3%	0.5%	0%
Tachycardia	0.3%	0.5%	0%
Akathisia	0%	1.0%	0%

Discontinuation for extrapyramidal symptoms (including Parkinsonism, akathisia, dystonia, and tardive dyskinesia) was 1% in placebo-treated patients, and 3.4% in active control-treated patients in a double-blind, placebo- and active-controlled trial.

Schizophrenia - Pediatrics

Approximately 7% (7/106), of RISPERDAL®-treated patients discontinued treatment due to an adverse event in a double-blind, placebo-controlled trial, compared with 4% (2/54) placebo-treated patients. The adverse reactions associated with discontinuation for at least one RISPERDAL®-treated patient were somnolence (2%), dizziness (2%), anorexia (1%), anxiety (1%), ataxia (1%), hypotension (1%), and palpitation (1%).

Bipolar Mania - Adults

In double-blind, placebo-controlled trials with RISPERDAL® as monotherapy, approximately 6% (25/448) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 5% (19/424) of placebo-treated patients. The adverse reactions associated with discontinuation in RISPERDAL®-treated patients were:

Table 8. Adverse Reactions Associated With Discontinuation in 2 or More RISPERDAL®-Treated Adult Patients in Bipolar Mania Clinical Trials

	RISPERDAL®	
Adverse Reaction	1-6 mg/day (N=448)	Placebo (N=424)
Parkinsonism	0.4%	0%
Somnolence	0.2%	0%
Dizziness	0.2%	0%
Dystonia	0.2%	0%
SGOT increased	0.2%	0.2%
SGPT increased	0.2%	0.2%

Bipolar Mania - Pediatrics

In a double-blind, placebo-controlled trial 12% (13/111) of RISPERDAL®-treated patients discontinued due to an adverse event, compared with 7% (4/58) of placebo-treated patients. The adverse reactions associated with discontinuation in more than one RISPERDAL®-treated pediatric patient were somnolence (5%), nausea (3%), abdominal pain (2%), and vomiting (2%).

Autistic Disorder - Pediatrics

In the two 8-week, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder (n = 156), one RISPERDAL®-treated patient discontinued due to an adverse reaction (Parkinsonism), and one placebo-treated patient discontinued due to an adverse event.

6.6 Dose Dependency of Adverse Reactions in Clinical Trials

Extrapyramidal Symptoms

Data from two fixed-dose trials in adults with schizophrenia provided evidence of dose-relatedness for extrapyramidal symptoms associated with RISPERDAL® treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day), including (1) a Parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	RISPERDAL® 2 mg	RISPERDAL® 6 mg	RISPERDAL® 10 mg	RISPERDAL® 16 mg
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	11%	15%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day):

Dose Groups	RISPERDAL® 1 mg	RISPERDAL® 4 mg	RISPERDAL® 8 mg	RISPERDAL® 12 mg	RISPERDAL® 16 mg
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	11%	17%	18%	20%

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Other Adverse Reactions

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse reactions: somnolence, vision abnormal, dizziness, palpitations, weight increase, erectile dysfunction, ejaculation disorder, sexual function abnormal, fatigue, and skin discoloration.

6.7 Changes in Body Weight

The proportions of RISPERDAL® and placebo-treated adult patients with schizophrenia meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%). In a pool of placebo-controlled 3-week studies in adult patients with acute mania, the incidence of weight increase of ≥ 7% at endpoint was comparable in the RISPERDAL® (2.5%) and placebo (2.4%) groups, and was slightly higher in the active-control group (3.5%).

Changes in body weight were also evaluated in pediatric patients *[see Use in Specific Populations (8.4)]*

6.8 Changes in ECG

Between-group comparisons for pooled placebo-controlled trials in adults revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute). In pooled placebo-controlled acute mania trials in adults, there were small decreases in mean heart rate, similar among all treatment groups.

In the two placebo-controlled trials in children and adolescents with autistic disorder (aged 5 – 16 years) mean changes in heart rate were an increase of 8.4 beats per minute in the RISPERDAL® groups and 6.5 beats per minute in the placebo group. There were no other notable ECG changes.

In a placebo-controlled acute mania trial in children and adolescents (aged 10 – 17 years), there were no significant changes in ECG parameters, other than the effect of RISPERDAL® to transiently increase pulse rate (< 6 beats per minute). In two controlled schizophrenia trials in adolescents (aged 13 – 17 years), there were no clinically meaningful changes in ECG parameters including corrected QT intervals between treatment groups or within treatment groups over time.

6.9 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of risperidone; because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency: agranulocytosis, alopecia, anaphylactic reaction, angioedema, atrial fibrillation, diabetic ketoacidosis in

reported in RISPERDAL®-treated patients who participated in other studies, including double-blind, active-controlled and open-label studies in schizophrenia and bipolar mania studies in pediatric patients with psychiatric disorders other than schizophrenia, bipolar mania, or autistic disorder, and studies in elderly patients with dementia.

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Nausea	1.4%	0%	0%
Agitation	1.1%	1.0%	0%
Parkinsonism	0.8%	0%	0%
Somnolence	0.8%	0.5%	0%
Dystonia	0.5%	0%	0%
Abdominal pain	0.5%	0%	0%
Hypotension postural	0.3%	0.5%	0%
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Akathisia	0%	1.0%	0%

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Dose Groups	Placebo	RISPERDAL® 2 mg	RISPERDAL® 6 mg	RISPERDAL® 10 mg	RISPERDAL® 16 mg
Parkinsonism	1.2	0.9	1.8	2.4	2.6
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Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day):

Dose Groups	RISPERDAL® 1 mg	RISPERDAL® 4 mg	RISPERDAL® 8 mg	RISPERDAL® 12 mg	RISPERDAL® 16 mg
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Changes in body weight were also evaluated in pediatric patients *[see Use in Specific Populations (8.4)]*

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Between-group comparisons for pooled placebo-controlled trials in adults revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute). In pooled placebo-controlled acute mania trials in adults, there were small decreases in mean heart rate, similar among all treatment groups.

In the two placebo-controlled trials in children and adolescents with autistic disorder (aged 5 – 16 years) mean changes in heart rate were an increase of 8.4 beats per minute in the RISPERDAL® groups and 6.5 beats per minute in the placebo group. There were no other notable ECG changes.

In a placebo-controlled acute mania trial in children and adolescents (aged 10 – 17 years), there were no significant changes in ECG parameters, other than the effect of RISPERDAL® to transiently increase pulse rate (< 6 beats per minute). In two controlled schizophrenia trials in adolescents (aged 13 – 17 years), there were no clinically meaningful changes in ECG parameters including corrected QT intervals between treatment groups or within treatment groups over time.

6.9 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of risperidone; because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency: agranulocytosis, alopecia, anaphylactic reaction, angioedema, atrial fibrillation, diabetic ketoacidosis in

the placebo group). A similar trend was observed in the mean change from baseline in body mass index.

When treating pediatric patients with RISPERDAL® for any indication, weight gain should be assessed against that expected with normal growth. *[See also Adverse Reactions (6.7)]*

Somnolence

Somnolence was frequently observed in placebo-controlled clinical trials of pediatric patients with autistic disorder. Most cases were mild or moderate in severity. These events were most often of early onset with peak incidence occurring during the first two weeks of treatment, and transient with a median duration of 16 days. Somnolence was the most commonly observed adverse event in the clinical trial of bipolar disorder in children and adolescents, as well as in the schizophrenia trials in adolescents. As was seen in the autistic disorder trials, these events were most often of early onset and transient in duration. *[See also Adverse Reactions (6.1, 6.2, 6.3)]* Patients experiencing persistent somnolence may benefit from a change in dosing regimen *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

Hyperprolactinemia, Growth, and Sexual Maturation

RISPERDAL® has been shown to elevate prolactin levels in children and adolescents as well as in adults *[see Warnings and Precautions (5.6)]*. In double-blind, placebo-controlled studies of up to 8 weeks duration in children and adolescents (aged 5 to 17 years) with autistic disorder or psychiatric disorders other than autistic disorder, schizophrenia, or bipolar mania, 49% of patients who received RISPERDAL® had elevated prolactin levels compared to 2% of patients who received placebo. Similarly, in placebo-controlled trials in children and adolescents (aged 10 to 17 years) with bipolar disorder, or adolescents (aged 13 to 17 years) with schizophrenia, 82–87% of patients who received RISPERDAL® had elevated levels of prolactin compared to 3–7% of patients on placebo. Increases were dose-dependent and generally greater in females than in males across indications.

In clinical trials in 1885 children and adolescents, galactorrhea was reported in 0.8% of RISPERDAL®-treated patients and gynecomastia was reported in 2.3% of RISPERDAL®-treated patients.

The long-term effects of RISPERDAL® on growth and sexual maturation have not been fully evaluated.

8.5 Geriatric Use

Clinical studies of RISPERDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.4, 2.5)]*. While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg twice daily followed by careful titration *[see Warnings and Precautions (5.7)]*. Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration (2.4)]*.

Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis

In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus RISPERDAL® when compared to patients treated with RISPERDAL® alone or with placebo plus furosemide. No pathological mechanism has been identified to explain this finding; and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of RISPERDAL® regardless of concomitant use with furosemide. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. *[See Boxed Warning and Warnings and Precautions (5.1)]*

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

RISPERDAL® (risperidone) is not a controlled substance.

9.2 Abuse

RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

9.3 Dependence

RISPERDAL® has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

10 OVERDOSAGE

10.1 Human Experience

Premarketing experience included eight reports of acute RISPERDAL® overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse reactions reported since market introduction related to RISPERDAL® overdose include prolonged QT interval and convulsions. Torsade de pointes has been reported in association with combined overdose of RISPERDAL® and paroxetine.

10.2 Management of Overdosage

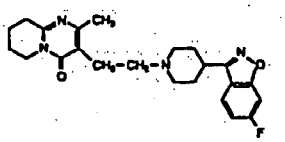
In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Because of the rapid disintegration of RISPERDAL® M-TAB® Orally Disintegrating Tablets, pill fragments may not appear in gastric contents obtained with lavage.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

11 DESCRIPTION

RISPERDAL® contains risperidone, a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® Tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. RISPERDAL® tablets contain the following inactive ingredients: colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). The 0.25 mg, 0.5 mg, 2 mg, 3 mg, and 4 mg tablets also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. RISPERDAL® Oral Solution contains the following inactive ingredients: tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL® M-TAB® Orally Disintegrating Tablets are available in 0.5 mg (light coral), 1 mg (light coral), 2 mg (coral), 3 mg (coral), and 4 mg (coral) strengths. RISPERDAL® M-TAB® Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil. In addition, the 2 mg, 3 mg, and 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablets contain xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of RISPERDAL®, as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10^{-4} M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

12.2 Pharmacodynamics

The clinical effect from RISPERDAL® results from the combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone *[see Clinical Pharmacology*

R. 3123

(12.3)]. Antagonism at receptors other than D_2 and $5HT_2$ *[see Clinical Pharmacology (12.1)]* may explain some of the other effects of RISPERDAL®.

12.3 Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Pharmacokinetic studies showed that RISPERDAL® M-TAB® Orally Disintegrating Tablets and RISPERDAL® Oral Solution are bioequivalent to RISPERDAL® Tablets.

Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg twice daily). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, RISPERDAL® can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism and Drug Interactions

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through *N*-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone *[see Drug Interactions (7.12)]*. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) of poor metabolizers given RISPERDAL® do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., carbamazepine, phenytoin, rifampin, and phenobarbital) with RISPERDAL® may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone *[see Drug Interactions (7.11)]*. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely *[see Drug Interactions 7.12)]*.

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of 14C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease *[see Dosage and Administration (2.4) and Warnings and Precautions (5.16)]*.

Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease *[see Dosage and Administration (2.4) and Warnings and Precautions (5.16)]*.

Elderly

In healthy elderly subjects, renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients *[see Dosage and Administration (2.4)]*.

Pediatric

The pharmacokinetics of risperidone and 9-hydroxyrisperidone in children were similar to those in adults after correcting for the difference in body weight.

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63 mg/kg, 2.5 mg/kg, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) for schizophrenia (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

			Multiples of Maximum Human Dose in mg/m² (mg/kg)	
Tumor Type	Species	Sex	Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6.0 (37.5)	1.5 (9.4)
Mammary gland neoplasm, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5-6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown *[see Warnings and Precautions (5.6)]*.

Mutagenesis

No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, *in vitro* rat hepatocyte DNA-repair assay, *in vivo* micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility

Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m² basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the MRHD on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

14 CLINICAL STUDIES

14.1 Schizophrenia

Adults

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4- to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS) were employed.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (twice-daily schedule), RISPERDAL® was generally superior to

R. 3124

placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2 mg/day, 6 mg/day, 10 mg/day, and 16 mg/day, on a twice-daily schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1 mg/day, 4 mg/day, 8 mg/day, 12 mg/day, and 16 mg/day, on a twice-daily schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a once-daily schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (>20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

Pediatrics

The efficacy of RISPERDAL® in the treatment of schizophrenia in adolescents aged 13–17 years was demonstrated in two short-term (6 and 8 weeks), double-blind controlled trials. All patients met DSM-IV diagnostic criteria for schizophrenia and were experiencing an acute episode at time of enrollment. In the first trial (study #1), patients were randomized into one of three treatment groups: RISPERDAL® 1-3 mg/day (n = 55, mean modal dose = 2.6 mg), RISPERDAL® 4-6 mg/day (n = 51, mean modal dose = 5.3 mg), or placebo (n = 54). In the second trial (study #2), patients were randomized to either RISPERDAL® 0.15-0.6 mg/day (n = 132, mean modal dose = 0.5 mg) or RISPERDAL® 1.5–6 mg/day (n = 125, mean modal dose = 4 mg). In all cases, study medication was initiated at 0.5 mg/day (with the exception of the 0.15-0.6 mg/day group in study #2, where the initial dose was 0.05 mg/day) and titrated to the target dosage range by approximately Day 7. Subsequently, dosage was increased to the maximum tolerated dose within the target dose range by Day 14. The primary efficacy variable in all studies was the mean change from baseline in total PANSS score.

Results of the studies demonstrated efficacy of RISPERDAL® in all dose groups from 1-6 mg/day compared to placebo, as measured by significant reduction of total PANSS score. The efficacy on the primary parameter in the 1-3 mg/day group was comparable to the 4-6 mg/day group in study #1, and similar to the efficacy demonstrated in the 1.5–6 mg/day group in study #2. In study #2, the efficacy in the 1.5-6 mg/day group was statistically significantly greater than that in the 0.15-0.6 mg/day group. Doses higher than 3 mg/day did not reveal any trend towards greater efficacy.

14.2 Bipolar Mania - Monotherapy

Adults

The efficacy of RISPERDAL® in the treatment of acute manic or mixed episodes was established in two short-term (3-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (YMRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the YMRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=246), limited to patients with manic episodes, which involved a dose range of RISPERDAL® 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 4.1 mg/day), RISPERDAL® was superior to placebo in the reduction of YMRS total score.

(2) In another 3-week placebo-controlled trial (n=286), which involved a dose range of 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 5.6 mg/day), RISPERDAL® was superior to placebo in the reduction of YMRS total score.

Pediatrics

The efficacy of RISPERDAL® in the treatment of mania in children or adolescents with Bipolar I disorder was demonstrated in a 3-week, randomized, double-blind, placebo-controlled, multicenter trial including patients ranging in ages from 10 to 17 years who were experiencing a manic or mixed episode of bipolar I disorder. Patients were randomized into one of three treatment groups: RISPERDAL® 0.5-2.5 mg/day (n = 50, mean modal dose = 1.9 mg), RISPERDAL® 3-6 mg/day (n = 61, mean modal dose = 4.7 mg), or placebo (n = 58). In all cases, study medication was initiated at 0.5 mg/day and titrated to the target dosage range by Day 7, with further increases in dosage to the maximum tolerated dose within the targeted dose range by Day 10. The primary rating instrument used for assessing efficacy in this study was the mean change from baseline in the total YMRS score.

Results of this study demonstrated efficacy of RISPERDAL® in both dose groups compared with placebo, as measured by significant reduction of total YMRS score. The efficacy on the primary parameter in the 3-6 mg/day dose group was comparable to the 0.5-2.5 mg/day dose group. Doses higher than 2.5 mg/day did not reveal any trend towards greater efficacy.

14.3 Bipolar Mania – Combination Therapy

The efficacy of RISPERDAL® with concomitant lithium or valproate in the treatment of acute manic or mixed episodes was established in one controlled trial in adult patients who met the DSM-IV criteria for Bipolar I Disorder. This trial included patients with or without psychotic features and with or without a rapid-cycling course.

(1) In this 3-week placebo-controlled combination trial, 148 in- or outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL®, placebo, or an active comparator, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.8 mg/day), combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.4 mEq/L or 50 mcg/mL to 120 mcg/mL, respectively) was superior to lithium or valproate alone in the reduction of YMRS total score.

(2) In a second 3-week placebo-controlled combination trial, 142 in- or outpatients on lithium, valproate, or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL® or placebo, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.7 mg/day), combined with lithium, valproate, or carbamazepine (in therapeutic ranges of 0.6 mEq/L to 1.4 mEq/L for lithium, 50 mcg/mL to 125 mcg/mL for valproate, or 4-12 mcg/mL for carbamazepine, respectively) was not superior to lithium, valproate, or carbamazepine alone in the reduction of YMRS total score. A possible explanation for the failure of this trial was induction of risperidone and 9-hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxyrisperidone.

14.4 Irritability Associated with Autistic Disorder

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of irritability associated with autistic disorder was established in two 8-week, placebo-controlled trials in children and adolescents (aged 5 to 16 years) who met the DSM-IV criteria for autistic disorder. Over 90% of these subjects were under 12 years of age and most weighed over 20 kg (16-104.3 kg).

Efficacy was evaluated using two assessment scales: the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression - Change (CGI-C) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I). The ABC-I subscale measured the emotional and behavioral symptoms of autism, including aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. The CGI-C rating at endpoint was a co-primary outcome measure in one of the studies.

The results of these trials are as follows:

(1) In one of the 8-week, placebo-controlled trials, children and adolescents with autistic disorder (n=101), aged 5 to 16 years, received twice daily doses of placebo or RISPERDAL® 0.5-3.5 mg/day on a weight-adjusted basis. RISPERDAL®, starting at 0.25 mg/day or 0.5 mg/day depending on baseline weight (< 20 kg and ≥ 20 kg, respectively) and titrated to clinical response (mean modal dose of 1.9 mg/day, equivalent to 0.06 mg/kg/day), significantly improved scores on the ABC-I subscale and on the CGI-C scale compared with placebo.

(2) In the other 8-week, placebo-controlled trial in children with autistic disorder (n=55), aged 5 to 12 years, RISPERDAL® 0.02 to 0.06 mg/kg/day given once or twice daily, starting at 0.01 mg/kg/day and titrated to clinical response (mean modal dose of 0.05 mg/kg/day, equivalent to 1.4 mg/day), significantly improved scores on the ABC-I subscale compared with placebo.

Long-Term Efficacy

Following completion of the first 8-week double-blind study, 63 patients entered an open-label study extension where they were treated with RISPERDAL® for 4 or 6 months (depending on whether they received RISPERDAL® or placebo in the double-blind study). During this open-label treatment period, patients were maintained on a mean modal dose of RISPERDAL® of 1.8-2.1 mg/day (equivalent to 0.05 - 0.07 mg/kg/day).

Patients who maintained their positive response to RISPERDAL® (response was defined as ≥ 25% improvement on the ABC-I subscale and a CGI-C rating of 'much improved' or 'very much improved') during the 4-6 month open-label treatment phase for about 140 days, on average, were randomized to receive RISPERDAL® or placebo during an 8-week, double-blind withdrawal study (n=39 of the 63 patients). A pre-planned interim analysis of data from patients who completed the withdrawal study (n=32), undertaken by an independent Data Safety Monitoring Board, demonstrated a significantly lower relapse rate in the RISPERDAL® group compared with the placebo group. Based on the interim analysis results, the study was terminated due to demonstration of a statistically significant effect on relapse prevention. Relapse was defined as ≥ 25% worsening on the most recent assessment of the ABC-I subscale (in relation to baseline of the randomized withdrawal phase).

16 HOW SUPPLIED/STORAGE AND HANDLING

RISPERDAL® (risperidone) Tablets

RISPERDAL® (risperidone) Tablets are imprinted "JANSSEN" on one side and either "Ris 0.25", "Ris 0.5", "R1", "R2", "R3", or "R4" according to their respective strengths.

0.25 mg dark yellow, capsule-shaped tablets: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50, hospital unit dose blister packs of 100 NDC 50458-301-01.

0.5 mg red-brown, capsule-shaped tablets: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50, hospital unit dose blister packs of 100 NDC 50458-302-01.

1 mg white, capsule-shaped tablets: bottles of 60 NDC 50458-300-06, hospital unit dose blister packs of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange, capsule-shaped tablets: bottles of 60 NDC 50458-320-06, hospital unit dose blister packs of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

R. 3125

3 mg yellow, capsule-shaped tablets: bottles of 60 NDC 50458-330-06, hospital unit dose blister packs of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green, capsule-shaped tablets: bottles of 60 NDC 50458-350-06, hospital unit dose blister packs of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) Oral Solution

RISPERDAL® (risperidone) 1 mg/mL Oral Solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

RISPERDAL® M-TAB® (risperidone) Orally Disintegrating Tablets

RISPERDAL® M-TAB® (risperidone) Orally Disintegrating Tablets are etched on one side with "R0.5", "R1", "R2", "R3", or "R4" according to their respective strengths. RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are packaged in blister packs of 4 (2 X 2) tablets. Orally Disintegrating Tablets 3 mg and 4 mg are packaged in a child-resistant pouch containing a blister with 1 tablet.

0.5 mg light coral, round, biconvex tablets: 7 blister packages (4 tablets each) per box, NDC 50458-395-28, long-term care blister packaging of 30 tablets NDC 50458-395-30.

1 mg light coral, square, biconvex tablets: 7 blister packages (4 tablets each) per box, NDC 50458-315-28, long-term care blister packaging of 30 tablets NDC 50458-315-30.

2 mg coral, square, biconvex tablets: 7 blister packages (4 tablets each) per box, NDC 50458-325-28.

3 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-335-28.

4 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-355-28.

Storage and Handling

RISPERDAL® Tablets should be stored at controlled room temperature 15°- 25°C (59°-77°F).

Protect from light and moisture.

RISPERDAL® 1 mg/mL Oral Solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.

RISPERDAL® M-TAB® Orally Disintegrating Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F).

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

17.1 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration *[see Warnings and Precautions (5.7)]*.

17.2 Interference with Cognitive and Motor Performance

Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely *[see Warnings and Precautions (5.8)]*.

17.3 Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy *[see Use in Specific Populations (8.1)]*.

17.4 Nursing

Patients should be advised not to breast-feed an infant if they are taking RISPERDAL® *[see Use in Specific Populations (8.3)]*.

17.5 Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions *[see Drug Interactions (7)]*.

17.6 Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL® *[see Drug Interactions (7.1)]*.

17.7 Phenylketonurics

Phenylalanine is a component of aspartame. Each 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.84 mg phenylalanine; each 3 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.63 mg phenylalanine; each 2 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.42 mg phenylalanine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

7503238
Revised August 2008
©Ortho-McNeil-Janssen Pharmaceuticals, Inc. 2007

RISPERDAL® Tablets are manufactured by:
Janssen Ortho LLC, Gurabo, Puerto Rico 00778
RISPERDAL® Oral Solution is manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium
RISPERDAL® M-TAB® Orally Disintegrating Tablets are manufactured by:
Janssen Ortho LLC, Gurabo, Puerto Rico 00778

RISPERDAL® Tablets, RISPERDAL® M-TAB® Orally Disintegrating Tablets, and Oral Solution are manufactured for:
Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560



01RS2013

JURE 01150081
Confidential/Produced in Litigation Pursuant to Protective Order

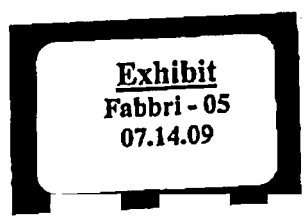
Diabetes Package Insert Revision

Field Training
November, 2003

For Training Purposes Only
Not To Be Used in a Selling Situation

R. 3127

Plaintiff Ex. 357



General Background

All atypical manufacturers, including Janssen, received an FDA request to add a warning to the PI regarding hyperglycemia and diabetes mellitus

Request was based on case reports and epidemiologic studies suggesting an increased risk of glucose abnormalities

Relationship is not completely understood

- Increasing incidence of diabetes in the general population
- Elevated risk of diabetes in schizophrenic patients

Lilly implemented diabetes warning for Zyprexa in mid-September

Janssen agreed to modified version of class label

Not based upon any new data for RISPERDAL

R. 3128

JJRE 01150082
Confidential/Produced in Litigation Pursuant to Protective Orde

Updated Package Insert

JJRE 01150083
Confidential/Produced in Litigation Pursuant to Protective Order

R. 3129

WARNINGS

Hyperglycemia and Diabetes Mellitus: *Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.*

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should have glucose monitoring undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Diabetes Warning Summary

Hyperglycemia-related adverse events have been reported in patients treated with atypical antipsychotics

The relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood

All patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia

- Patients with diabetes mellitus or have risk factors for diabetes should undergo blood glucose monitoring as outlined in the revised package insert

R. 3130

JJRE 01150084
Confidential/Produced in Litigation Pursuant to Protective Orde

Diabetes Warning Summary (cont.)

The proposed FDA warning included an additional sentence at the end of the first paragraph that stated:

- "The available data are insufficient to provide reliable estimates of differences in hyperglycemia related adverse event risk among the marketed atypical antipsychotics."
- Janssen requested the FDA to remove this sentence based upon epidemiologic studies that demonstrated a low risk of diabetes with Risperdal

The proposed FDA warning also suggested blood glucose testing "at baseline" for patients with risk factors for diabetes

- Risperdal label suggests blood glucose testing "at the beginning of treatment" for patients with risk factors for diabetes

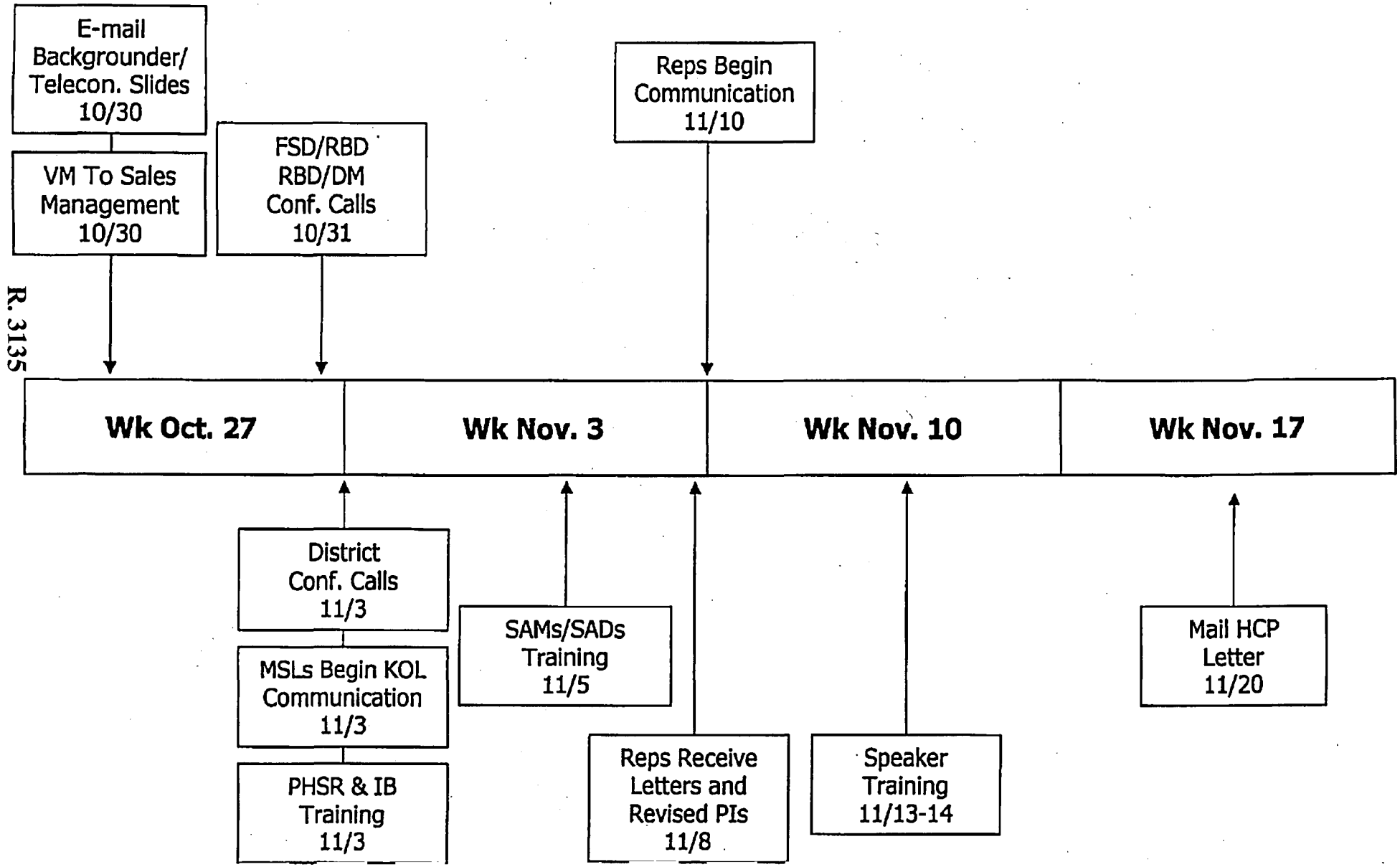
R. 3131

JJRE 01150085
Confidential/Produced in Litigation Pursuant to Protective Order

Communication Plan

JJRE 01150088
Confidential/Produced in Litigation Pursuant to Protective Order

Diabetes Roll-Out Timeline



R. 3135

JJRE 01150089
Confidential/Produced in Litigation Pursuant to Protective Order

Healthcare Provider Letter

JJRE 0115009(
Confidential/Produced in Litigation Pursuant to Protective Orde

Dear Healthcare Provider,

The Food and Drug Administration (FDA) has requested all manufacturers of atypical antipsychotics to include a warning regarding hyperglycemia and diabetes mellitus in their product labeling. In addition to Janssen, the FDA made this request to the following manufacturers:

AstraZeneca – Seroquel® (quetiapine)
Bristol-Myers Squibb – Abilify™ (aripiprazole)
Eli Lilly and Company – Zyprexa® (olanzapine)
Novartis – Clozaril® (clozapine)
Pfizer – Geodon® (ziprasidone)

R.3136

In an effort to keep you updated with the most current product information available for the management of your patients, enclosed please find updated prescribing information for RISPERDAL® (risperidone).

Hyperglycemia-related adverse events have infrequently been reported in patients receiving RISPERDAL. Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research[1-8] suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

For additional information about RISPERDAL or any other Janssen product, please call 1-800-JANSSEN (526-7736) from 9AM to 5PM EST, Monday through Friday.

Who Will Receive Communication?

- Physicians
  - Psychiatrists
  - Neurologists
  - Primary Care
- Pharmacists
- Pharmacies
  - Hospital
  - Managed Care

⇒ **Hand-delivered to called-on healthcare providers, mailed to non called-on audience**

R. 3137

JJRE 01150091
Confidential/Produced in Litigation Pursuant to Protective Order

Sales Direction

Sales representatives should personally deliver a copy of the HCP letter to every called-on customer according to the call plan for one rotation

- If the physician is available, communicate the package insert revision and bridge to selling RISPERDAL
- If the physician is not available, leave letter with the office manager or nurse. On next visit by representative, or any counterpart:
  - ✓check in with physician to ensure receipt of letter and discuss any questions physician may have
  - ✓If physician has not received or reviewed letter, review package insert revision

HCP=Healthcare Professional

R. 3138

JJRE 01150092
Confidential/Produced in Litigation Pursuant to Protective Order

Sales Direction

If HCP has additional questions, refer to Medical Services

Record post call analysis in Siebel

- Utilize drop down menu to document either: delivery of letter and review of new label or delivery of letter only

HCP=Healthcare Professional

R. 3139

JJRE 01150093
Confidential/Produced in Litigation Pursuant to Protective Order

Other Communication Vehicles

Promotional Speakers Bureau

Speakers scheduled to speak for a remaining 2003 program will be trained on new diabetes warning and slides

- Teleconference training
- Updated slide deck will be shipped

Remaining speakers will be trained on diabetes during bipolar mania speaker training

Key Opinion Leaders

Medical Science Liaisons will begin informing Key Opinion Leaders of label change beginning week November 3

R. 3140

JJRE 01150094
Confidential/Produced in Litigation Pursuant to Protective Orde

10/31 Teleconference Times

	FSD/RBD	Host
CNS/HSR/Eldercare/LTC	11:00am-12:00pm	John/Jeni/Christi
Primary Care	11:00am-12:00pm	Carmen/Ed

	RBD/DM	Host
Eldercare/LTC Group	12:00 pm-1:00pm	Riley/Jeni/Brian
CNS/HSR	1:00pm-2:00pm	John/Jeni/Christi
Primary Care	12:00pm-1:00pm 1:00pm-2:00pm 1:00pm-2:00pm	Carmen/Ed Carmen Riley/Ed

JJRE 01150095
Confidential/Produced in Litigation Pursuant to Protective Order

Diabetes Package Insert Revision

Field Training
November, 2003

For Training Purposes Only
Not To Be Used in a Selling Situation

JJRE 01150096
Confidential/Produced in Litigation Pursuant to Protective Order
R. 3142

General Background

- All atypical manufacturers, including Janssen, received an FDA request to add a warning to the PI regarding hyperglycemia and diabetes mellitus
- Request was based on case reports and epidemiologic studies suggesting an increased risk of glucose abnormalities
- Relationship is not completely understood
  - Increasing incidence of diabetes in the general population
  - Elevated risk of diabetes in schizophrenic patients
- Lilly implemented diabetes warning for Zyprexa in mid-September
- Janssen agreed to modified version of class label
- Not based upon any new data for RISPERDAL

JJRE 0115009
Confidential/Produced in Litigation Pursuant to Protective Orde
R. 3143

Updated Package Insert

WARNINGS

Hyperglycemia and Diabetes Mellitus: *Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.*

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should have glucose monitoring undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

JJRE 01150098
Confidential/Produced in Litigation Pursuant to Protective Order
R. 3144

Diabetes Warning Summary

- Hyperglycemia-related adverse events have been reported in patients treated with atypical antipsychotics
- The relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood
- All patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia
  - Patients with diabetes mellitus or have risk factors for diabetes should undergo blood glucose monitoring as outlined in the revised package insert

JJRE 0115009
Confidential/Produced in Litigation Pursuant to Protective Orde
R. 3145

Diabetes Warning Summary (cont.)

- The proposed FDA warning included an additional sentence at the end of the first paragraph that stated:
  - "The available data are insufficient to provide reliable estimates of differences in hyperglycemia related adverse event risk among the marketed atypical antipsychotics."
  - Janssen requested the FDA to remove this sentence based upon epidemiologic studies that demonstrated a low risk of diabetes with Risperdal
- The proposed FDA warning also suggested blood glucose testing "at baseline" for patients with risk factors for diabetes
  - Risperdal label suggests blood glucose testing "at the beginning of treatment" for patients with risk factors for diabetes

JJRE 01150100
Confidential/Produced in Litigation Pursuant to Protective Order
R. 3146

JJRE 01150101
Confidential/Produced in Litigation Pursuant to Protective Order
R. 3147

RISPERDAL and Diabetes

- ADVERSE REACTIONS as noted in the RISPERDAL Package Insert:
  - Metabolic and Nutritional Disorders
    - Infrequent (0.1%-1%): *Diabetes Mellitus*
    - Rare (< 0.1%): *Hypoglycemia*
  - Urinary System Disorder
    - Frequent (> 1%): *Polyuria/Polydipsia**
  - Postintroduction Reports
    - *Diabetes mellitus aggravated, including diabetic ketoacidosis; hyperglycemia*

*Incidence based on elicited reports

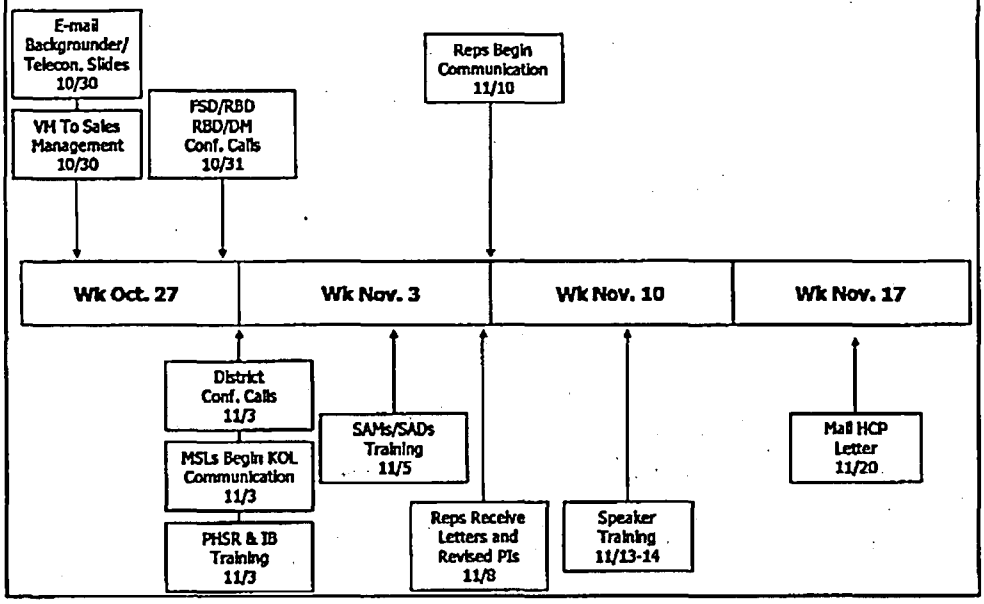
Causal relationship has not been established.

JJRE 01150102
Confidential/Produced in Litigation Pursuant to Protective Order
R. 3148

Communication Plan

JJRE 01150103
Confidential/Produced in Litigation Pursuant to Protective Order
R. 3149

Diabetes Roll-Out Timeline



JJRE 01150104
Confidential/Produced in Litigation Pursuant to Protective Order
R. 3150

Healthcare Provider Letter

Dear Healthcare Provider,

The Food and Drug Administration (FDA) has requested all manufacturers of atypical antipsychotics to include a warning regarding hyperglycemia and diabetes mellitus in their product labeling. In addition to Janssen, the FDA made this request to the following manufacturers:

AstraZeneca – Seroquel® (quetiapine)
Bristol-Myers Squibb – Abilify™ (aripiprazole)
Eli Lilly and Company – Zyprexa® (olanzapine)
Novartis – Clozaril® (clozapine)
Pfizer – Geodon® (ziprasidone)

In an effort to keep you updated with the most current product information available for the management of your patients, enclosed please find updated prescribing information for RISPERDAL® (risperidone).

Hyperglycemia-related adverse events have infrequently been reported in patients receiving RISPERDAL. Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research[1-6] suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

For additional information about RISPERDAL or any other Janssen product, please call 1-800-JANSSEN (526-7736) from 9AM to 6PM EST, Monday through Friday.

JJRE 0115010
Confidential/Produced in Litigation Pursuant to Protective Orde
R. 3151

Who Will Receive Communication?

- Physicians
  - Psychiatrists
  - Neurologists
  - Primary Care
- Pharmacists
- Pharmacies
  - Hospital
  - Managed Care

⇒ **Hand-delivered to called-on healthcare providers, mailed to non called-on audience**

JJRE 01150106
Confidential/Produced in Litigation Pursuant to Protective Order
R. 3152

Sales Direction

- Sales representatives should personally deliver a copy of the HCP letter to every called-on customer according to the call plan for one rotation
  - If the physician is available, communicate the package insert revision and bridge to selling RISPERDAL
  - If the physician is not available, leave letter with the office manager or nurse. On next visit by representative, or any counterpart:
    - ✓check in with physician to ensure receipt of letter and discuss any questions physician may have
    - ✓If physician has not received or reviewed letter, review package insert revision

HCP=Healthcare Professional

JJRE 01150107
Confidential/Produced in Litigation Pursuant to Protective Order
R. 5155

Sales Direction

- If HCP has additional questions, refer to Medical Services
- Record post call analysis in Siebel
  - Utilize drop down menu to document either: delivery of letter and review of new label or delivery of letter only

HCP=Healthcare Professional

JJRE 01150108
Confidential/Produced in Litigation Pursuant to Protective Order
R. 3154

Other Communication Vehicles

Promotional Speakers Bureau

- Speakers scheduled to speak for a remaining 2003 program will be trained on new diabetes warning and slides
  - Teleconference training
  - Updated slide deck will be shipped
- Remaining speakers will be trained on diabetes during bipolar mania speaker training

Key Opinion Leaders

- Medical Science Liaisons will begin informing Key Opinion Leaders of label change beginning week November 3

JJRE 0115010
Confidential/Produced in Litigation Pursuant to Protective Ord
R. 3153

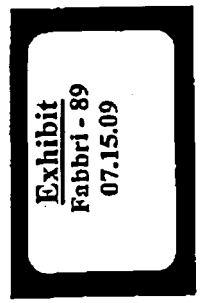
10/31 Teleconference Times

	FSD/RBD	Host
CNS/HSR/Eldercare/LTC	11:00am-12:00pm	John/Jeni/Christi
Primary Care	11:00am-12:00pm	Carmen/Ed

	RBD/DM	Host
Eldercare/LTC Group	12:00 pm-1:00pm	Riley/Jeni/Brian
CNS/HSR	1:00pm-2:00pm	John/Jeni/Christi
Primary Care	12:00pm-1:00pm 1:00pm-2:00pm 1:00pm-2:00pm	Carmen/Ed Carmen Riley/Ed

JJRE 01150110
Confidential/Produced in Litigation Pursuant to Protective Order
R. 3156

JJRE 06826907
Confidential/Produced in Litigation Pursuant to Protective Or



Field Training
October 31, 2003

For Training Purposes Only
Not To Be Used in a Selling Situation

R. 3157

Plaintiff Ex. 387

Agenda

Introduction

Diabetes Label Revision

RISPERDAL® CONSTA™ QA

R. 3158

JJRE 0682690
Confidential/Produced in Litigation Pursuant to Protective Orde

Diabetes Label Revision

Confidential/Produced in Litigation Pursuant to Protective C

General Background

All atypical manufacturers, including Janssen, received an FDA request to add a warning to the PI regarding hyperglycemia and diabetes mellitus

Request was based on case reports and epidemiologic studies suggesting an increased risk of glucose abnormalities

Relationship is not completely understood

- Increasing incidence of diabetes in the general population
- Elevated risk of diabetes in schizophrenic patients

Lilly implemented diabetes warning for Zyprexa in mid-September

Janssen agreed to modified version of class label

Not based upon any new data for RISPERDAL

R. 3160

JJRE 0682691
Confidential/Produced in Litigation Pursuant to Protective O

Updated Package Insert

JJRE 0682691
Confidential/Produced in Litigation Pursuant to Protective Orde

R. 3161

WARNINGS

Hyperglycemia and Diabetes Mellitus: *Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.*

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Diabetes Warning Summary

Hyperglycemia-related adverse events have been reported in patients treated with atypical antipsychotics

- The relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood

All patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia

  - Patients who develop symptoms of hyperglycemia, have diabetes mellitus or have risk factors for diabetes should undergo blood glucose monitoring as outlined in the revised package insert

R. 3162

JJRE 06826917
Confidential/Produced in Litigation Pursuant to Protective O

Diabetes Warning Summary (cont.)

- The proposed FDA warning included an additional sentence at the end of the first paragraph that stated:
  - "The available data are insufficient to provide reliable estimates of differences in hyperglycemia related adverse event risk among the marketed atypical antipsychotics."
  - Upon Janssen's request, the FDA agreed to remove this sentence based upon epidemiologic studies that demonstrated a low risk of diabetes with Risperdal
- The proposed FDA warning also suggested blood glucose testing "at baseline" for patients with risk factors for diabetes
  - Risperdal label suggests blood glucose testing "at the beginning of treatment" for patients with risk factors for diabetes

R. 3163

JJRE 0682691
Confidential/Produced in Litigation Pursuant to Protective Orde

RISPERDAL and Diabetes

	RISPERDAL	Placebo
Double-blind trials (n=2033)	0%	0%
Double-blind + open-label trials (n=2607)	0.2%	N/A

R. 3164

JJRE 0682691
Confidential/Produced in Litigation Pursuant to Protective O

RISPERDAL and Diabetes

ADVERSE REACTIONS as noted in the RISPERDAL Package Insert:

- Metabolic and Nutritional Disorders
  - Infrequent (0.1%-1%): *Diabetes Mellitus*
  - Rare (< 0.1%): *Hypoglycemia*
- Urinary System Disorder
  - Frequent (> 1%): *Polyuria/Polydipsia**
- Postintroduction Reports
  - *Diabetes mellitus aggravated, including diabetic ketoacidosis; hyperglycemia*

*Incidence based on elicited reports

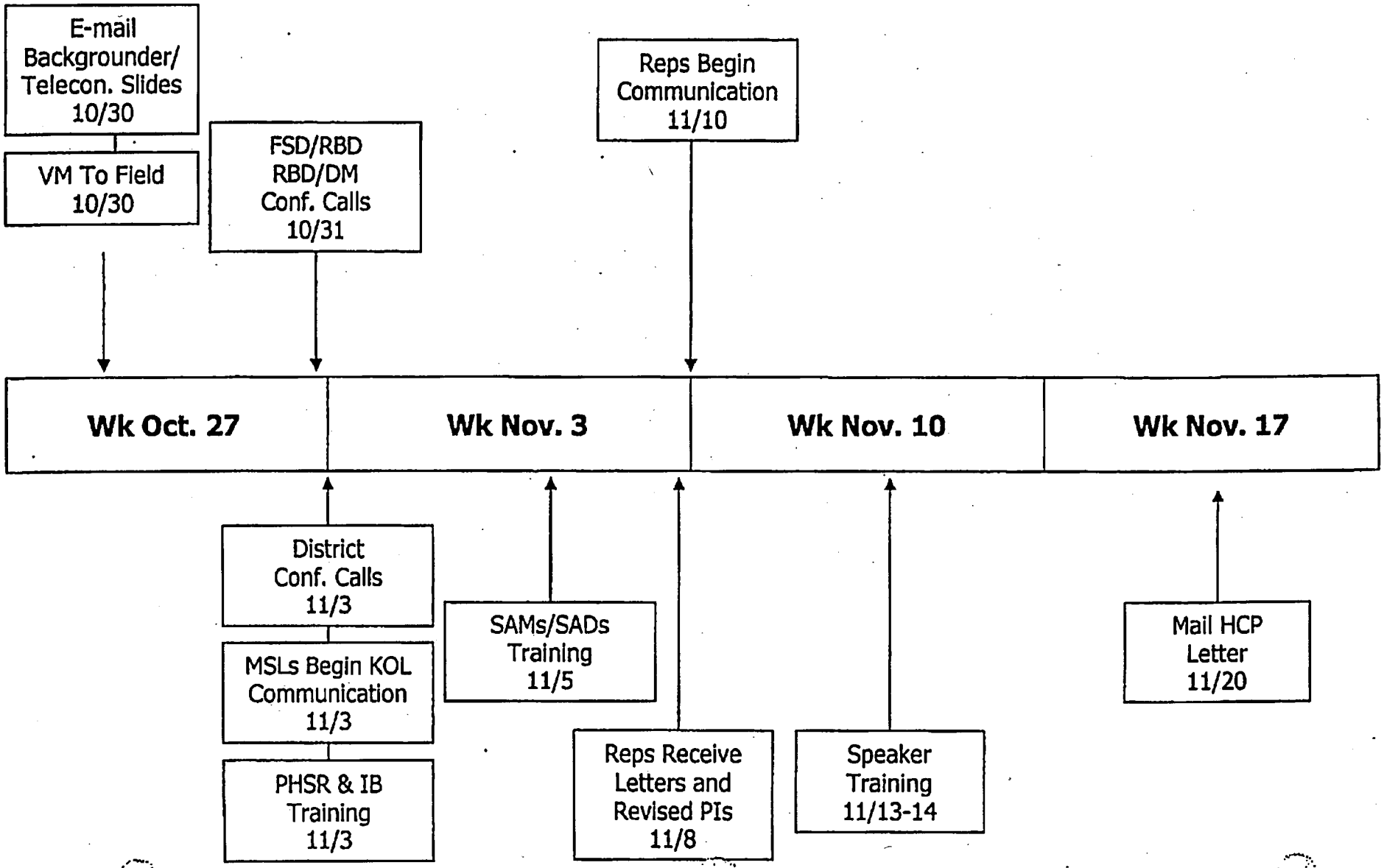
R. 3165

JJRE 0682691
Confidential/Produced in Litigation Pursuant to Protective Orde

Communication Plan

Confidential/Produced in Litigation Pursuant to Protective Orde
JJRE 0682691

Diabetes Roll-Out Timeline



R. 3167

JJRE 0682691
Confidential/Produced in Litigation Pursuant to Protective Orde

Healthcare Provider Letter

Dear Healthcare Provider,

The Food and Drug Administration (FDA) has requested all manufacturers of atypical antipsychotics to include a warning regarding hyperglycemia and diabetes mellitus in their product labeling. In addition to Janssen, the FDA made this request to the following manufacturers:

AstraZeneca – Seroquel® (quetiapine)
Bristol-Myers Squibb – Abilify™ (aripiprazole)
Eli Lilly and Company – Zyprexa® (olanzapine)
Novartis – Clozaril® (clozapine)
Pfizer – Geodon® (ziprasidone)

In an effort to keep you updated with the most current product information available for the management of your patients, enclosed please find updated prescribing information for RISPERDAL® (risperidone).

Hyperglycemia-related adverse events have infrequently been reported in patients receiving RISPERDAL. Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research[1-8] suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

For additional information about RISPERDAL or any other Janssen product, please call 1-800-JANSSEN (526-7736) from 9AM to 5PM EST, Monday through Friday.

R. 3168

JJRE 06826915
Confidential/Produced in Litigation Pursuant to Protective Or

Who Will Receive Communication?

- Physicians
  - Psychiatrists
  - Neurologists
  - Primary Care
- Pharmacists
- Pharmacies
  - Hospital
  - Managed Care

⇒ **Hand-delivered to called-on healthcare providers, mailed to non called-on audience**

R. 3169

JJRE 0682691
Confidential/Produced in Litigation Pursuant to Protective Orde

Sales Direction

Sales representatives should personally deliver a copy of the HCP letter to every called-on customer according to the call plan for one rotation

- If the physician is available, communicate the package insert revision and bridge to selling RISPERDAL
- If the physician is not available, leave letter with the office manager or nurse. On next visit by representative, or any counterpart:
  - ✓check in with physician to ensure receipt of letter and discuss any questions physician may have
  - ✓If physician has not received or reviewed letter, review package insert revision

HCP=Healthcare Professional

R. 3170

JJRE 06826926
Confidential/Produced in Litigation Pursuant to Protective Or

Sales Direction

- If HCP has additional questions, refer to Medical Services Record post call analysis in Siebel
  - Utilize drop down menu to document either: delivery of letter and review of new label or delivery of letter only

HCP=Healthcare Professional

R. 3171

JJRE 0682692
Confidential/Produced in Litigation Pursuant to Protective Orde

Other Communication Vehicles

Promotional Speakers Bureau

Speakers scheduled to speak for a remaining 2003 program will be trained on new diabetes warning and slides

- Teleconference training
- Updated slide deck will be shipped

Remaining speakers will be trained on diabetes during bipolar mania speaker training

Key Opinion Leaders

Medical Science Liaisons will begin informing Key Opinion Leaders of label change beginning week November 3

R. 3172

JJRE 0682602
Confidential/Produced in Litigation Pursuant to Protective O

NOW APPROVED !!!

NEW

Risperdal CONSTA™

risperidone Long-Acting Injection

Confidential/Produced in Litigation Pursuant to Protective O

RISPERDAL® CONSTA™
Pre-Launch FAQs

JJRE 0682692
Confidential/Produced in Litigation Pursuant to Protective O

"RISPERDAL CONSTA causes tumors."

- Can you help me understand what you mean? (Doctor will likely mention pre-clinical/non-approvable, or perhaps clinical).
- All manufacturers of atypical antipsychotics conduct pre-clinical animal studies and have reports of tumors in multiple body systems in their labels.
- Importantly, FDA has noted in labeling for all atypical antipsychotics (including RISPERDAL CONSTA) that the relevance of animal findings to human risk is unknown.
- RISPERDAL CONSTA is now approved in 40 countries, has been on the market for over a year in the UK and Germany, and some patients from clinical trials have been on RISPERDAL CONSTA for up to five years. To date, there have been no such reported events deemed drug-related in humans.
- I look forward to speaking to you more about the benefits of RISPERDAL CONSTA in early December.

R. 3174

RISPERDAL® CONSTA™
Pre-Launch FAQs

"RISPERDAL CONSTA causes osteodystrophy which is linked to prolactin."

Can you help me understand what you're referring to? [Doctor will likely mention pre-clinical/non-approvable, or perhaps clinical].

Animal tumors considered prolactin-mediated are described in animal studies for all atypical antipsychotics.

Again, the relevance of animal findings to patient care is unknown.

I look forward to talking to you again in early December, about the benefits of RISPERDAL CONSTA.

R. 3175

JJRE 06826925
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10/31 Teleconference Times

	FSD/RBD	Host(s)
CNS/HSR	9:00am-10:00am EST	Carmen/Christi/Dave 877-494-5165 #261768
EC/LTC	11:00am-12:00pm EST	Riley/Christi/Anwar 866-703-9405 #356392
Primary Care	11:00am-12:00pm EST	Carmen/Tom 877-494-5165 #140356

	RBD/DM	Host
Eldercare/LTC Group	1:00 pm-2:00pm EST	Riley/Jeni/Brian 866-703-9405 #356392
CNS/HSR	Per RBD	RBD
Primary Care	1:00pm-2:00pm EST 2:00pm-3:00pm EST 3:00pm-4:00pm EST	Carmen/Tom 877-494-5165 #140356 Carmen/Tom 877-494-5165 #140356 Carmen/Tom 877-494-5165 #140356

R. 3176

JJRE 068269
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Field Training

October 31, 2003

For Training Purposes Only
Not To Be Used in a Selling Situation

JJRE 06826927
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R. 3177

Agenda

- Introduction
- Diabetes Label Revision
- RISPERDAL® CONSTA™ QA

JJRE 06826928
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R. 3178

Diabetes Label Revision

JJRE 06826929
Confidential/Produced in Litigation Pursuant to Protective Or
R. 3179

General Background

- All atypical manufacturers, including Janssen, received an FDA request to add a warning to the PI regarding hyperglycemia and diabetes mellitus
- Request was based on case reports and epidemiologic studies suggesting an increased risk of glucose abnormalities
- Relationship is not completely understood
  - Increasing incidence of diabetes in the general population
  - Elevated risk of diabetes in schizophrenic patients
- Lilly implemented diabetes warning for Zyprexa in mid-September
- Janssen agreed to modified version of class label
- Not based upon any new data for RISPERDAL

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R. 3180

Updated Package Insert

WARNINGS

Hyperglycemia and Diabetes Mellitus: *Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.*

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should have glucose monitoring undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

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R. 3181

Diabetes Warning Summary

- Hyperglycemia-related adverse events have been reported in patients treated with atypical antipsychotics
- The relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood
- All patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia
  - Patients who develop symptoms of hyperglycemia, have diabetes mellitus or have risk factors for diabetes should undergo blood glucose monitoring as outlined in the revised package insert

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R. 3182

Diabetes Warning Summary (cont.)

- The proposed FDA warning included an additional sentence at the end of the first paragraph that stated:
  - "The available data are insufficient to provide reliable estimates of differences in hyperglycemia related adverse event risk among the marketed atypical antipsychotics."
  - Upon Janssen's request, the FDA agreed to remove this sentence based upon epidemiologic studies that demonstrated a low risk of diabetes with Risperdal
- The proposed FDA warning also suggested blood glucose testing "at baseline" for patients with risk factors for diabetes
  - Risperdal label suggests blood glucose testing "at the beginning of treatment" for patients with risk factors for diabetes

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R. 3184

RISPERDAL and Diabetes

- ADVERSE REACTIONS as noted in the RISPERDAL Package Insert:
  - Metabolic and Nutritional Disorders
    - Infrequent (0.1%-1%): *Diabetes Mellitus*
    - Rare (< 0.1%): *Hypoglycemia*
  - Urinary System Disorder
    - Frequent (> 1%): *Polyuria/Polydipsia**
  - Postintroduction Reports
    - *Diabetes mellitus aggravated, including diabetic ketoacidosis; hyperglycemia*

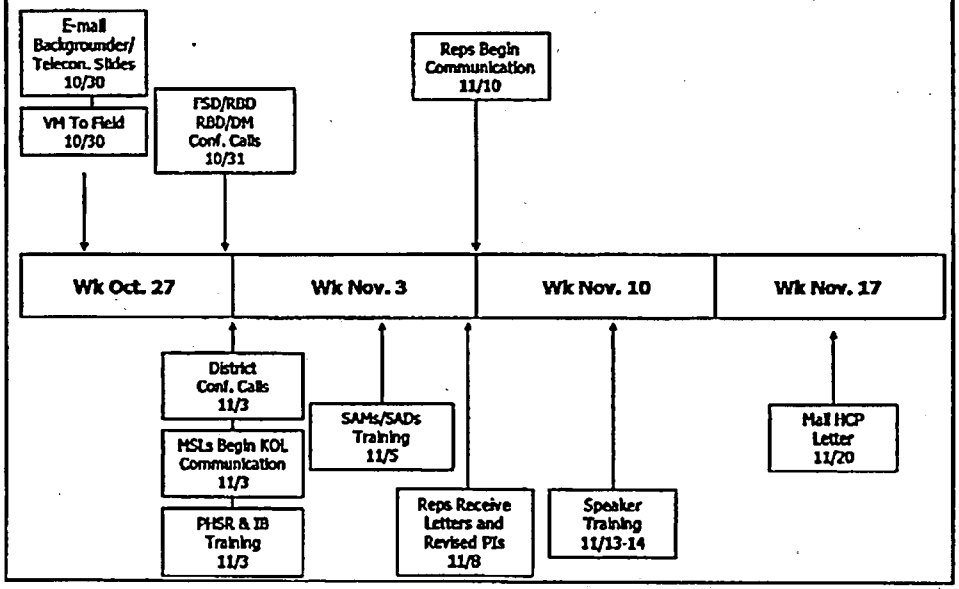
*Incidence based on elicited reports

Causal relationship has not been established.

Communication Plan

JJRE 0682693
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R. 3186

Diabetes Roll-Out Timeline



JJRE 06826937
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R. 3187

Healthcare Provider Letter

Dear Healthcare Provider,

The Food and Drug Administration (FDA) has requested all manufacturers of atypical antipsychotics to include a warning regarding hyperglycemia and diabetes mellitus in their product labeling. In addition to Janssen, the FDA made this request to the following manufacturers:

AstraZeneca – Seroquel® (quetiapine)
Bristol-Myers Squibb – Abilify™ (aripiprazole)
Eli Lilly and Company – Zyprexa® (olanzapine)
Novartis – Clozaril® (clozapine)
Pfizer – Geodon® (ziprasidone)

In an effort to keep you updated with the most current product information available for the management of your patients, enclosed please find updated prescribing information for RISPERDAL® (risperidone).

Hyperglycemia-related adverse events have infrequently been reported in patients receiving RISPERDAL. Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research[1-6] suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

For additional information about RISPERDAL or any other Janssen product, please call 1-800-JANSSEN (526-7736) from 9AM to 5PM EST, Monday through Friday.

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R. 3188

Who Will Receive Communication?

- Physicians
  - Psychiatrists
  - Neurologists
  - Primary Care
- Pharmacists
- Pharmacies
  - Hospital
  - Managed Care

⇒ **Hand-delivered to called-on healthcare providers, mailed to non called-on audience**

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R. 3189

Sales Direction

- Sales representatives should personally deliver a copy of the HCP letter to every called-on customer according to the call plan for one rotation
  - If the physician is available, communicate the package insert revision and bridge to selling RISPERDAL
  - If the physician is not available, leave letter with the office manager or nurse. On next visit by representative, or any counterpart:
    - ✓check in with physician to ensure receipt of letter and discuss any questions physician may have
    - ✓If physician has not received or reviewed letter, review package insert revision

HCP=Healthcare Professional

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R. 3190

Sales Direction

- If HCP has additional questions, refer to Medical Services
- Record post call analysis in Siebel
  - Utilize drop down menu to document either: delivery of letter and review of new label or delivery of letter only

HCP=Healthcare Professional

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R. 3191

Other Communication Vehicles

Promotional Speakers Bureau

- Speakers scheduled to speak for a remaining 2003 program will be trained on new diabetes warning and slides
  - Teleconference training
  - Updated slide deck will be shipped
- Remaining speakers will be trained on diabetes during bipolar mania speaker training

Key Opinion Leaders

- Medical Science Liaisons will begin informing Key Opinion Leaders of label change beginning week November 3

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R. 3192

NOW APPROVED !!!



JJRE 06826943
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R. 3193

RISPERDAL® CONSTA™
Pre-Launch FAQs

"RISPERDAL CONSTA causes tumors."

- Can you help me understand what you mean? (Doctor will likely mention pre-clinical/non-approvable, or perhaps clinical).
- All manufacturers of atypical antipsychotics conduct pre-clinical animal studies and have reports of tumors in multiple body systems in their labels.
- Importantly, FDA has noted in labeling for all atypical antipsychotics (including RISPERDAL CONSTA) that the relevance of animal findings to human risk is unknown.
- RISPERDAL CONSTA is now approved in 40 countries, has been on the market for over a year in the UK and Germany, and some patients from clinical trials have been on RISPERDAL CONSTA for up to five years. To date, there have been no such reported events deemed drug-related in humans.
- I look forward to speaking to you more about the benefits of RISPERDAL CONSTA in early December.

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R. 3194

RISPERDAL® CONSTA™
Pre-Launch FAQs

"RISPERDAL CONSTA causes osteodystrophy which is linked to prolactin."

- Can you help me understand what you're referring to? [Doctor will likely mention pre-clinical/non-approvable, or perhaps clinical].
- Animal tumors considered prolactin-mediated are described in animal studies for all atypical antipsychotics.
- Again, the relevance of animal findings to patient care is unknown.
- I look forward to talking to you again in early December, about the benefits of RISPERDAL CONSTA.

JJRE 06826945
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R. 3195

10/31 Teleconference Times

	FSD/RBD	Host(s)
CNS/HSR	9:00am-10:00am EST	Carmen/Christi/Dave 877-494-5165 #261768
EC/LTC	11:00am-12:00pm EST	Riley/Christi/Anwar 866-703-9405 #356392
Primary Care	11:00am-12:00pm EST	Carmen/Tom 877-494-5165 #140356

	RBD/DM	Host
Eldercare/LTC Group	1:00 pm-2:00pm EST	Riley/Jeni/Brian 866-703-9405 #356392
CNS/HSR	Per RBD	RBD
Primary Care	1:00pm-2:00pm EST 2:00pm-3:00pm EST 3:00pm-4:00pm EST	Carmen/Tom 877-494-5165 #140356 Carmen/Tom 877-494-5165 #140356 Carmen/Tom 877-494-5165 #140356

JJRE 06826946
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R. 3196

JJRErev 04247347
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RISPERDAL® and US Diabetes Label Text

IDC decision required:

Permission for meeting with the FDA on the current Risperdal diabetes labeling to :

- ensure accurate label text that is aligned with full set of Risperdal data
- prevent potential disadvantage vs. future labels of newer atypicals which may have a similar low risk for diabetes as risperidone.

R. 3197

- Ivo Caers, Risperdal Team Leader
- Sagar Adusumalli, Risperdal Regulatory Leader
- Mariëlle Eerdekens, Risperdal Clinical Leader
- Ramy Mahmoud, Janssen US CNS Medical Affairs

IDC Meeting

January 13, 2004

Johnson & Johnson

Exhibit
Caers - 46
08.20.09

Plaintiff Ex. 4.55

Risperdal and US Diabetes Label Text

Agenda

Regulatory background and history

Status of atypical antipsychotics diabetes label

Risperdal data
- epidemiology
- physiology
- clinical trials
- pharmacovigilance

Recommendation, potential risks and benefits

Potential outcomes

Proposed action plan

R. 3198

JJRErev 04247346
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Risperdal and US Diabetes Label Text

Regulatory Background and History

2002 Apr	Submission of revised US label including hyperglycemia to A.E. Post-introduction reports
2002 Nov 19	FDA approval of April 2002 label revision
2003 Sept 12	FDA sends proposed label for oral Risperdal class warning on diabetes and hyperglycemia
2003 Sept 17	Eli Lilly publicly announces FDA request for diabetes class warning and its inclusion in US Zyprexa label
2003 Oct 27	Compromise with FDA on Risperdal diabetes class warning text leading to approval of Risperdal Consta
2003 Nov 19	J. Racoosin (FDA) expressed willingness to review additional data and reconsider its position (ADA/APA consensus meeting)
2003 Dec 3	Inclusion of Risperdal class warning text in oral label with approval in bipolar mania
2003 Dec 29	Symbyax (olanzapine + fluoxetine, Lilly) approval with diabetes class warning identical to the one agreed upon for Risperdal

R. 3199

JJRErev 04247349
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Risperdal and US Diabetes Label Text

FDA position

- Primary source is a recent epidemiological study in VA population showing an increased risk for diabetes with 3 studied atypical antipsychotics (Zyprexa, Risperdal, Seroquel), assumed to be consistent with existing literature.
- Severe cases of hyperglycemia and associated symptoms incl. fatalities have been reported on all 3 of these compounds.
  Reported on all "studied" atypical antipsychotics => class effect.
  However, some (newcomers) in class may lack data.
- Prescribers need guidance on how to handle / prevent risk => need for monitoring guidelines.

R. 3200

JJREv 04247350
Confidential/Produced in Litigation Pursuant to Protective Order

FDA Proposed Hyperglycemia Labeling and agreed upon text for Risperdal (Consta) (Modifications in Underline/Strikethrough)

JJRErev 04247351
Confidential/Produced in Litigation Pursuant to Protective Order

R. 3201

WARNINGS

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics ~~studied~~. Precise risk estimates for hyperglycemia-related adverse events in patients with atypical antipsychotics are not available. ~~The available data are insufficient to provide reliable risk estimates of differences in hyperglycemia-related adverse event risk among the marketed atypical antipsychotics.~~

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at <u>the beginning of treatment</u> ~~baseline~~ and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Status of Atypical Antipsychotics Label in the US

FDA Hyperglycemia/Diabetes Class WARNING label: 9/11/03

ZYPREXA / SYMBYAX (olanzapine-fluoxetine combination)
- Accepted the FDA proposed class WARNING
- Implemented in September 2003
- Lilly informed physicians on October 6, 2003
- October 2003 "Risperdal revision" of class warning included in newly approved Symbyax label December 2003

RISPERDAL
- Accepted a revision of the FDA proposed class WARNING label
- Implemented in October 2003
- JPI informed physicians on November 10, 2003

SEROQUEL / GEODON / ABILIFY
- Not accepted yet, announced they will discuss with FDA
- Negotiations likely ongoing

R. 3202

JJRErev 0424735
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Atypical Antipsychotics and Diabetes; Commercial Overview

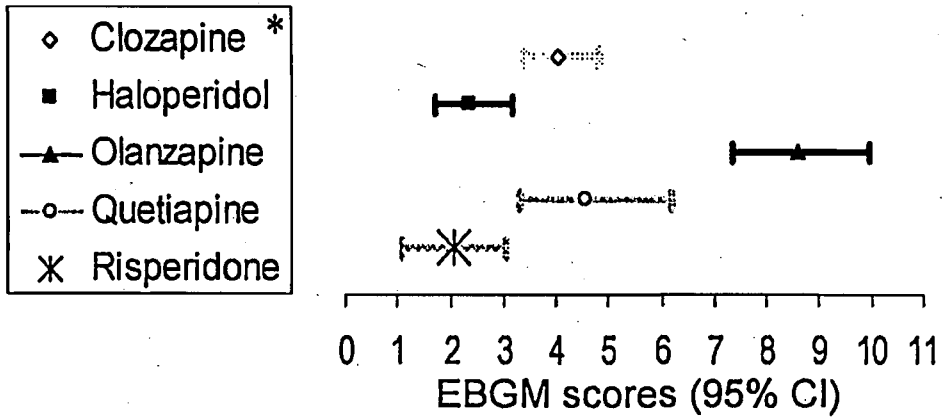
- Lilly's misleading promotion in 2002 continued despite complaints to Lilly and FDA
- Janssen disseminates diabetes reprints to HPC since March 2003
- Intense media coverage of diabetes issue (Aug-Oct '03)
- No Lilly issued DDL
- Janssen: HCP communication 11/10/2003
- FDA request for DDL on 11/21/2003 (J&JPRD response 11/26/03)
- Sales impact minimal to date due to Risperdal viewed as positively differentiated from Zyprexa
- Significant risk of being associated with Zyprexa if other atypicals receive differentiated label (precaution)

R. 3203

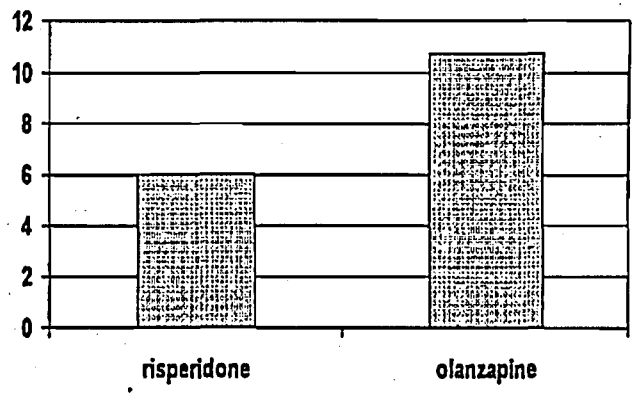
JJRErev 04247353
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Epidemiology Evidence: Risk of Diabetes Events with Atypical Antipsychotics

Comparative Rates of Life-Threatening Events from MedWatch Data Analysis



Incidence of DKA per 10,000 patients



Relative Risk 1.6 (p<0.05)

- In all 4 studies compared to untreated patients, risperidone demonstrated no difference in risk for diabetes
  - Olanzapine risk higher in all four studies (43-480%)
- In 10 of 13 studies, risperidone demonstrated equal or less risk for diabetes compared to conventional antipsychotics
- In 8 of 11 studies, risperidone demonstrated significantly lower risk of diabetes compared to olanzapine (risk 20-319% higher)

* *Launches: H 1969, Cloz 1991, Ris 1994, Ola 1996, Quet 1997*

R. 3204

JJRErev 04247354
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Physiology evidence; Insulin Sensitivity and ß-cell Function

	Effect on Insulin Sensitivity		Effect on β-cell Function	
	Risperidone	Other Drugs	Risperidone	Other Drugs
Hyperglycemic Clamp (Sowell)	?	?	NO	↑ INSULIN (OLZ)
Euglycemic Clamp (Beasley)	NO	NO	N/A	N/A
Hyperglycemic/ Euglycemic Clamp in dogs (Bergman and Ader)	NO	↓ HEPATIC SI (OLZ)	NO	↓ B-CELL FUNCTION (OLZ)
FSIVGTT (Cagliero and Henderson)	NO	↓ SI (OLZ and CLO)	NO	NO

R. 3205

JJREv 04247355
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Data from Clinical Trials

- 12,000 patients treated for up to 3 months
- 7,500 patients treated for > 6 months

glucose related AE's		children	adults	elderly	Total
short term	risperidone (n=8458)	0.00 %*	0.52 %	2.17 %	0.72 %
	placebo (n=1825)	0.00 %*	0.43 %	1.70 %	0.88 %
	olanzapine (n=536)	-	0.87 %	1.28 %*	0.93 %
	haloperidol (n=920)	-	0.25 %	0.85 %*	0.33 %
long term	risperidone (n=6590)	0.13 %	1.51 %	2.66 %	1.49 %
	olanzapine (n=300)	-	1.66 %	-	1.66 %
	haloperidol (n=579)	-	1.55 %	-	1.55 %

* *denominator < n=200*

R. 3206

JJRErev 04247350
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Data from Risperdal Pharmacovigilance

- Total estimated patient exposure: 17,200,000 patients
- 375 reports of glucose related AE's, 12 patients died (diabetic ketoacedosis: 34 reports, diabetic coma: 10 reports)
- In 4 cases deterioration of glucose control in known stabilized diabetic patients was reported to be temporarily related to Risperdal initiation.
  In 1 case, a possible positive rechallenge occurred.

R. 3207

JJRErev 04247357
- Confidential/Produced in Litigation Pursuant to Protective Order -

Summary of evidence re. Risperdal and risk for diabetes

- Epidemiology evidence does not support increased risk of diabetes with risperidone
  - Serious life-threatening events (e.g. DKA) not more common than with Haldol
  - Weight of evidence; diabetes is not more common than in untreated or conventional antipsychotic treated patients and less common than with olanzapine and clozapine
- The clinical database suggests that disturbances of glucose metabolism are not very common and not different between risperidone and placebo
- The PV database does not suggest an increased risk for diabetes or related events
- Risperidone does not effect insulin secretion or β-cell function.

R. 3208

JJRErev 04247350
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Summary of Evidence => appropriate Label Text

Recommendation:

Precaution covering;

- Hyperglycemia and exacerbation of diabetes have been reported
- No established causal relationship
- Monitoring may be desirable in line with good clinical practice

R. 3209

JJRErev 04247359
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Risperdal and US Diabetes Label Text

Potential benefits and risks of re-opening negotiations with FDA;

Risks

- Relationship with FDA
  => loss of confidence by FDA in J&JPRD commitment and its credibility
- => impact on future CNS projects / approvals

Benefits

- Earlier insight in FDA preparedness for label compromises
  => potential to mitigate our risk for competitive disadvantage
- Differentiated label vs. Zyprexa confirming present perception in the market and clinical impressions
- Differentiated US label will support maintaining current differentiation ex-US labels

R. 3210

JJRErev 04247360
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Potential outcomes

Background:

- FDA expressed willingness to review additional data and reconsider its position (J. Racoosin, ADA/APA consensus meeting, Nov 2003)
- Our perceived "weight of evidence" demonstrating low diabetes risk with risperidal may be interpreted differently by the FDA.

R. 3211

Outcomes	Probablitity
Avoid having a worse label than future labels of other "low risk" atypical antipsychotics	Moderate
Precaution text rather than warning	Low

JJRErev 04247361
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Proposed Action Plan

- Subject to January 13 IDC endorsement;
  - Meeting with FDA to discuss significant differentiation in label

- Timing;
  - Request for meeting; Jan 2004
  - If FDA grants a meeting, briefing document to FDA mid February 2004
  - FDA Meeting: 2nd half March 2004

R. 3212

JJRErev 04247362
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RISPERDAL® and US Diabetes Label Text

IDC decision required:

Permission for meeting with the FDA on the current Risperdal diabetes labeling to :

- ensure accurate label text that is aligned with full set of Risperdal data
- prevent potential disadvantage vs. future labels of newer atypicals which may have a similar low risk for diabetes as risperidone.

- Ivo Caers, Risperdal Team Leader
- Sagar Adusumalli, Risperdal Regulatory Leader
- Mariëlle Eerdekens, Risperdal Clinical Leader
- Ramy Mahmoud, Janssen US CNS Medical Affairs

IDC Meeting

January 13, 2004

Johnson & Johnson

R. 3213 JJREv 0424736
Confidential/Produced in Litigation Pursuant to Protective Order

Risperdal and US Diabetes Label Text

Agenda

Regulatory background and history

Status of atypical antipsychotics diabetes label

Risperdal data - epidemiology
- physiology
- clinical trials
- pharmacovigilance

Recommendation, potential risks and benefits

Potential outcomes

Proposed action plan

R. 3214 JJREv 04247364
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Risperdal and US Diabetes Label Text

Regulatory Background and History

2002 Apr	Submission of revised US label including hyperglycemia to A.E. Post-introduction reports
2002 Nov 19	FDA approval of April 2002 label revision
2003 Sept 12	FDA sends proposed label for oral Risperdal class warning on diabetes and hyperglycemia
2003 Sept 17	Eli Lilly publicly announces FDA request for diabetes class warning and its inclusion in US Zyprexa label
2003 Oct 27	Compromise with FDA on Risperdal diabetes class warning text leading to approval of Risperdal Consta
2003 Nov 19	J. Racoosin (FDA) expressed willingness to review additional data and reconsider its position (ADA/APA consensus meeting)
2003 Dec 3	Inclusion of Risperdal class warning text in oral label with approval in bipolar mania
2003 Dec 29	Symbyax (olanzapine + fluoxetine, Lilly) approval with diabetes class warning identical to the one agreed upon for Risperdal

R. 3215 JJREv 0424736
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Risperdal and US Diabetes Label Text

FDA position

- Primary source is a recent epidemiological study in VA population showing an increased risk for diabetes with 3 studied atypical antipsychotics (Zyprexa, Risperdal, Seroquel), assumed to be consistent with existing literature.
- Severe cases of hyperglycemia and associated symptoms incl. fatalities have been reported on all 3 of these compounds.
  Reported on all "studied" atypical antipsychotics => class effect.
  However, some (newcomers) in class may lack data.
- Prescribers need guidance on how to handle / prevent risk => need for monitoring guidelines.

R. 3216 JJREv 04247366
Confidential/Produced in Litigation Pursuant to Protective Order

FDA Proposed Hyperglycemia Labeling and agreed upon text for Risperdal (Consta) (Modifications in Underline/Strikethrough)

WARNINGS

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics ~~studied~~. Precise risk estimates for hyperglycemia-related adverse events in patients with atypical antipsychotics are not available. ~~The available data are insufficient to provide reliable risk estimates of differences in hyperglycemia-related adverse event risk among the marketed atypical antipsychotics.~~

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment ~~baseline~~ and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

R. 3217 JJREv 0424736
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Status of Atypical Antipsychotics Label in the US

FDA Hyperglycemia/Diabetes Class WARNING label: 9/11/03

ZYPREXA / SYMBYAX (olanzapine-fluoxetine combination)
- Accepted the FDA proposed class WARNING
- Implemented in September 2003
- Lilly informed physicians on October 6, 2003
- October 2003 "Risperdal revision" of class warning included in newly approved Symbyax label December 2003

RISPERDAL
- Accepted a revision of the FDA proposed class WARNING label
- Implemented in October 2003
- JPI informed physicians on November 10, 2003

SEROQUEL / GEODON / ABILIFY
- Not accepted yet, announced they will discuss with FDA
- Negotiations likely ongoing

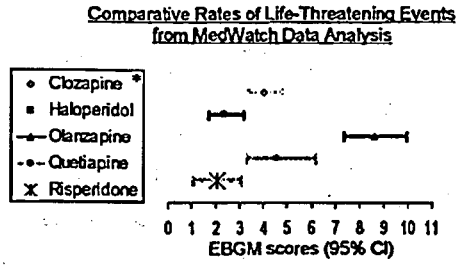
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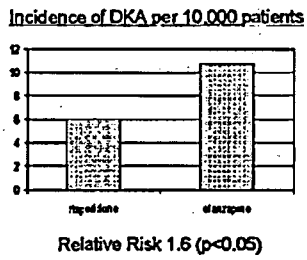
Atypical Antipsychotics and Diabetes; Commercial Overview

- Lilly's misleading promotion in 2002 continued despite complaints to Lilly and FDA
- Janssen disseminates diabetes reprints to HPC since March 2003
- Intense media coverage of diabetes issue (Aug-Oct '03)
- No Lilly issued DDL
- Janssen: HCP communication 11/10/2003
- FDA request for DDL on 11/21/2003 (J&JPRD response 11/26/03)
- Sales impact minimal to date due to Risperdal viewed as positively differentiated from Zyprexa
- Significant risk of being associated with Zyprexa if other atypicals receive differentiated label (precaution)

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Epidemiology Evidence: Risk of Diabetes Events with Atypical Antipsychotics





- In all 4 studies compared to untreated patients, risperidone demonstrated no difference in risk for diabetes
  - Olanzapine risk higher in all four studies (43-480%)
- In 10 of 13 studies, risperidone demonstrated equal or less risk for diabetes compared to conventional antipsychotics
- In 8 of 11 studies, risperidone demonstrated significantly lower risk of diabetes compared to olanzapine (risk 20-319% higher)

* *Launches: H 1969, Cloz 1991, Ris 1994, Ola 1996, Quet 1997*

Risperdal Hyperglycemia/Diabetes Labeling Johnson & Johnson Confidential IDC, January 13, 2004 8

In a study utilizing data from the FDA MedWatch database, we examined the strength of the association between antipsychotic usage and reports of life-threatening diabetes-related events. Life-threatening events were defined as DKA and diabetic coma. An empirical bayesian geometric mean or EBGM score was calculated for 5 different antipsychotics. An EBGM score is the ratio of observed to expected number of events for a given medication. For example, a drug with a score of 4 would have 4 times the number of events observed as compared to the number which could be expected during the same time period. In understanding the results of this study, let's use haloperidol patients as the reference group because it's use has not been linked to an increased rate of incident diabetes. Patients receiving clozapine, olanzapine and quetiapine have a significantly higher rate of life-threatening events, 4 to 8 times the expected rate, as compared to those receiving haloperidol, while risperidone patients were no different than haloperidol patients.

In order to better evaluate the risk of DKA among atypical antipsychotic users, an epidemiological study of a very large database was conducted. In a study of over 100,000 of patients from the California Medicaid database, risperidone patients demonstrated an incident rate of DKA of 6 per 10,000 while olanzapine patients had a rate of over 10 per 10,000. In logistic analyses, this resulted in a 60% increased relative risk for DKA with olanzapine use.

Based on pharmacovigilance and epidemiological evidence, serious and life-threatening events like DKA have not been associated with risperidone unlike some other antipsychotics.

Differences exist in the excess risk of diabetes among atypical antipsychotics. Four studies evaluated the risk as compared to an untreated similar patient population and all four found that the risk among risperidone patients was no different than an

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Physiology evidence; Insulin Sensitivity and ß-cell Function

	Effect on Insulin Sensitivity		Effect on β-cell Function	
	Risperidone	Other Drugs	Risperidone	Other Drugs
Hyperglycemic Clamp (Sowell)	?	?	NO	↑ INSULIN (OLZ)
Euglycemic Clamp (Beasley)	NO	NO	N/A	N/A
Hyperglycemic/ Euglycemic Clamp in dogs (Bergman and Ader)	NO	↓ HEPATIC SI (OLZ)	NO	↓ B-CELL FUNCTION (OLZ)
FSIVGTT (Cagliero and Henderson)	NO	↓ SI (OLZ and CLO)	NO	NO

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Data from Clinical Trials

- 12,000 patients treated for up to 3 months
- 7,500 patients treated for > 6 months

glucose related AE's		children	adults	elderly	Total
short term	risperidone (n=8458)	0.00 %*	0.52 %	2.17 %	0.72 %
	placebo (n=1825)	0.00 %*	0.43 %	1.70 %	0.88 %
	olanzapine (n=536)	-	0.87 %	1.28 %*	0.93 %
	haloperidol (n=920)	-	0.25 %	0.85 %*	0.33 %
long term	risperidone (n=6590)	0.13 %	1.51 %	2.66 %	1.49 %
	olanzapine (n=300)	-	1.66 %	-	1.66 %
	haloperidol (n=579)	-	1.55 %	-	1.55 %

** denominator < n=200*

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Data from Risperdal Pharmacovigilance

- Total estimated patient exposure: 17,200,000 patients
- 375 reports of glucose related AE's, 12 patients died (diabetic ketoacedosis: 34 reports, diabetic coma: 10 reports)
- In 4 cases deterioration of glucose control in known stabilized diabetic patients was reported to be temporarily related to Risperdal initiation.
  In 1 case, a possible positive rechallenge occurred.

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Summary of evidence re. Risperdal and risk for diabetes

- Epidemiology evidence does not support increased risk of diabetes with risperidone
  - Serious life-threatening events (e.g. DKA) not more common than with Haldol
  - Weight of evidence; diabetes is not more common than in untreated or conventional antipsychotic treated patients and less common than with olanzapine and clozapine
- The clinical database suggests that disturbances of glucose metabolism are not very common and not different between risperidone and placebo
- The PV database does not suggest an increased risk for diabetes or related events
- Risperidone does not effect insulin secretion or β-cell function.

The purpose of this presentation today is to provide evidence that there is little or no risk of diabetes with risperidone treatment. At the end of this presentation, I would like to be able to conclude that:

Epidemiolgy evidence does not support risk of diabetes with risperidone.

Risperidone does not effect insulin secretion or β-cell function.

And finally serious and life-threatening events (like DKA) have not been associated with risperidone use.

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Summary of Evidence => appropriate Label Text

Recommendation:

Precaution covering;

- Hyperglycemia and exacerbation of diabetes have been reported
- No established causal relationship
- Monitoring may be desirable in line with good clinical practice

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Risperdal and US Diabetes Label Text

Potential benefits and risks of re-opening negotiations with FDA:

Risks	*Benefits*
• Relationship with FDA => loss of confidence by FDA in J&JPRD commitment and its credibility • => impact on future CNS projects / approvals	• Earlier insight in FDA preparedness for label compromises => potential to mitigate our risk for competitive disadvantage • Differentiated label vs. Zyprexa confirming present perception in the market and clinical impressions • Differentiated US label will support maintaining current differentiation ex-US labels

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Potential outcomes

Background:

- FDA expressed willingness to review additional data and reconsider its position (J. Racoosin, ADA/APA consensus meeting, Nov 2003)
- Our perceived "weight of evidence" demonstrating low diabetes risk with risperidal may be interpreted differently by the FDA.

Outcomes	Probablitity
Avoid having a worse label than future labels of other "low risk" atypical antipsychotics	Moderate
Precaution text rather than warning	Low

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Proposed Action Plan

- Subject to January 13 IDC endorsement;
  - Meeting with FDA to discuss significant differentiation in label
- Timing;
  - Request for meeting; Jan 2004
  - If FDA grants a meeting, briefing document to FDA mid February 2004
  - FDA Meeting: 2nd half March 2004

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JANSSEN PHARMACEUTICA INC.

IMPORTANT CORRECTION OF DRUG INFORMATION

July 21, 2004

Dear Health Care Provider:

The Food and Drug Administration's (FDA) Division of Drug, Marketing, Advertising, and Communications (DDMAC) has asked us to contact you because Janssen Pharmaceutica Products, L.P. recently received a Warning Letter concerning the promotion of Risperdal® (risperidone). This letter provides important corrective information about Risperdal relating to hyperglycemia and Diabetes Mellitus.

The Warning Letter concludes that Janssen disseminated a Risperdal Dear Health Care Provider (DHCP) dated November 10, 2003 that omitted material information about Risperdal, minimized potentially fatal risks, and made misleading claims suggesting superior safety to other atypical antipsychotics without adequate substantiation, in violation of the Federal Food, Drug and Cosmetic Act.

Specifically, the Warning Letter stated that the DHCP letter omitted important information regarding hyperglycemia and diabetes, including the potential consequences and the recommendation of regular glucose control monitoring that was added to the approved product labeling for Risperdal; minimized the potentially fatal risks of hyperglycemia-related adverse events such as ketoacidosis, hyperosmolar coma and death; minimized the importance of blood glucose monitoring; suggested that Risperdal did not increase the risk of diabetes, contradicting the Warning in the revised product labeling; and made misleading claims suggesting that Risperdal has a lower risk of hyperglycemia and diabetes than other atypical antipsychotics without adequate substantiation which is inconsistent with the Prescribing Information for Risperdal.

(Continued on reversed side)

1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200
(609) 730-2000

Exhibit
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08.20.09

Plaintiff Ex. 438

JJRE 01151830

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In order to provide you with complete and accurate information regarding hyperglycemia and Diabetes Mellitus relative to Risperdal, please be advised that the Risperdal Prescribing Information was updated with the addition of the Warning in November 2003.

WARNINGS

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

If you have any questions regarding this important safety information, please contact Janssen Medical Affairs at 1-800-JANSSEN. Please refer to the full prescribing information for Risperdal included with this letter. As always, we request that serious adverse events be reported to Janssen at 1-800-JANSSEN or the FDA MedWatch program by phone (1-800-FDA-0178), or by e-mail (www.fda.gov).

Sincerely,

Ramy Mahmoud, MD, MPH
Vice President, CNS
Janssen Medical Affairs, LLC
Enclosure: Risperdal Package Insert

01-RS1516

JJRE 01151831
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Exhibit
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08.20.09

TOPLINE RESULTS

Report date: 9 Sep 1999	**Tracking number:** GBSR-99-010
Trial number: RIS-USA-113)	**Clinical Phase:** IV
Title: Risperidone vs. olanzapine in the treatment of Schizophrenia-Extension trial	

Trial Statistician(s):	Ben Lyons, Ph. D
Trial M.D.:	Al Derivan, MD
Global Biometrics Leader (GBL):	Akiko Okamoto, Sc. D
Global Medical Leader (GML):	Al Derivan, MD
Global Product Leader (GPL):	Ivo Caers, Ph. D

Trial Design

- Multicenter, randomised, double-blind, placebo-controlled trial, with two parallel treatment groups: Risperidone (2-6 mg BID) and Olanzapine (5-20 mg BID). This is a double blinded follow up trial to RIS-USA-112.
- Treatment duration/Trial duration: 44 Weeks.
- Primary Safety Variable: Incidence of 7% Weight gain.
- Secondary Safety Variable: Incidence of EPS related AEs.
- Primary population for safety analysis: All patients who took study medication.
- Primary population for efficacy analysis: All patients in non-excluded sites who have at least one post-baseline assessment.
- Primary efficacy variable/Primary time point: PANSS / END POINT.
- Expected effect size and planned sample size: 56% of Olanzapine patients and 32% of risperidone patients will experience a 7% or more gain in weight from entry into RIS-USA-112 at any time during treatment. It was determined that 188 patients randomised per group into RIS-USA-112 were needed.

Primary objective: Show superiority over Olanzapine in the incidence of 7% increase in weight from entry into RIS-USA-112 at any time during treatment.

Preliminary Statistical Conclusions: P-value for the Incidence of 7% weight gain in Risperidone vs. Olanzapine : 0.189 (46.7% vs. 54.8%).

The results in this summary have been verified by the global biometrics and submission team statisticians and programmers. Nevertheless, it is possible that these results may differ slightly from what will appear in the final Clinical Trial Report (CTR). Results presented in the CTR will be the final, fully validated results of this trial.
All information about the trial results is considered confidential and no further discussions or dissemination of results occur with anyone else until approval is given from the head of Clinical R&D and Regulatory Affairs, Worldwide.

RESULTS

1. MAIN FEATURES OF THE TRIAL

There are no major differences in baseline or trial termination characteristics between olanzapine and risperidone treated patients. Table 3 lists the number of patients in each of the excluded sites.

Table 1. Baseline Characteristics

Trial disposition and subject characteristics	Risperidone	Olanzapine	Total
# subjects who completed RIS-USA-112	149	160	309
# of RIS-USA-112 completers who did not enter RIS-USA-113	22	18	40
Total who entered RIS-USA-113	127	142	269
# of subjects not treated	1	1	2
Total Subjects	126	141	267
Gender (M/F)	89/37	94/47	183/84
Age: mean, median (min-max), yrs	41 40 (20,64)	39.1 39 (18 , 62)	40 40 (18, 64)
Race (Caucasian / Other)	73 / 53	75 / 66	148 / 119

Table 2. Trial Termination

Trial termination reasons	Risperidone	Olanzapine
Total all subjects	126	141
Total discontinued	61	58
D/C'd due to adverse event	14	15
D/C'd due to insufficient response	4	3
D/C'd due to withdrawn consent	20	21
D/C'd due to non-compliance	8	9
D/C'd due to lost to follow up	7	4
Other	8	6

Table 3. Subjects Excluded from Primary Efficacy analysis

Excluded Subjects	Risperidone	Olanzapine
Total all subjects	126	141
Total in Non-Excluded Sites	115	129
# in Excluded Site 1	2	2
# in Excluded Site 2	9	10

2. SAFETY

The primary population for the safety analysis is all patients enrolled at all sites.

2.1. Primary Safety Analysis Variable

Note that here, and through out this report, change is relative to the baseline of RIS-USA-112. There appears to be no difference in the incidence of 7% weight gain in the two groups. The graph of cumulative weight change, Figure 1 attached, shows that at end point the two groups have similar weight change profiles which diverge only around the +10% weight level. Table 6 below and Figure 2 attached display the mean weight change for the two groups over time. Both support the finding of significant weight gain in the risperidone treated patients, especially at week 52, i.e. 52 weeks from RIS-USA-112 randomisation.

Table 4. Incidence of 7% Weight Gain at any time during treatment for all patients

7% Weight Gain	Risperidone	Olanzapine	P-value[1]
Yes	57 (46.7%)	74 (54.8%)	
No	65 (53.3%)	61 (45.2%)	
Total	122	135	0.189

1:Cochran-Mantel-Haenszel test controlling for investigator

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Table 5. Summary of weight change form RIS-USA-112 randomisation for all patients

Parameter	Risperidone N	Risperidone Mean[1]	Risperidone (SE)	Olanzapine N	Olanzapine Mean[1]	Olanzapine (SE)	p-value for Treatment Difference[2]
Weight (KG)							
Basleine	122	83.15	(1.65)	136	84.37	(1.90)	0.712
Week 8	117	2.07*	(0.35)	130	3.79*	(0.35)	<.001
Week 12	111	2.47*	(0.47)	131	4.29*	(0.47)	0.006
Week 16	105	2.78*	(0.51)	122	4.79*	(0.60)	0.007
Week 20	96	2.89*	(0.66)	114	5.75*	(0.65)	0.003
Week 36	74	3.52*	(0.80)	87	6.33*	(0.90)	0.030
Week 52	57	5.93*	(1.06)	71	5.99*	(1.16)	0.869
End Point	122	4.57*	(0.66)	135	5.32*	(0.77)	0.424
BMI							
Baseline	122	28.4	(0.55)	136	29.3	(0.66)	0.350
Week 52	57	1.99*	(0.35)	71	2.05*	(0.40)	0.982
Endpoint	122	1.54*	(0.22)	135	1.86*	(0.27)	0.336

1: Baseline values are mean of the actual score. Mean changes from baseline are shown for other visits.
2: Analysis of covariance model with factors of baseline score, investigator and treatment.
*: Statistically significant change from baseline (paired t-test)

2.2. Secondary Safety Analysis Variables

There is no statistically significant difference between the rate of spontaneous EPS related adverse events. Table 6 shows only events that emerged, worsened, or re-emerged during RIS-USA-113. Table 7 includes events that occurred in either RIS-USA-113 or RIS-USA-112. Here the rates are nearly equivalent.

Table 6. Spontaneous adverse event rate of extrapyramidal symptoms for all patients during RIS-USA-113. Only events that emerged, re-emerged, or worsened during RIS-USA-113 are reported.

	Risperidone	Olanzapine	P-value[1]
EPS related AE	22 (17.5%)	18 (12.8%)	
No EPS related AE	104 (82.5%)	123 (87.2%)	
Total	126	141	0.167

1:Cochran-Mantel-Haenszel test controlling for investigator.

Table 7. Spontaneous adverse event rate of extrapyramidal symptoms for all patients in RIS-USA-113 that occurred in either RIS-USA-112 or 113.

	Risperidone	Olanzapine	P-value[1]
EPS related AE	39 (31.0%)	43 (30.5%)	
No EPS related AE	87 (69.0%)	98 (69.5%)	
Total	126	141	0.783

1:Cochran-Mantel-Haenszel test controlling for investigator.

There is some evidence that the patients treated with risperidone experience more intense extrapyramidal symptoms. At end point the average total ESRS scores of both patient groups declined but the patients in the olanzapine group did so significantly more ($p = .009$): mean risperidone change was -0.7 (SE = .55) and mean olanzapine change was –2.0 (SE = .46).

The incidence of diabetes is shown in Table 8. All patients randomised into RIS-USA-112 are included and the rates are nearly equivalent. Diabetes was not reported as an adverse event.

Table 8. Incidence of Diabetes defined as HbA1c increasing to over 7% for patients with HbA1c under 7% at entry into RIS-USA-112. All patients randomised into RIS-USA-112 are included here.

	Risperidone	Olanzapine	P-value[1]
Increase in HbA1c	5 (2.8%)	4 (2.2%)	
No Increase in HbA1c	173 (97.2%)	177 (97.8%)	
Total	178	181	0.710

1:Cochran-Mantel-Haenszel test controlling for investigator.

2.3. Adverse Events

Table 9 lists the AEs that occurred in more than 5% of the patients in either treatment group. Only events that emerged during the 44 weeks of RIS-USA-113, re-emerged after ending in RIS-USA-112, or worsened in severity from RIS-USA-112 are listed.

Table 9. Incidence of Common AEs (i.e. reported by more than 5% of patients in either treatment group). Only AEs that emerged, re-emerged, or worsened from RIS-USA-112 are listed.

SOC/Preferred term	Risperidone		Olanzapine	
Total all subjects*	126		141	
Total With at least one AE	105		121	
	N	%	N	%
HEADACHE	29	23.02	21	14.89
RHINITIS	20	15.87	19	13.48
SOMNOLENCE	13	10.32	26	18.44
ANXIETY	19	15.08	15	10.64
AGITATION	18	14.29	15	10.64
DEPRESSION	13	10.32	16	11.35
INSOMNIA	12	9.52	16	11.35
PSYCHOSIS	12	9.52	13	9.22
MOUTH DRY	12	9.52	12	8.51
HALLUCINATION	6	4.76	13	9.22
WEIGHT INCREASE	4	3.17	15	10.64
BACK PAIN	4	3.17	12	8.51
CONSTIPATION	6	4.76	10	7.09
DIZZINESS	4	3.17	12	8.51
PARANOID REACTION	10	7.94	6	4.26
PAIN	8	6.35	7	4.96
VISION ABNORMAL	6	4.76	9	6.38
INJURY	7	5.56	7	4.96
SALIVA INCREASED	7	5.56	6	4.26
COUGHING	7	5.56	5	3.55
DYSPEPSIA	9	7.14	1	0.71
HYPERKINESIA	8	6.35	2	1.42
HYPERPROLACTINAEMIA	9	7.14	0	0.00

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2.4. Serious adverse events

Table 10 shows the serious adverse events that occurred to four or more patients. Psychosis was the most common serious AE and also the most common AE that led to trial termination, see table 11.

Table 10. Serious Adverse Events*

SOC/Preferred term	Risperidone	Olanzapine
Total all subjects	126	141
Total subjects with at least one serious AE	26	21
Psychosis	10	11
Paranoid Reaction	5	3
Agitation	1	4
Delusion	4	1
Hallucination	2	3
Anxiety	1	3
Depression	2	2

* Only events that emerged, re-emerge, or worsened during RIS-USA-113 are reported here.

Table 11. Adverse Events* that led the discontinuation of two or more patients

SOC/Preferred term	Risperidone	Olanzapine
Total all subjects	126	141
Subjects who discontinued due to AE	14	15
Psychosis	8	4
Agitation	0	4
Paranoid Reaction	1	1
Suicide Attempt	1	2
Aggressive Reaction	0	2
Weight Increase	1	2
Hallucination	0	2

*Events may have begun during RIS-USA-112.

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2.5. Deaths

No Deaths occurred in this study.

2.6. ECG

There were no significant differences between the treatment groups in mean change from 112 baseline to end point in any of the ECG variables: Heart rate, PR interval, QRS width, QT Interval, or QTc interval. Table 12 summarises important changes in QTc intervals.

Table 11. QTc change for all patients

QTc Change	Risperidone (N=121)		Olanzapine (N=141)	
Endpoint	N	%	N	%
> 60 msec increase	4	3.31	1	0.71
30 - 60 msec increase	10	8.26	15	10.64
Unchanged (± 29 msec)	89	73.55	116	82.27
30 - 60 msec decrease	14	11.57	7	4.96
> 60 msec decrease	4	3.31	2	1.42

2.7. Anti-Parkinson Medication

Table 11 shows the number of patients who began taking of Anti-Parkinson medication during RIS-USA-113. Patients who began taking medication from RIS-USA-112 are not re-counted. There is no difference in the rates.

Table 12. Number of Patients who began Anti-Parkinson Medication at any time during RIS-USA-113

	Risperidone	Olanzapine	P-value[1]
Used Anti-Parkinson Medication	7 (5.6%)	8 (5.7%)	0.922
Did not use Anti-Parkinson Medication	119 (94.4%)	133 (94.3%)	
Total	126	141	

1:Cochran-Mantel-Haenszel test controlling for investigator.

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2.8 Prolactin

Table 13 gives a summary of prolactin using the study entry into RIS-USA-112 as baseline. Results are similar to those found in RIS-USA-112.

Table 13. Summary of Prolactin for all patients

	Risperidone			Olanzapine		
Prolactin value	Total N[1]	Mean	(SE)	Total N[1]	Mean	(SE)
Male	79			83		
Baseline		15.90	(1.58)		15.98	(1.62)
Endpoint		33.53	(2.98)		10.57	(0.79)
Female						
Baseline	33	26.70	(4.92)	42	46.90	(7.81)
Endpoint		71.27	(10.86)		26.60	(3.82)
Prolactin > 40ng/ml	Total N[2]	N	(%)	Total N[2]	N	(%)
Male						
Baseline	79	4	(5.06)	85	5	(5.09)
Endpoint	89	25	(28.09)	92	0	(0.00)
Female						
Baseline	33	7	(21.21)	42	18	(42.86)
Endpoint	37	25	(67.58)	47	9	(19.15)

1: Total number of subjects who had prolactin assessments at both baseline and endpoint.
2: Total number of subjects with lab values at each visit.

3. EFFICACY

The primary population for the efficacy analysis is all patients enrolled in non-excluded sites.

3.1. Primary efficacy variable – Positive and Negative Symptoms of Schizophrenia (PANSS) scores for patients enrolled in non-excluded sites.

Table 14 and Figure 4, attached, shows that there are no statistical differences between the olanzapine and risperidone treated patients at end point in any of the major PANSS domains except disorganised thoughts where olanzapine treated patients show significantly more improvement than risperidone patients at end point. Patients treated with olanzapine had numerically larger declines at end point than the risperidone patients on all PANSS domains. For the Total PANSS domain at end point, Figure 3 attached

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indicates that generally those patients treated with olanzapine had slightly larger declines in Total PANSS than patients treated with risperidone.

Table 14. Summary of PANSS scores for patients enrolled at non-excluded sites. Baseline is randomisation of RIS-USA-112.

	Risperidone			Olanzapine			p-value for Treatment Difference[2]
Parameter	N	Mean[1]	(SE)	N	Mean[1]	(SE)	
Total PANSS							
Baseline	110	81.3	(1.31)	125	80.6	(1.17)	0.470
Week 52	55	-20.2*	(1.80)	69	-21.8*	(2.14)	0.566
Endpoint	110	-15.6*	(1.81)	125	-19.4*	(1.64)	0.210
Positive Symptoms							
Baseline	110	24.1	(0.54)	125	23.5	(0.52)	0.235
Week 52	55	-6.96*	(0.67)	69	-6.71*	(0.73)	0.912
Endpoint	110	-5.81*	(0.69)	125	-5.82*	(0.59)	0.976
Negative Symptoms							
Baseline	110	21.6	(0.63)	125	21.1	(0.56)	0.790
Week 52	55	-4.69*	(0.69)	69	-5.59*	(0.76)	0.911
Endpoint	110	-3.68*	(0.62)	125	-4.76*	(0.57)	0.291
Disorganised thoughts							
Baseline	110	18.1	(0.55)	125	17.8	(0.43)	0.436
Week 52	55	-3.75*	(0.57)	69	-4.64*	(0.68)	0.089
Endpoint	110	-2.89*	(0.53)	125	-4.30*	(0.50)	0.032
Uncontrolled Hostility/Excitement							
Baseline	110	7.2	(0.29)	125	7.4	(0.23)	0.975
Week 52	55	-2.29*	(0.40)	69	-1.80*	(0.33)	0.818
Endpoint	110	-1.35*	(0.30)	125	-1.55*	(0.30)	0.987
Anxiety/Depression							
Baseline	110	10.30	(0.32)	125	10.78	(0.30)	0.275
Week 52	55	-2.49*	(0.47)	69	-3.04*	(0.45)	0.600
Endpoint	110	-1.89*	(0.38)	125	-2.90*	(0.36)	0.130

R 3240 JJRIS 02541061
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1: Baseline values are mean of the actual score. Mean changes from baseline are shown for other visits.
2: Analysis of covariance model with factors of baseline score, investigator and treatment.
*: Statistically significant change from baseline (paired t-test)

Table 15 below displays the number of patients out of all patients who were randomised at non-excluded sites in RIS-USA-112 who had a 50% decrease in Total PANSS score and then maintained that level until they left the trial. Table 16 displays the number of patients who had a 20% decrease in Total PANSS score and maintained that level for at least three consecutive visits. In both cases more olanzapine treated patients maintained these levels but neither times to onset were significantly different.

Table 15. Patients in non-excluded sites who had a 50% decrease in Total PANSS and maintained that response. All patients randomised into 112 at non-excluded sites are included here.

50% Sustained Decrease	Risperidone	Olanzapine	P-value[1]
Yes	3 (1.6%)	9 (4.8%)	
No	180 (98.4%)	177 (95.2%)	
Total	183	186	0.32

1: Test for Treatment group difference on time to onset using logrank test controlling for investigator. Patients with out baseline PANSS measurements excluded.

Table 16. Patients in non-excluded sites who had a 20% decrease in Total PANSS and maintained that response for three or more consecutive visits. All patients randomised into 112 at non-excluded sites are included here.

20% Sustained Decrease	Risperidone	Olanzapine	P-value[1]
Yes	88 (48.1%)	93 (50.0%)	
No	95 (55.9%)	93 (50.0%)	
Total	183	186	0.46

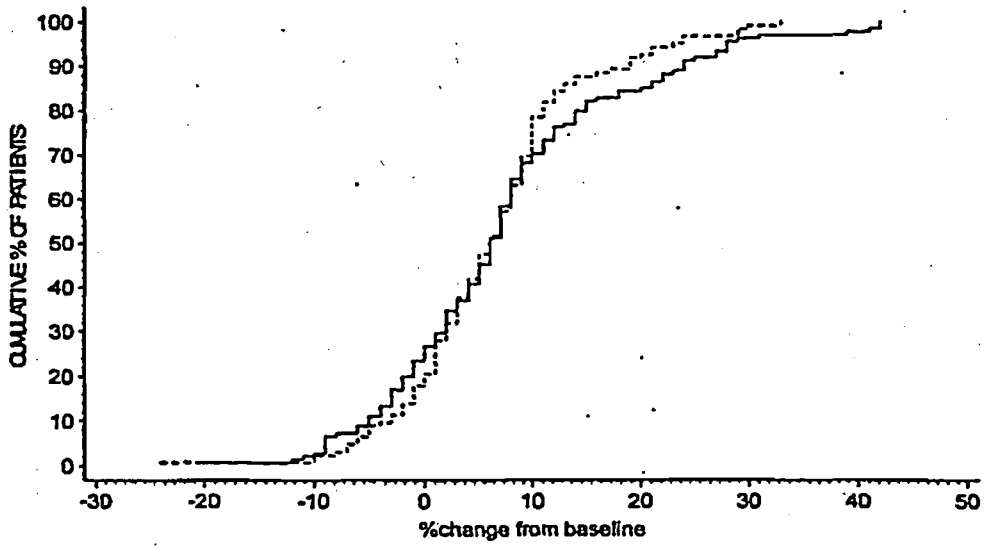
1: Test for Treatment group difference on time to onset using log-rank test controlling for investigator. Patients with out baseline PANSS measurements excluded.

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4. SUPPORTING DISPLAYS AND GRAPHS

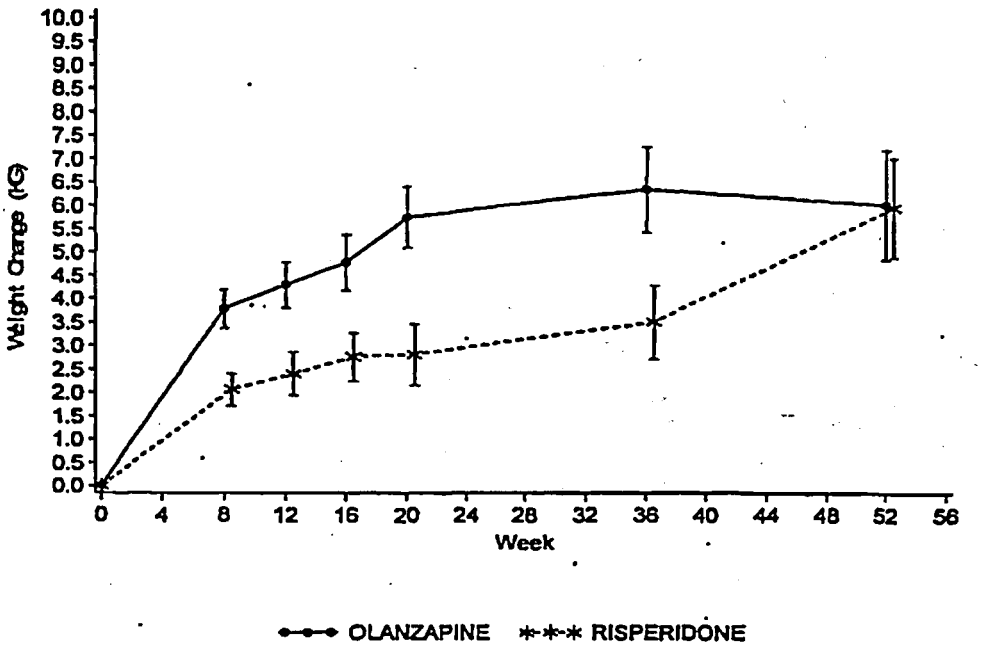
Attached are computer-generated tables and graphs displaying the results in more detail.

FIGURE 1: Cumulative Distribution of % Change in Weight at END POINT
RIS-USA-113



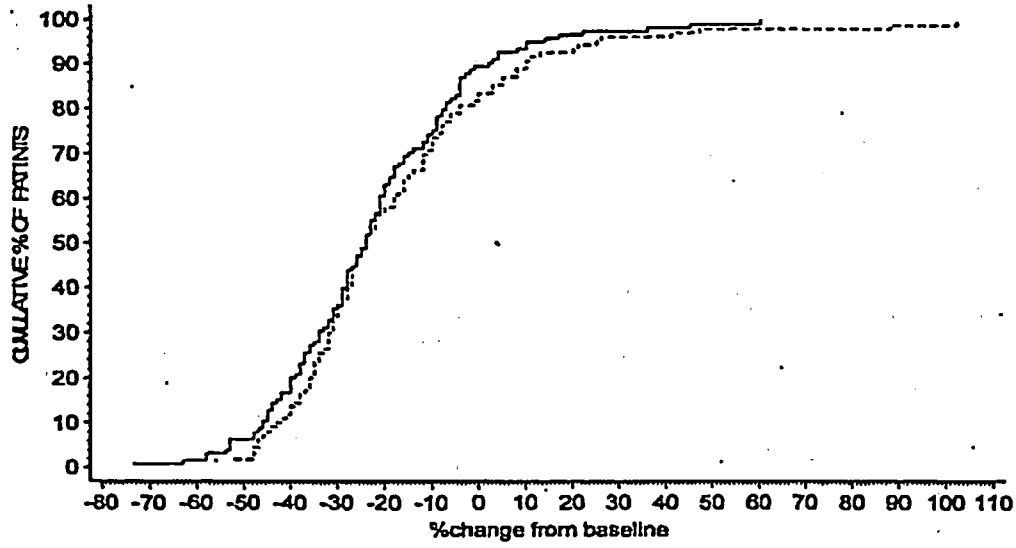
R 3242 JJRIS 02541063
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Figure 2: Average Weight Change from RIS-USA-112 Randomization +/- SE
RIS-USA-113



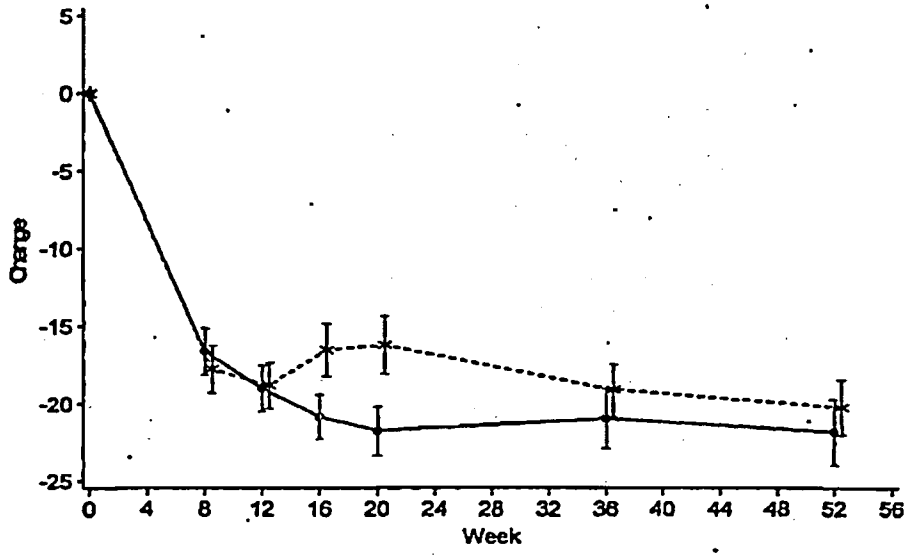
R 3243
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FIGURE 3: Cumulative Distribution of % Change in Total PANSS at End Point
RIS-USA-113: Patients in Non-Excluded Sites



OLANZAPINE (N = 129) ----- RISPERIDONE (N= 115)

Figure 4: Average Change in Total PANSS from RIS-USA-112 Randomisation +/- SE
RIS-USA-113: Patients in Non-Excluded Sites



OLANZAPINE *-*-* RISPERIDONE

DOT
Draft: 08 September 1999

JJRIS 02541065
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Confidential/Produced in Litigation Pursuant to Protective Order

From: Reines, Scott [PRDUS] [/o=JNJ/ou=JANUSTI/cn=Recipients/cn=SReines] on behalf of Reines, Scott [PRDUS]
Sent: Thursday, October 23, 2003 12:15 AM
To: Pruden, Gary [JANUS]
Cc: Jack Grebb [PRDUS] (E-mail)
Subject: FW: DDL, Lilly
Importance: High

Garry -

Lilly's DDL is pretty clever. How much commercial liability would we incur if we sent a similar letter about Risperdal, assuming the FDA is unwilling to communicate the issue?

Regards.

Scott

-----Original Message-----
From: Brann, Edward [PRDUS]
Sent: Wednesday, October 22, 2003 2:20 PM
To: Pruden, Gary [JANUS]; Deloria, Carmen [JANUS]; Fabbri, David [JANUS]; Bastean, Jeni [JANUS]; Adusumalli, Vidyasagar [PRDUS]; Caers, Ivo [PRDBE]; Eerdekens, Marielle [PRDBE]; Mahmoud, Ramy [JANUS]; Greenspan, Andrew [JANUS]; Gharabawi, Georges [JANUS]; Grebb, Jack [PRDUS]; Singer, Jack M [PRDUS]; Miller, Peter [JANUS]; Delap, Robert [PRDUS]; Neil, Garry [PRDUS]; Desantis, Patricia L [PRDUS]; Reines, Scott [PRDUS]; Grossman, Fred [PRDUS]; Rielly-Gauvin, Katherine [PGSM]; Merchant, Susan [PRDUS]; Chester, Michael [JANUS]
Cc: Berry, Sally [PRDUS]
Subject: FW: DDL, Lilly
Importance: High

Everyone,

Attached is the communication Lilly sent physicians earlier this month. It contains a very brief letter (date: Oct. 6th) and a copy of their press release (Sept. 17).

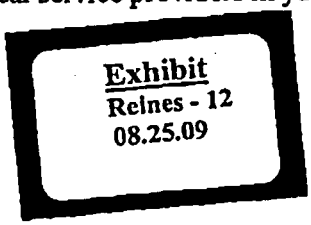
In forwarding this, I do not believe it violates the spirit of the credo, since the PR is posted on Lilly's website, and the ltr appears to be widely distributed and not intended to be confidential.
Ned

-----Original Message-----
From: sally berry [redacted]
Sent: Wednesday, October 22, 2003 1:37 PM
To: ebrann@prdus.jnj.com
Subject: DDL, Lilly

Ned, please keep my sources confidential. This e-mail program does not allow me to delete that info.

Sally

Surf and talk on the phone at the same time with broadband Internet access. Get high-speed for as low as $29.95/month.*
*Depending on the local service providers in your area.



From: Reines, Scott [PRDUS] [/o=JNJ/ou=JANUSTI/cn=Recipients/cn=SReines] on behalf of Reines, Scott [PRDUS]
Sent: Sunday, November 30, 2003 11:47 PM
To: Grebb, Jack [PRDUS]
Subject: RE: Letter to FDA

Jack -

Do you think that's sufficient? I'm troubled by the liberties they've taken. To me it seems like off-label promotion of differences among the atypical agents.

Regards.

Scott

-----Original Message-----
From: Grebb, Jack [PRDUS]
Sent: Sunday, November 30, 2003 6:29 PM
To: Reines, Scott [PRDUS]; Grossman, Fred [PRDUS]
Subject: RE: Letter to FDA

Scott,
The letter would have been approved by the CDT Leader and the CDT regulatory leader.
Jack

-----Original Message-----
From: Reines, Scott [PRDUS]
Sent: Saturday, November 29, 2003 11:59 AM
To: Fred Grossman [PRDUS] (E-mail); Jack Grebb [PRDUS] (E-mail)
Cc: Garry Neil [PRDUS] (E-mail)
Subject: RE: Letter to FDA

<< Message: FW: Letter to FDA >>
Fred / Jack -

What was the internal clearance procedure for Ramy's letter? Did PRD have any signoff?

Thanks.

Scott

-----Original Message-----
From: Adusumalli, Vidyasagar [PRDUS]
Sent: Wednesday, November 26, 2003 12:19 PM
To: Reines, Scott [PRDUS]
Subject: FW: Letter to FDA

Scott, FYI

-----Original Message-----
From: Adusumalli, Vidyasagar [PRDUS]
Sent: Wednesday, November 26, 2003 11:23 AM
To: Neil, Garry [PRDUS]; Singer, Jack M [PRDUS]
Cc: Grebb, Jack [PRDUS]; Caers, Ivo [PRDBE]; Mahmoud, Ramy [JANUS]; Grossman, Fred [PRDUS]; Brann, Edward [PRDUS]; Eerdekens, Marielle [PRDBE]; Rielly-Gauvin, Katherine [PGSM]; Pruden, Gary [JANUS]; Vergis, Janet [PGSMUS]; Koury, Loraine [PRDUS]
Subject: FW: Letter to FDA

Exhibit
Reines - 49
08.25.09

Jack and Garry,

FYI attached is a J&JPRD/JPI reply to the FDA request for a DDL on the Hyperglycemia/Diabetes Warning for Risperdal. The letter was reviewed by the PRD/JPI Team. JPI's proactive communication of the Warning to physicians and healthcare providers is also attached. We will be sending these documents to FDA this afternoon.

Regards
Sagar

<< File: FDA ltr 112503 (Diabetes).doc >>

<< File: 7872_LETTER_LINKS.pdf >>

JJRE 02106568
Confidential/Produced in Litigation Pursuant to Protective Order
R. 3248

facsimile
TRANSMITTAL

[redacted]

To:	Megan Zoschg, Pharm.D.
Sponsor:	Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
Fax #:	(609) 730-3091
Re:	Hyperglycemia and Diabetes letter dated 9/11/03
Date:	September 12, 2003
Pages:	4 (including cover letter)

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify me by telephone and return it to me at the address below by mail. Thank you.

From the desk of...
Robbin Nighswander, R.Ph., M.S.
Supervisory Regulatory Health Project Manager
Division of Neuropharmacological Drug Products
HFD-120
Food and Drug Administration
Rockville, Maryland 20857

301-594-5591
Fax 301-594-2858

Exhibit
DeSantis – 13
08.27.09

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-272
NDA 20-588
NDA 21-444

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Claude McGowan, Ph.D.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Dr. McGowan:

Please refer to your new drug application (NDA) for Risperdal (risperidone) Tablets and Oral Solution and Risperdal MTAB (risperidone) Orally Disintegrating Tablets.

After reviewing the available data pertaining to the use of atypical antipsychotic medications and diabetes mellitus adverse events, we have concluded that the product labeling for all atypical antipsychotics should be updated to include information about these events.

While we acknowledge that the relationship between atypical antipsychotic use and diabetes mellitus adverse events has not been completely described, we believe the safe use of Risperdal can be enhanced by informing prescribers and patients about these events. Increased attention to the signs and symptoms of diabetes mellitus may lead to earlier detection and appropriate treatment, and thus reduce the risk for the most serious outcomes.

We request that the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of the drug:

WARNINGS
Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including Risperdal. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics studied. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. The available data are insufficient to provide reliable estimates of differences in hyperglycemia-related adverse event risk among the marketed atypical antipsychotics.

JJRE 02929547
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R. 3250

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at baseline and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Although we believe that the labeling changes accurately reflect the currently available information about antipsychotic use and diabetes mellitus, we acknowledge that additional labeling changes may be required as new information becomes available. Areas that require additional research include, but are not limited to, identification of subpopulations at greatest risk for diabetes mellitus adverse events, exploration of the relative risk for diabetes mellitus adverse events among the different antipsychotics, and evaluation of potential mechanisms of action.

Please submit twenty copies of final printed labeling, ten of which are individually mounted on heavyweight paper or similar material, exactly as specified above as a "Supplement - Changes Being Effected." Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

JJRE 0292954E
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R. 3251

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
9/11/03 03:14:51 PM

JJRE 02929549
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R. 3252

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-272

DEC 29

Janssen Research Foundation
Attention: Ruth Wasserman
Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

RECEIVED
JAN 0 4 1994
R. A. WASSERMAN

Dear Ms. Wasserman:

Reference is made to your New Drug Application (NDA) dated April 15, 1992, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for RISPERDAL® (risperidone) 1 mg, 2 mg, 3 mg, 4 mg, and 5 mg Tablets.

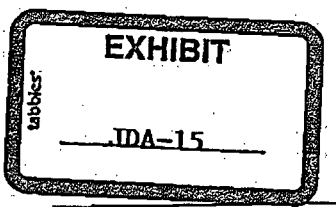
We also acknowledge receipt of your additional communications dated:

May 1, 1992	June 4, 1992	June 22, 1992
June 26, 1992	June 30, 1992	July 7, 1992
July 9, 1992	July 14, 1992	July 16, 1992
September 30, 1992	October 27, 1992	October 28, 1992
October 30, 1992	November 9, 1992	November 20, 1992
November 24,1992	December 7, 1992	December 9, 1992
December 21, 1992	December 22, 1992	December 23, 1992
February 1, 1993	February 2, 1993	February 10(2), 1993
March 5, 1993	March 9, 1993	March 11, 1993
March 15, 1993	March 25(2), 1993	March 29(2), 1993
March 30(2), 1993	March 31, 1993	April 1, 1993
April 2(2), 1993	April 8, 1993	April 13, 1993
May 4(2), 1993	May 12, 1993	May 14, 1993
May 17(2), 1993	May 24, 1993	June 3, 1993
June 18, 1993	July 1, 1993	July 6, 1993
July 9, 1993	August 10, 1993	August 20, 1993
August 23, 1993	August 25, 1993	August 27, 1993
September 24, 1993	October 13, 1993	October 28, 1993

We have completed our review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final text of labeling attached to this letter. Accordingly, the application, with these labeling revisions, is approved, effective as of the date of this letter.

Labeling

Accompanying this letter (ATTACHMENT 1) is the verbatim text of the labeling under which RISPERDAL® may be marketed.



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Biopharmaceutics

Dissolution Specifications

(a) The following "interim" dissolution specification for all strengths of Risperdal® tablets are required:

Method:	USP Apparatus II (Paddle) at 50 rpm
Media:	500 mL of 0.1 N HCl
	NLT 80% drug released in 45 minutes

(b) Within three months of the date of this approvable action, you are requested to submit dissolution data on 12 individual tablets, for each strength of Risperdal® tablets manufactured at both the sites (Beerse, Belgium and Gurabo, Puerto Rico) according to the dissolution method specified below:

USP apparatus (Paddle method) at 50 rpm in 500 mL of simulated gastric fluid (without pepsin and a pH of 1.2) at 37±0.5°C.

You have apparently conducted some dissolution using this method and based on limited data, it appears that simulated gastric fluid may reduce the variability and accelerate drug release for all the tablet strengths as compared to the current medium which is 0.1 N HCl. This may allow for setting of a more appropriate dissolution specification.

Bio-Waiver

The tablet cores for each of the five dosage strengths proposed for marketing are proportionally identical for all excipients. There are minor differences in the film coating for each of the tablet strengths representing the different color additives. Therefore, a waiver of in vivo bioequivalence study for the 2 mg, 3 mg, and 5 mg strength tablets manufactured at Beerse, Belgium and also in vivo bioequivalence study between the two manufacturing sites (Beerse, Belgium and Gurabo, Puerto Rico) for all the tablet strengths (1, 2, 3, 4, and 5 mg) are granted, based on the linear kinetics of the drug and on in vitro dissolution profiles submitted in this application for this immediate release product.

Post-Marketing Studies

Although you have provided clear evidence of the effectiveness and safety of RISPERDAL®, a number of important questions related to its optimal use remain to be answered. We note your agreement to carry out the following studies after approval:

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Clinical

Long-Term Effectiveness Studies:

Although the evidence submitted unequivocally documents the short-term efficacy of RISPERDAL® in the management of the manifestations of psychosis, there is no evidence bearing directly on the effectiveness of this drug in the maintenance treatment of remitted/partially remitted psychotic patients. Because it is likely that Risperdal will be widely used for these purposes, it is critical that appropriate clinical studies be undertaken to evaluate its safety and effectiveness in long-term use.

We note your submitted protocol for a study of relapse prevention and staff of the Division of Neuropharmacological Drug Products expect to discuss this and any other proposals with you.

Pharmacokinetic Interaction Study:

Although *in vitro* studies suggest that risperidone is not a potent inhibitor of cytochrome P450IID6, only *in vivo* studies would be capable of confirming whether or not risperidone or its active metabolite have a clinically important effect on the pharmacokinetics of other drugs metabolized by this isozyme. Consequently, an *in vivo* study is needed to explore the potential for such interaction. It is possible that a detailed submission of literature study N97249, which reported no effect of risperidone 6 mg on the metabolic ratio of dextromethorphan, will be sufficient.

Pharmacology

A lack of understanding of the mechanism underlying the high rate of perinatal mortality observed in rat pups impairs the ability of prescribers to make an informed judgement in the use of this drug product. Studies to clarify this matter are therefore needed.

The segment III reproduction studies and a multigenerational study in rats revealed an increase in pup mortality during the first four days of lactation for pups born to dams receiving risperidone at doses ranging from 0.16 to 5 mg/kg/day. Because it cannot be determined if this effect on survival is related to effects of the drug on the developing fetus in utero or is secondary to maternal neglect, we have labeled risperidone pregnancy category C. We recommend that you conduct a cross-fostering experiment in order to determine whether the deaths occurred as a result of fetal abnormalities or if they occurred because of other problems during lactation. If this experiment clearly establishes that the adverse effect on pup mortality is occurring as a result of maternal neglect rather than an effect of drug on the fetus, the labeling may be changed from pregnancy category C to pregnancy category B.

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We suggest a study comparing a control group and the high dose group (5 mg/kg/day) treated from gestation day 15 through postnatal day 21. Each group should contain 20 pregnant dams. Half of the dams in each group should be removed from the cage after giving birth and placed with a litter from the other treatment group for nursing. All groups should continue nursing through day 21 postpartum.

MANUFACTURING AND CONTROLS

The validation of the analytical methods has not been completed for this application. We would appreciate your full cooperation in resolving any problems that may arise.

Promotional Material

Please submit, in triplicate, the advertising copy that you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Neuropharmacological Drug Products and two copies to the Division of Marketing, Advertising and Communications, HFD-240, Room 17B-17. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

At the present time, we would consider any advertisement or promotional labeling for RISPERDAL® false, misleading, or lacking fair balance under sections 502(a) and 502(n) of the Act if there is presentation of data that conveys the impression that risperidone is superior to haloperidol or any other marketed antipsychotic drug product with regard to safety or effectiveness.

Please submit 12 copies of the FPL as soon as it is available. Seven of the copies should be individually mounted on heavy-weight paper or similar material. The submission should be designated for administrative purposes as "FPL for approved NDA 20-272". Approval of the submission by FDA is not required before the labeling may be used. Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required. We remind you that you must comply with the requirements for an approved NDA as set forth under 21 CFR 314.80 and 314.81

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENT

JJRP 0044421
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PDR®

51

EDITION

1997

PHYSICIANS' DESK REFERENCE®

Plaintiff Ex. 631

Janssen Pharmaceutica—Cont.

Pediatric Use: Safety and effectiveness in children have not established.

Geriatric Use: Steady-state plasma levels are generally higher in older than in younger patients, due to a moderate prolongation of the elimination half-life. Therapeutic doses, however, are similar to those used in younger adults. The rate of adverse experiences in patients greater than 65 years of age was similar to that in younger adults.

ADVERSE REACTIONS

In the U.S. clinical trial population of 1728 patients (comprising 506 with gastroesophageal reflux disorders, and the remainder with other motility disorders) the following adverse experiences were reported in more than 1% of patients treated with PROPULSID® (cisapride) and at least as often on PROPULSID® as on placebo. The percent of patients who discontinued treatment is displayed in parenthesis.

System/Adverse Event	PROPULSID® N=1042	Placebo N=686
Central & Peripheral Nervous Systems		
Headache	19.3% (1.1%)	17.1% (0.4%)
Gastrointestinal		
Diarrhea	14.2 (0.7)	10.3 (0.1)
Abdominal pain	10.2 (1.2)	7.7 (0.9)
Nausea	7.6 (1.0)	7.6 (0.3)
Constipation	6.7 (0.1)	3.4 (0.0)
Flatulence	3.5 (0.4)	3.1 (0.4)
Dyspepsia	2.7 (0.1)	1.0 (0.0)
Respiratory System		
Rhinitis	7.3 (0.1)	5.7 (0.1)
Sinusitis	3.6 (0.0)	3.5 (0.0)
Coughing	1.5 (0.2)	1.2 (0.0)
Resistance Mechanism		
Viral infection	3.6 (0.2)	3.2 (0.0)
Upper respiratory tract infection	3.1 (0.0)	2.8 (0.0)
Body as a Whole		
Pain	3.4 (0.0)	2.3 (0.0)
Fever	2.2 (0.1)	1.5 (0.0)
Urinary System		
Urinary tract infection	2.4 (0.0)	1.9 (0.0)
Micturition frequency	1.2 (0.1)	0.6 (0.0)
Psychiatric		
Insomnia	1.9 (0.3)	1.3 (0.4)
Anxiety	1.4 (0.1)	1.0 (0.1)
Nervousness	1.4 (0.2)	0.7 (0.0)
Skin & Appendages		
Rash	1.6 (0.0)	1.6 (0.3)
Pruritus	1.2 (0.1)	1.0 (0.0)
Musculoskeletal System		
Arthralgia	1.4 (0.1)	1.2 (0.0)
Vision		
Abnormal vision	1.4 (0.2)	0.3 (0.0)
Reproductive, Female		
Vaginitis	1.2 (0.0)	0.9 (0.0)

The following adverse events also reported in more than 1% of PROPULSID® patients were more frequently reported on placebo: dizziness, vomiting, pharyngitis, chest pain, fatigue, back pain, depression, dehydration, and myalgia. Diarrhea, abdominal pain, constipation, flatulence, and rhinitis all occurred more frequently in patients using 20 mg of PROPULSID® than in patients using 10 mg.

Additional adverse experiences reported to occur in 1% or less of patients in the U.S. clinical studies are: dry mouth, somnolence, palpitation, migraine, tremor, and edema.

In other U.S. and international trials and in foreign marketing experience, there have been rare reports of seizures and extrapyramidal effects, tachycardia, elevated liver enzymes, hepatitis, thrombocytopenia, leukopenia, aplastic anemia, pancytopenia, and granulocytopenia. The relationship of PROPULSID® to the event was not clear in these cases.

There have been rare cases of sinus tachycardia reported. Rechallenge precipitated relapse in some of those patients.

Rare cases of cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation, in some cases resulting in death, have been reported. Most of these patients had been receiving multiple other medications and had pre-existing cardiac disease or risk factors for arrhythmias. A causal relationship to PROPULSID® has not been established.

OVERDOSAGE

Reports of overdosage with PROPULSID® (cisapride) include an adult who took 540 mg and for 2 hours experienced retching, borborygmi, flatulence, stool frequency and urinary frequency. A one-month-old male infant received 2 mg/kg of cisapride, 10 times the prescribed dose, four times per day for 5 days. The patient developed third degree heart block and subsequently died of right ventricular perforation caused by pacemaker wire insertion.

Treatment should include gastric lavage and/or activated charcoal, close observation and general supportive measures.

In instances of overdose, patients should be evaluated for possible QT prolongation and for factors that can predispose to the occurrence of ventricular arrhythmias, including torsades de pointes.

Single oral doses of cisapride at 4000 mg/kg, 160 mg/kg, 1280 mg/kg and 640 mg/kg were lethal in adult rats, neonatal rats, mice, and dogs, respectively. Symptoms of acute toxicity were ptosis, tremors, convulsions, dyspnea, loss of righting reflex, catalepsy, catatonia, hypotonia and diarrhea.

DOSAGE AND ADMINISTRATION

5 mL (1 teaspoon) suspension=5 mg.

Adults: Initiate therapy with one 10 mg tablet of PROPULSID® (cisapride) or 10 mL of the suspension 4 times daily at least 15 minutes before meals and at bedtime. In some patients the dosage will need to be increased to 20 mg, given as above, to obtain a satisfactory result.

In elderly patients, steady-state plasma levels are generally higher due to a moderate prolongation of the elimination half-life. Therapeutic doses, however, are similar to those used in younger adults.

HOW SUPPLIED

PROPULSID® tablets are provided as scored white tablets debossed "Janssen" and P/10 containing the equivalent of 10 mg of cisapride in blister packages of 100 (NDC 50458-430-01) and in bottles of 100 (NDC 50458-430-10) and 500 (NDC 50458-430-50).

PROPULSID® is also provided as blue tablets, debossed "Janssen" and P/20, containing the equivalent of 20 mg cisapride in blister packages of 100 (NDC 50458-440-01) and in bottles of 100 (NDC 50458-440-10) and bottles of 250 (NDC 50458-440-25).

PROPULSID® Suspension is provided as a bright pink homogeneous suspension containing 1 mg/mL of cisapride in 16 oz. bottles containing 450 mL (NDC 50458-450-45).

Store at 15°–25°C (59°–77°F). Protect the tablets from moisture. The 20 mg tablets should also be protected from light.

JANSSEN PHARMACEUTICA
Titusville, NJ 08560

Revised August 1994, September 1995, February 1996

U.S. Patent No. 4,962,115

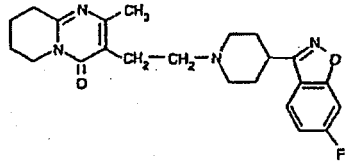
Shown in Product Identification Guide, page 318

RISPERDAL®

[ris'pər dāl]
(risperidone) Tablets

DESCRIPTION

RISPERDAL® (risperidone) is an antipsychotic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® for oral use is available in tablets of 1 mg (white, scored), 2 mg (orange), 3 mg (yellow), and 4 mg (green). Inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 2, 3, and 4 mg also contain talc and titanium dioxide. The 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are; tartaric acid, benzoic acid, sodium hydroxide and purified water (formulation F68).

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the therapeutic effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for serotonin type 2 ($5HT_2$), dopamine type 2 (D_2), and H_1 histaminergic receptors. Risperidone antagonizes other receptors, but with lower affinity.

RISPERDAL® has low to moderate affinity (Ki of 9.8 to 49 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$ and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the α_1 adrenergic receptors, and high affinity for a haloperidol-sensitive sigma site, and binds to α_2 adrenergic receptors at concentrations $>10^{-5}$ M) for cholinergic muscarinic and β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Risperidone is well absorbed, as illustrated in an absolute bioavailability study involving a single 1 mg oral dose and a dose as a solution in three healthy male subjects. Mean recovery of radioactivity at one week was 84% with 70% in the urine and 15% in the feces.

Risperidone is extensively metabolized in the liver by cytochrome $P_{450}IID_6$ to a major active metabolite, 9-hydroxyrisperidone, which is the predominant antipsychotic plasma metabolite. Risperidone appears approximately equi-effective with 9-hydroxyrisperidone with respect to receptor binding activity and in animals. (A second minor pathway is *N*-dealkylation.) Consequently, the clinical effect of the drug is due to the combined concentrations of risperidone and 9-hydroxyrisperidone are dose proportional over the [illegible] 16 mg daily (0.5 to 8 mg BID). The relative bioavailability of risperidone from a tablet was 94% compared to a solution. Food does not affect the extent of absorption of risperidone. Thus, risperidone may be given with or without meals. The absolute bioavailability of risperidone was 70% (CV=25%).

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is cytochrome P-[illegible] debrisoquin hydroxylase, the enzyme responsible for the polymorphism of many neuroleptics, antidepressants, beta blockers, and other drugs. Cytochrome P-[illegible] genetic polymorphism (about 6-8% of [illegible] low percent of Asians have little or no activity, "poor metabolizers") and to inhibition by a variety of [illegible] and some non-substrates, notably quinidine. [illegible] bolizers convert risperidone rapidly into [illegible] done, while poor metabolizers convert it [illegible] Extensive metabolizers, therefore, have [illegible] and higher 9-hydroxyrisperidone concentrations than poor metabolizers. Following oral administration of a tablet, mean peak plasma concentrations occur [illegible] hour. Peak 9-hydroxyrisperidone occurs [illegible] in extensive metabolizers, and 17 hours in poor metabolizers.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours in extensive metabolizers and 30 hours (CV=[illegible]) in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and within 4 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Because risperidone and 9-hydroxyrisperidone are approximately equi-effective, the sum of their concentrations is the dose-related plasma analytic moiety. The pharmacokinetics of the sum of risperidone and 9-hydroxyrisperidone, after single and multiple dosing, are similar in extensive and poor metabolizers. The mean elimination half-life of about 20 hours can be used when comparing adverse reaction rates in extensive and poor metabolizers in controlled and open studies. No differences were seen.

Risperidone could be subject to two kinds of drug interactions. First, inhibitors of cytochrome P-[illegible] interfere with conversion of risperidone to 9-hydroxyrisperidone. This in fact occurs with quinidine, giving rise to a similar profile in recipients a risperidone pharmacokinetic profile similar to that in poor metabolizers. The favorable and advanced [illegible] peridone in patients receiving quinidine has been evaluated, but observations in a modest number of patients (approximately equal to 70) of poor metabolizers given quinidine does not suggest important differences between extensive and poor metabolizers. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by cytochrome $P_{450}IID_6$. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (see PRECAUTIONS and DRUG INTERACTIONS).

The plasma protein binding of risperidone is low. It is bound over the in vitro concentration range of 0.5 to 20 ng/mL. Binding is decreased with increasing concentrations of [illegible] tein. The plasma binding of 9-hydroxyrisperidone is similar. Neither the parent nor the metabolite displaces [illegible] from the plasma binding sites. High [illegible] tions of sulfamethazine (100 μg/mL) [illegible] and carbamazepine (10 μg/mL) caused only [illegible]

...l that this drug's ...
...a combination of ...
...($5HT_2$) antagonism ...
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...(P... 4L©.
...selective ...
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...t, a... mine type 2 ...
...ntaminergic recep...
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...erotonin $5HT_{1C}$, $5HT_1$ ...
...(Ki of 620 to 800 nM) ...
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...oximately equi-effective ...
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...nd minor pathway is ...
...linical effect of the drug ...
...centrations of risperidone ...
...dose proportional over ...
...1.5 to 8 mg BID). The ...
...lone from a tablet was ...
...solution. Food does not ...
...rption of risperidone. ...
...without meals. The ...
...lone was 70% (CV = ...
...catalyzing hydroxylation ...
...eridone is cytochrome ...
...ydroxylase, the enzyme ...
...y neuroleptics, antidepressants ...
...ier drugs. Cytochrome ...
...orphism (about 6-8% of ...
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...) and to inhibition by a ...
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...hydroxyrisperidone ...
Following oral administration ...
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...eridone, after single and ...
...ensive and poor metabolizers ...
...ation half-life of about ...
...lverse reaction rates in ...
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...ould be subject to two ...
...inhibitors of cytochrome ...
...ersion of risperidone to ...
...ccurs with quinidine, ...
...peridone pharmacokinetics ...
...zers. The favorable and ...
...atients receiving quinidine ...
...servations in a modest ...
...o 70) of poor metabolizers ...
...portant differences ...
...ers. It would also be ...
...metabolism of other ...
...soHD_6. Relatively weak ...
...sr ...ts this is unlikely ...
...I' ...CTIONS).
...r ... binding of risperidone ...
...ro concentration range ...
...increasing concentrations ...
...ma binding of 9-hydroxyrisperidone ...
...arent nor the metabolite ...
...na binding sites. High ...
...nethazine (100 μg/mL) ...
...epine (10 μg/mL) ...

...of risperidone at 10 ng/mL and 9-hydroxy... 50 ng/mL, changes of unknown clinical ...

...in patients with moderate to severe ...
...ance of the sum of risperidone and its ...
...decreased by 60% compared to young ...
...RISPERDAL® doses should be reduced ...
...renal disease (See PRECAUTIONS and ...
...ADMINISTRATION).
...While the pharmacokinetics of risperidone ...
...ts with liver disease were comparable to ...
...healthy subjects, the mean free fraction of ...
...ma was increased by about 35% because ...
...concentration of both albumin and α_1-acid ...
...RISPERDAL® doses should be reduced in ...
...disease (See PRECAUTIONS and DOSAGE ...
...INISTRATION).
...elderly subjects renal clearance of both ...
...9-hydroxyrisperidone was decreased, and ...
...lives were prolonged compared to young ...
...Dosing should be modified accordingly in ...
...ts (See DOSAGE AND ADMINISTRATION).

...*Effects:* No specific pharmacokinetic ...
...ed to investigate race and gender effects, ...
...pharmacokinetic analysis did not identify ...
...ces in the disposition of risperidone due to ...
...corrected for body weight or not) or race.

...RISPERDAL® in the management of the ...
...psychotic disorders was established in ...
...6- to 8-week) controlled trials of psychotic ...
...of DSM III-R criteria for schizophrenia. ...
...ts were used for assessing psychiatric ...
...in these studies, among them the Brief ...
...g Scale (BPRS), a multi-item inventory of ...
...thology traditionally used to evaluate the ...
...tment in psychosis. The BPRS psychosis ...
...l disorganization, hallucinatory behavior, ...
...d unusual thought content) is considered a ...
...ful subset for assessing actively ...
...chronic patients. A second traditional as... ...
...ical Global Impression (CGI), reflects the ...
...trained observer, fully familiar with the ...
...of schizophrenia, about the overall clinical ...
...ve. In addition, two more recently developed ...
...ell evaluated scales, were employed; these ...
...tive and Negative Syndrome Scale (PANSS) ...
...for Assessing Negative Symptoms (SANS). ...
...trials follow:
...placebo-controlled trial (n=160) involving ...
...RDAL® in doses up to 10 mg/day (BID ...
...RDAL® was generally superior to placebo ...
...score, on the BPRS psychosis cluster, and ...
...ior to placebo on the SANS.
...placebo-controlled trial (n=513) involving 4 ...
...SPERDAL® (2, 6, 10, and 16 mg/day, on a ...
...4 RISPERDAL® groups were generally ...
...on the BPRS total score, BPRS psychosis ...
...verity score; the 3 highest RISPERDAL® ...
...generally superior to placebo on the ...
...subscale. The most consistently positive ...
...measures were seen for the 6 mg dose group, ...
...suggestion of increased benefit from larger ...
...dose comparison trial (n=1356) involving 5 ...
...SPERDAL® (1, 4, 8, 12, and 16 mg/day, on a ...
...the four highest RISPERDAL® dose groups ...
...superior to the 1 mg RISPERDAL® dose ...
...total score, BPRS psychosis cluster, and CGI ...
...some of the dose groups were superior to the 1 ...
...PANSS negative subscale. The most consistent ...
...responses were seen for the 4 mg dose group.

...AND USAGE
...risperidone) is indicated for the manage... ...
...manifestations of psychotic disorders ...
...efficacy of RISPERDAL® was established ...
...to 8 weeks) controlled trials of schizophrenic ...
...CLINICAL PHARMACOLOGY).
...of RISPERDAL® in long-term use, that is, ...
...8 weeks, has not been systematically evalu... ...
...trials. Therefore, the physician who elects ...
...DAL® for extended periods should periodically ...
...the long-term usefulness of the drug for the ...
...(See DOSAGE AND ADMINISTRA...

...RAINDICATIONS
...risperidone) is contraindicated in patients ...
...hypersensitivity to the product.

...ant Syndrome (NMS)
...ical symptom complex sometimes referred to ...
...Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Potential for Prearrhythmic Effects: Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12-16 mg/day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrhythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL® treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 1 mg BID in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (See DOSAGE AND ADMINISTRATION). A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., (dehydration and hypovolemia). Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures: During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL® treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (See CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism: Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to other antipsychotic agents. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. The electrocardiograms of approximately 380 patients who received RISPERDAL® or 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the data revealed one finding of potential concern, i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen

Continued on next page

Janssen Pharmaceutica—Cont.

in the smaller placebo group. There were 3 such episodes in approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See WARNINGS AND PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²), and an increase in the free fraction of the risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (See DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance: Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed an infant if they are taking RISPERDAL®.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking RISPERDAL®.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Drugs that Inhibit Cytochrome $P_{450}IID_6$ and Other P_{450} Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome $P_{450}IID_6$, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n is approximately equal to 70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made. In vitro studies showed that drugs metabolized by other P_{450} isozymes, including 1A1, 1A2, IIC9, MP, and IIIA4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome $P_{450}IID_6$: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome $P_{450}IID_6$. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

TUMOR TYPE	SPECIES	SEX	MULTIPLE OF MAXIMUM HUMAN DOSE in mg/m² (mg/kg)	
			LOWEST EFFECT LEVEL	HIGHEST NO EFFECT LEVEL
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6 (37.5)	1.5 (9.4)
Mammary gland neoplasms, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (See Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis: No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose on a mg/m² basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the human dose on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C: The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats and in one Segment II study in New Zealand rabbits. The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the human dose on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses 0.1 to 3 times the human dose on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose 1.5 times higher than the human dose on a mg/m² basis. Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERDAL® therapy is unknown.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

Nursing Mothers

It is not known whether or not risperidone is excreted in human milk. In animal studies, risperidone and 9-hydroxyrisperidone were excreted in breast milk. Therefore, women receiving RISPERDAL® should not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. A lower starting dose is recommended for all geriatric patients reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased renal, or cardiac function, and a greater frequency of hypotension (See CLINICAL PHARMACOLOGY, SPECIAL POPULATIONS, and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 9% percent (244/2697) of risperidone-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared to 7% on placebo and 10% on active control. The most common events (≥0.3%) associated with discontinuation and considered to be possibly or probably related included:

Adverse Event	RISPERDAL®
Extrapyramidal symptoms	2.1%
Dizziness	0.7%
Hyperkinesia	0.6%
Somnolence	0.5%
Nausea	0.3%

Suicide attempt was associated with discontinuation of RISPERDAL® treated patients compared to placebo patients, but, given the almost 40-fold longer exposure time in RISPERDAL® compared to placebo, this is unlikely that suicide attempt is a risperidone adverse event (See PRECAUTIONS). The incidence of extrapyramidal symptoms was 0% in placebo-treated patients and 3.8% in active-control patients in the pivotal trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Trials: In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in the RISPERDAL® groups and at least twice the placebo rate were: anxiety, somnolence, extrapyramidal symptoms, constipation, nausea, dyspepsia, rhinitis, and tachycardia.

Adverse events were also elicited in one of these trials (i.e., in the fixed-dose trial comparing placebo and doses of 2, 6, 10, and 16 mg/day) with a standardized checklist for detecting adverse events. As expected, this more sensitive than spontaneous reporting. By this method, following additional common adverse events were present at at least 5% and twice the placebo: increased dream activity, increased salivation, accommodation disturbances, reduced libido, ejaculation disturbances, diarrhea, weight gain, diminished sexual desire, erectile dysfunction, anorgasmia, dysfunction, and orgastic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL® Treated Patients: The following enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL® treated patients treated for up to 8 weeks as among placebo-treated patients in placebo-controlled trials. Results of two 6- to 8-week controlled trials in which RISPERDAL® doses of 2, 6, 10, or 16 mg/day were compared to placebo, the dose comparison trial, or up to a maximum dose of 16 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤10 mg/day and >10 mg/day) who spontaneously reported at least one event of the type listed at some time during their treatment. Patients receiving 2, 6, or 10 mg did not differ materially from those receiving 16 mg. The adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in a clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescriber with some basis for estimating the relationship of side effects to drug and nondrug factors in the population studied.

Table 1:

Body System/ Preferred Term	Treatment Experience 6- to 8-week ≤10 mg/day (N=2036)	>10 mg/day (N=661)	Placebo (N=1409)	Ris 2 (N=120)	Ris 4 (N=120)	Ris 8 (N=120)	Ris 12 (N=120)	Ris 16 (N=120)
Psychiatric Disorders								
Insomnia	12%	13%	11%	13%	13%	13%	13%	13%
Agitation	3%	4%	3%	0.9%	1.7%	1.7%	1.7%	1.7%

	12%	20%	9%
	3%	8%	1%
	1%	3%	1%
	17%	34%	16%
	14%	12%	12%
	4%	7%	1%
	7%	13%	3%
	6%	4%	3%
	5%	10%	4%
	5%	7%	4%
	4%	1%	0%
	2%	0%	1%
	2%	0%	0%
	10%	8%	4%
	3%	3%	1%
	2%	1%	1%
	2%	3%	0%
	1%	0%	0%
	2%	0%	1%
	2%	3%	1%
	2%	3%	0%
	2%	5%	1%
	2%	4%	0%
	1%	0%	0%
	3%	3%	1%
	2%	1%	1%
	2%	3%	0%
	3%	5%	0%

Vital Sign Changes: RISPERDAL® is associated with orthostatic hypotension and tachycardia (See PRECAUTIONS).

Weight changes: The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6- to 8-week placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes: A between group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (See PRECAUTIONS).

ECG Changes: The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (See WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® (risperidone) were administered to 2607 patients in phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology (Note: These events are marked with an asterisk in the listings that follow).

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders: Frequent: increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: Frequent: increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-Intestinal Disorders: Frequent: anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: Frequent: fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders: Frequent: increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders: Infrequent: abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders: Frequent: polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-skeletal System Disorders: Infrequent: myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female: Frequent: menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: Infrequent: increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: Infrequent: epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: Infrequent: anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male: Frequent: erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders: Rare: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders: Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: Rare: bitter taste.

* Incidence based on elicited reports.

Post introduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL. A causal relationship with RISPERDAL has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychologic Dependence: RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Premarketing experience includes eight reports of acute RISPERDAL® overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QI. Another case, involving an estimated overdose of 36 mg, was

Continued on next page

Janssen Pharmaceutica—Cont.

associated with a seizure. Postmarketing experience indicates reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia and hypotension. Other adverse events reported since market introduction which were temporally, (but not necessarily causally) related to RISPERDAL® overdose, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

ual Initial Dose: RISPERDAL® (risperidone) should be dministered on a BID schedule, generally beginning with 1 g BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. In some patients, slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1 mg BID are recommended. Antipsychotic efficacy was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL®, however, maximal effect was generally seen in a range of 4 to 6 mg/day. Doses above 6 mg/day were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Dosage in Special Populations: The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of the risperidone, possibly resulting in an enhanced effect (See CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (See PRECAUTIONS).

Maintenance Therapy: While there is no body of evidence available to answer the question of how long the patient treated with RISPERDAL® should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on RISPERDAL®, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching from Other Antipsychotics: There are no systematically collected data to specifically address switching from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients, more gradual discontinuation may be most appropriate for other patients. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and "R" and the strength "1", "2", "3", or "4".

1 mg white, scored, tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01. bottles of 500 NDC 50458-300-50

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01. bottles of 500 NDC 50458-320-50

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01. bottles of 500 NDC 50458-330-50

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-10) is supplied in 100mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Patient Instructions (including illustrations) for using the RISPERDAL® (risperidone) calibrated dispensing-pipette are provided. Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice and low-fat milk; it is NOT compatible with either cola or tea, however.

STORAGE AND HANDLING - RISPERDAL® tablets should be stored at controlled room temperature (59°-77°F/15°-25°C) away from children, and should be protected from light and moisture.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature (59°-77°F/15°-25°C) away from children, and should be protected from light and freezing.

US Patent 4,804,663

July 1995, February 1996

JANSSEN
PHARMACEUTICA
Titusville, NJ 08560

Shown in Product Identification Guide, page 318

SPORANOX ℞

[spor'ah-nāks"]
(itraconazole)
100 mg capsules

WARNING: Coadministration of terfenadine with itraconazole is contraindicated. Serious cardiovascular adverse events, including death, ventricular tachycardia, and torsades de pointes have occurred in patients taking itraconazole concomitantly with terfenadine. This is due to elevated terfenadine concentrations caused by itraconazole. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections.

Another oral azole antifungal, ketoconazole, inhibits the metabolism of astemizole, resulting in elevated plasma concentrations of astemizole and its active metabolite desmethylastemizole, which may prolong QT intervals. Based on results of an *in vitro* study and the chemical resemblance of itraconazole and ketoconazole, coadministration of astemizole and itraconazole is contraindicated. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections.

Coadministration of cisapride with itraconazole is contraindicated. Serious cardiovascular adverse events including death, ventricular tachycardia, and torsades de pointes have occurred in patients taking itraconazole concomitantly with cisapride. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections.

DESCRIPTION

SPORANOX is the brand name for itraconazole, a synthetic triazole antifungal agent. Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. It may be represented by the following nomenclature:

(±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2R*,4S*)-2- (2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)- 1,3-dioxolan-4-yl]methoxy]phenyl] -1- piperazinyl]phenyl] -Δ²-1,2,4-triazolin-5-one

mixture with (±) -1 -[(R*)-sec-butyl]-4-[p-[4-[p-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1- piperazinyl]phenyl]-Δ²-1,2,4-triazolin-5-one

or

(±)-1-[(RS)-sec-butyl]-4-[p-[4-[p-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ²-1,2,4-triazolin-5-one

Itraconazole has a molecular formula of C[illegible], a molecular weight of 705.64. It is a white to [illegible] ish powder. It is insoluble in water, very [illegible] alcohols, and freely soluble in dichloromethane. [illegible] of 3.70 (based on extrapolation of values [illegible] thanolic solutions) and a log (n-octanol/water) coefficient of 5.66 at pH 8.1.

SPORANOX contains 100 mg of itraconazole [illegible] spheres. Inactive ingredients are gelatin, [illegible] methylcellulose, polyethylene glycol (PEG) [illegible] sucrose, titanium dioxide, FD&C Blue No. 1, [illegible] 2, D&C Red No. 22 and D&C Red No. 28.

CLINICAL PHARMACOLOGY

Mode of Action: *In vitro* studies have [illegible] itraconazole inhibits the cytochrome P-450-[illegible] thesis of ergosterol, which is a vital component [illegible] membranes.

Pharmacokinetics and Metabolism: Note: [illegible] concentrations reported below were measured [illegible] formance liquid chromatography (HPLC) [illegible] itraconazole. When itraconazole in plasma is [illegible] bioassay, values reported are approximately [illegible] than those obtained by HPLC due to the presence [illegible] active metabolite, hydroxyitraconazole. [illegible] section.)

The pharmacokinetics of itraconazole after [illegible] ministration and its absolute oral bioavailability [illegible] oral solution were studied in a randomized, [illegible] using six healthy male volunteers. The [illegible] ance averaged 381 ± 95 mL/min and the [illegible] distribution averaged 796 ± 185 L. The [illegible] oral bioavailability of itraconazole was [illegible] The oral bioavailability of itraconazole [illegible] SPORANOX (itraconazole capsules) is [illegible] meal. The pharmacokinetics of itraconazole [illegible] using six healthy male volunteers who received over design, single 100 mg doses of itraconazole [illegible] ylene glycol capsule, with or without a full meal. [illegible] six volunteers also received 50 mg or 200 mg of [illegible] in a cross-over design. In this study, only [illegible] concentrations were measured. Presented in the [illegible] are the respective pharmacokinetic parameters of itraconazole:

	50 mg (fed)	100 mg (fed)	100 mg (fasted)
C_{max} (ng/mL)	45 ± 16	132 ± 67	38 ± 20
T_{max} (hours)	3.2 ± 1.3	4.0 ± 1.1	3.8 ± [illegible]
$AUC_{0-\infty}$ (ng·h/mL)	567 ± 264	1899 ± 838	722 ± [illegible]

Values are means ± [illegible]

Doubling the SPORANOX dose results in [illegible] three-fold increase in the itraconazole [illegible] tions.

Values given in the table below represent [illegible] over pharmacokinetics study in which [illegible] unteers each took a single 200 mg dose of [illegible] or without a full meal:

	Itraconazole	
	Fed	Fasted
C_{max} (ng/mL)	239 ± 85	140 ± 65
T_{max} (hours)	4.5 ± 1.1	3.9 ± 1.0
AUC_{∞} (ng·h/mL)	3423 ± 1154	2094 ± 905
$t_{1/2}$ (hours)	21 ± 5	21 ± 7

Values are means ± [illegible]

Absorption of itraconazole under fasted [illegible] viduals with relative or absolute [illegible] tients with AIDS or volunteers taking [illegible] suppressors (e.g. H_2 inhibitors) [illegible] SPORANOX was administered with a [illegible] teen males with AIDS received [illegible] SPORANOX under fasted conditions [illegible] or 8 ounces of a cola beverage in a [illegible]

RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION

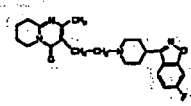
RISPERDAL® M-TAB®
(RISPERIDONE)
ORALLY DISINTEGRATING TABLETS

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Increased Mortality in Elderly Patients with Dementia–Related Psychosis
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. RISPERDAL® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL® M-TAB® Orally Disintegrating Tablets are available in 0.5 mg (light coral), 1 mg (light coral), 2 mg (coral), 3 mg (coral), and 4 mg (coral) strengths.

RISPERDAL® M-TAB® Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil. In addition, the 3 mg and 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablets contain xanthan gum.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10^{-4} M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Pharmacokinetic studies showed that RISPERDAL® M-TAB® Orally Disintegrating Tablets and RISPERDAL® Oral Solution are bioequivalent to RISPERDAL® Tablets.

Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (2 mcg/mL), and carbamazepine (10 mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism and Drug Interactions

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through *N*-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug (e.g., the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions (see PRECAUTIONS - Drug Interactions). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n≈70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment (see PRECAUTIONS – Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Administration of RISPERDAL® with Certain Other Medications).

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10% (see PRECAUTIONS – Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Administration of RISPERDAL® with Certain Other Medications).

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13) (see PRECAUTIONS – Drug Interactions).

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone (see PRECAUTIONS – Drug Interactions).

There were no significant interactions between risperidone (1 mg QD) and erythromycin (500 mg QID) (see PRECAUTIONS – Drug Interactions).

Cimetidine and ranitidine increased the bioavailability of risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of the active moiety, whereas ranitidine increased the AUC of the active moiety by 20%.

Amitriptyline did not affect the pharmacokinetics of risperidone or the active moiety.

In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

RISPERDAL® (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of ^{14}C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of the active moiety, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Special Populations

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly

In healthy elderly subjects, renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (see DOSAGE AND ADMINISTRATION).

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

CLINICAL TRIALS

Schizophrenia

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4- to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a

Plaintiff Ex. 640

R. 3263

particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS) were employed.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (> 20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

Bipolar Mania

Monotherapy

The efficacy of RISPERDAL® in the treatment of acute manic or mixed episodes was established in 2 short-term (3-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=246), limited to patients with manic episodes, which involved dose range of RISPERDAL® 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 4.1 mg/day), RISPERDAL® was superior to placebo in the reduction of Y-MRS total score.

(2) In another 3-week placebo-controlled trial (n=286), which involved a dose range of 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 5.6 mg/day), RISPERDAL® was superior to placebo in the reduction of Y-MRS total score.

Combination Therapy

The efficacy of risperidone with concomitant lithium or valproate in the treatment of acute manic or mixed episodes was established in one controlled trial in patients who met the DSM-IV criteria for Bipolar I Disorder. This trial included patients with or without psychotic features and with or without a rapid-cycling course.

(1) In this 3-week placebo-controlled combination trial, 148 in- or outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL®, placebo, or an active comparator, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.8 mg/day), combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.4 mEq/L or 50 mcg/mL to 120 mcg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 3-week placebo-controlled combination trial, 142 in- or outpatients on lithium, valproate, or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL® or placebo, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.7 mg/day), combined with lithium, valproate, or carbamazepine (in therapeutic ranges of 0.6 mEq/L to 1.4 mEq/L for lithium, 50 mcg/mL to 125 mcg/mL for valproate, or 4-12 mcg/mL for carbamazepine, respectively) was not superior to lithium, valproate, or carbamazepine alone in the reduction of Y-MRS total score. A possible explanation for the failure of this trial was induction of risperidone and 9-hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxyrisperidone.

INDICATIONS AND USAGE

Schizophrenia

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6- to 8-weeks) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see CLINICAL PHARMACOLOGY – Clinical Trials). Nevertheless, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Bipolar Mania

Monotherapy

RISPERDAL® is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL® was established in two placebo-controlled trials (3-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

Combination Therapy

The combination of RISPERDAL® with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL® in combination with lithium or valproate was established in one placebo-controlled (3-week) trial with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

The effectiveness of RISPERDAL® for longer-term use, that is, for more than 3 weeks of treatment of an acute episode, and for prophylactic use in mania, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. RISPERDAL® (risperidone) is not approved for the treatment of dementia-related psychosis (see Boxed Warning).

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that: (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. (See also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.)

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

R. 3264

PRECAUTIONS

General

Orthostatic Hypotension

RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2 and 3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures

During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL®-treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.)

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see PRECAUTIONS – Carcinogenesis, Mutagenesis, Impairment of Fertility). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high-dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for eliciting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism

Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic Effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness

Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL®, may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²), and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in these patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance

Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised not to breast-feed an infant if they are taking RISPERDAL®.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL®.

Phenylketonurics

Phenylalanine is a component of aspartame. Each 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.84 mg phenylalanine; each 3 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.63 mg phenylalanine; each 2 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.42 mg phenylalanine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Amitriptyline did not affect the pharmacokinetics of risperidone or the active moiety. Cimetidine and ranitidine increased the bioavailability of risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of the active moiety, whereas ranitidine increased the AUC of the active moiety by 20%.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Carbamazepine and Other Enzyme Inducers

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment.

Fluoxetine and Paroxetine

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Lithium

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13).

Valproate

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone.

Digoxin

RISPERDAL® (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism.

There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY).

Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times

R. 3265

the MRHD (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m² (mg/kg)	
			Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6.0 (37.5)	1.5 (9.4)
Mammary gland neoplasm, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5-6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS, General - Hyperprolactinemia).

Mutagenesis

No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, *in vitro* rat hepatocyte DNA-repair assay, *in vivo* micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility

Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m² basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the MRHD on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C

Teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m² basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m² basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m² basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m² basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to RISPERDAL® therapy is unknown. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9–hydroxyrisperidone are excreted in milk. Risperidone and 9–hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis

In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone when compared to patients treated with risperidone alone or with placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of RISPERDAL® regardless of concomitant use with furosemide. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. (See Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.)

ADVERSE REACTIONS

The following findings are based on the short-term, placebo-controlled, North American, premarketing trials for schizophrenia and acute bipolar mania. In patients with Bipolar I Disorder, treatment-emergent adverse events are presented separately for risperidone as monotherapy and as adjunctive therapy to mood stabilizers.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia. However, this information is also generally applicable to bipolar mania.

Associated With Discontinuation of Treatment

Schizophrenia

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in Phase 2 and 3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL®-related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients, but 3.8% in active-control patients in the Phase 2 and 3 trials.

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (10/134) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 6% (7/125) of placebo-treated patients. The adverse events associated with discontinuation and considered to be possibly, probably, or very likely drug-related included paroniria, somnolence, dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events occurred in one RISPERDAL®-treated patient (0.7%) and in no placebo-treated patients (0%).

In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, there was no overall difference in the incidence of discontinuation due to adverse events (4% for RISPERDAL® vs. 4% for placebo).

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials

Schizophrenia

In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events occurred at an incidence of at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observed adverse events associated with the use of RISPERDAL® (incidence of 5% or greater and at least twice that of placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, vision abnormal, and saliva increased. In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, the most commonly observed adverse events associated with the use of RISPERDAL® were somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, and urinary incontinence.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Patients - Schizophrenia

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent among RISPERDAL®-treated patients treated at doses of ≤10 mg/day than among placebo-treated patients in the pooled results of two 6- to 8-week controlled trials. Patients received RISPERDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

R. 3266

Table 1. Incidence of Treatment-Emergent Adverse Events In 6- to 8-Week Controlled Clinical Trials[1]

Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	9%	8%	1%
Aggressive reaction	1%	3%	1%
Central & peripheral nervous system			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory system			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a whole - general			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see ADVERSE REACTIONS – Dose Dependency of Adverse Events).

Adverse Events Occurring at an Incidence of 2% or More Among RISPERDAL®-Treated Patients - Bipolar Mania

Tables 2 and 3 display adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of RISPERDAL® (1-6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms.

Table 2. Incidence of Treatment-Emergent Adverse Events In a 3-Week, Placebo-Controlled Trial - Monotherapy in Bipolar Mania[1]

Body System/ Preferred Term	RISPERDAL® (N=134)	Placebo (N=125)
Central & peripheral nervous system		
Dystonia	18%	6%
Akathisia	16%	6%
Dizziness	11%	9%
Parkinsonism	6%	3%
Hypoaesthesia	2%	1%
Psychiatric		
Somnolence	28%	7%
Agitation	8%	6%
Manic reaction	8%	6%
Anxiety	4%	2%
Concentration impaired	2%	1%
Gastrointestinal system		
Dyspepsia	11%	6%
Nausea	11%	2%
Saliva increased	5%	1%
Mouth dry	3%	2%
Body as a whole - general		
Pain	5%	3%
Fatigue	4%	2%
Injury	2%	0%

Table 2. Incidence of Treatment-Emergent Adverse Events In a 3-Week, Placebo-Controlled Trial - Monotherapy in Bipolar Mania[1] (continued)

Body System/ Preferred Term	RISPERDAL® (N=134)	Placebo (N=125)
Respiratory system		
Sinusitis	4%	1%
Rhinitis	3%	2%
Coughing	2%	2%
Skin and appendages		
Acne	2%	0%
Pruritus	2%	1%
Musculo-Skeletal		
Myalgia	5%	2%
Skeletal pain	2%	1%
Metabolic and nutritional		
Weight increase	2%	0%
Vision disorders		
Vision abnormal	6%	2%
Cardiovascular, general		
Hypertension	3%	1%
Hypotension	2%	0%
Heart rate and rhythm		
Tachycardia	3%	2%

[1] Events reported by at least 2% of patients treated with RISPERDAL® are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: headache, tremor, insomnia, constipation, back pain, upper respiratory tract infection, pharyngitis, and arthralgia.

Table 3. Incidence of Treatment-Emergent Adverse Events In a 3-Week, Placebo-Controlled Trial - Adjunctive Therapy in Bipolar Mania[1]

Body System/ Preferred Term	RISPERDAL® + Mood Stabilizer (N=52)	Placebo + Mood Stabilizer (N=51)
Gastrointestinal system		
Saliva increased	10%	0%
Diarrhea	8%	4%
Abdominal pain	6%	0%
Constipation	6%	4%
Mouth dry	6%	4%
Tooth ache	4%	0%
Tooth disorder	4%	0%
Central & peripheral nervous system		
Dizziness	14%	2%
Parkinsonism	14%	4%
Akathisia	8%	0%
Dystonia	6%	4%
Psychiatric		
Somnolence	25%	12%
Anxiety	6%	4%
Confusion	4%	0%
Respiratory system		
Rhinitis	8%	4%
Pharyngitis	6%	4%
Coughing	4%	0%
Body as a whole - general		
Asthenia	4%	2%
Urinary system		
Urinary incontinence	6%	2%
Heart rate and rhythm		
Tachycardia	4%	2%
Metabolic and nutritional		
Weight increase	4%	2%
Skin and appendages		
Rash	4%	2%

[1] Events reported by at least 2% of patients treated with RISPERDAL® are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: dyspepsia, nausea, vomiting, headache, tremor, insomnia, chest pain, fatigue, pain, skeletal pain, hypertension, and vision abnormal.

Dose Dependency of Adverse Events

Extrapyramidal Symptoms

Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS.

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

lar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing id doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

Vital Sign Changes

RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Changes

The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes

A between-group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Changes

Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute).

Other Events Observed During the Premarketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® were administered to 2607 patients in Phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous ... and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not ...ible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included, except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders

Frequent: increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders

Frequent: increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastrointestinal Disorders

Frequent: anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders

Frequent: fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders

Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders

Frequent: increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, ...ified psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

...vascular Disorders

Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders

Infrequent: abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders

Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders

Frequent: polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-Skeletal System Disorders

Infrequent: myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female

Frequent: menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders

Infrequent: increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding, and Clotting Disorders

Infrequent: epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders

Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders

Infrequent: anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male

Frequent: erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders

Rare: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders

Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses

Rare: bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, benign pituitary adenomas, cerebrovascular disorder, including cerebrovascular accident, diabetes mellitus aggravated, including diabetic ketoacidosis, hyperglycemia, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychological Dependence

RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Premarketing experience included eight reports of acute RISPERDAL® (risperidone) overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® overdose, include torsade de pointes, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Because of the rapid disintegration of RISPERDAL® M-TAB® Orally Disintegrating Tablets, pill fragments may not appear in gastric contents obtained with lavage.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in

R. 3268

the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Schizophrenia

Adult Initial Dose

RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL®; however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 8 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day, and to a target dose of 4 mg QD on the third day (see CLINICAL PHARMACOLOGY – Clinical Trials). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching From Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

Bipolar Mania

Adult Dose

Risperidone should be administered on a once daily schedule, starting with 2 mg to 3 mg per day. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments/decrements of 1 mg per day, as studied in the short-term, placebo-controlled trials. In these trials, short-term (3 week) anti-manic efficacy was demonstrated in a flexible dosage range of 1-6 mg per day (see CLINICAL PHARMACOLOGY – Clinical Trials). RISPERDAL® doses higher than 6 mg per day were not studied.

Maintenance Therapy

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with risperidone. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of risperidone in such longer-term treatment (i.e., beyond 3 weeks).

Pediatric Use

Safety and effectiveness of RISPERDAL® in pediatric patients with schizophrenia or acute mania associated with Bipolar I Disorder have not been established.

Dosage in Special Populations

The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (see PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Co-Administration of RISPERDAL® with Certain Other Medications

Co-administration of carbamazepine and other enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with risperidone would be expected to cause decreases in the plasma concentrations of active moiety (the sum of risperidone and 9-hydroxyrisperidone), which could lead to decreased efficacy of risperidone treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. The dose of risperidone need not to be titrated accordingly when fluoxetine or paroxetine is co-administered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Directions for Use of RISPERDAL® M-TAB® Orally Disintegrating Tablets

Tablet Accessing

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are supplied in blister packs of 4 tablets each.

Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg are supplied in a child-resistant pouch containing a blister with 1 tablet each.

The child-resistant pouch should be torn open at the notch to access the blister. Do not open the blister until ready to administer. Peel back foil from the side to expose the tablet. DO NOT push the tablet through the foil, because this could damage the tablet.

Tablet Administration

Using dry hands, remove the tablet from the blister unit and immediately place the entire RISPERDAL® M-TAB® Orally Disintegrating Tablet on the tongue. The RISPERDAL® M-TAB® Orally Disintegrating Tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. RISPERDAL® M-TAB® Orally Disintegrating Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to split or to chew the tablet.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50, hospital unit dose packs of 100 NDC 50458-301-01.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50, hospital unit dose packs of 100 NDC 50458-302-01.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

RISPERDAL® M-TAB® (risperidone) Orally Disintegrating Tablets are etched on one side with "R0.5", "R1", "R2", "R3", and "R4", respectively. RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are packaged in blister packs of 4 (2 X 2) tablets. RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg are packaged in a child-resistant pouch containing a blister with 1 tablet.

0.5 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-395-28, long-term care packaging of 30 tablets NDC 50458-395-30.

1 mg light coral, square, biconvex tablets: 7 blister packages per box, NDC 50458-315-28, long-term care packaging of 30 tablets NDC 50458-315-30.

2 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-325-28.

3 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-335-28.

4 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-355-28.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.

Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.

Keep out of reach of children.

RISPERDAL® M-TAB® Orally Disintegrating Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F).

Keep out of reach of children.

Rx Only

7503231 Revised March 2006 ©Janssen 2003

RISPERDAL® tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico or Janssen-Cilag, SpA, Latina, Italy

RISPERDAL® oral solution is manufactured by:
Janssen Pharmaceutica N.V., Beerse, Belgium

RISPERDAL® M-TAB® Orally Disintegrating Tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico

RISPERDAL® tablets, RISPERDAL® M-TAB® Orally Disintegrating Tablets, and oral solution are distributed by:
Janssen, L.P., Titusville, NJ 08560

Janssen, L.P.

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OVERDOSAGE

Overdosage has not been reported.

DOSAGE AND ADMINISTRATION

PASER granules should be administered with other drugs to which the organism is known or expected to be susceptible. It is most commonly administered to patients with Multi-drug Resistant TB (MDR-TB) or in other situations in which therapy with isoniazid or rifampin is not possible due to a combination of resistance and/or tolerance. The adult dosage of four grams (one packet) three times per day or correspondingly smaller doses in children should be given by sprinking on apple sauce or yogurt or by swirling in the glass to suspend the granules in an acidic drink such as tomato or orange juice.

DO NOT USE if the packet is swollen or the granules have lost their tan color, turning dark brown or purple.

HOW SUPPLIED

Carton of 30 PASER packets (NDC 49938-107-04).

Each packet contains four grams aminosalicylic acid.

PASER granules are supplied in packets containing 4 grams of aminosalicylic acid for administration three times a day by suspension in an acidic drink or food with a pH less than 5. Examples include apple sauce, yogurt, tomato or orange juice.

Distributors and Pharmacists: Store below 59°F (15°C) (in a refrigerator or freezer).

Patients are urged to store PASER in a refrigerator or freezer. PASER packets may be stored at room temperature for short periods of time.

AVOID EXCESSIVE HEAT. DO NOT USE if packet is swollen or the granules have lost their tan color, turning dark brown or purple.

Caution: Federal, law prohibits dispensing without prescription.

JACOBUS PHARMACEUTICAL CO. INC.
P.O. Box 5290
Princeton, NJ 08540

2A JULY, 1996

Janssen L.P.

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FAX: (609) 730-3138

RISPERDAL®

[ris'per dăl]
(risperidone)
Tablets/Oral Solution

RISPERDAL® M-TAB®

[ris'per dăl]
(risperidone)
Orally Disintegrating Tablets

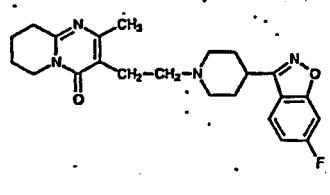
Rx

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. RISPERDAL® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2 - a] pyrimidin - 4 - one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL® M-TAB® Orally Disintegrating Tablets are available in 0.5 mg (light coral), 1 mg (light coral), 2 mg (light coral), 3 mg (coral), and 4 mg (coral) strengths.

RISPERDAL® M-TAB® Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil. In addition, the 3 mg and 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablets contain xanthan gum.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Pharmacokinetic studies showed that RISPERDAL® M-TAB® Orally Disintegrating Tablets and RISPERDAL® Oral Solution are bioequivalent to RISPERDAL® Tablets.

Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5–6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1–2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10 mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism and Drug Interactions

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone- to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through *N*-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug (e.g., the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug interactions (see PRECAUTIONS – Drug Interactions). If inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated. Clinical observations in a modest number (n=70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, coadministration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

In a drug interaction study in schizophrenic patients, subjects received risperidone titrated to 6 mg/day over 3 weeks, followed by concurrent administration with carbamazepine for an additional 3 weeks. During coadministration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and its 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment (see PRECAUTIONS – Drug Interactions and DOSAGE AND ADMINISTRATION – Administration of RISPERDAL® with Certain Other Medications).

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentrations of risperidone (given as a 6-mg/day dose, either as 3 mg BID or 6 mg QD) 2.5–2.8 fold and 3–9 fold respectively. Fluoxetine did not affect the plasma concentrations of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10% (see PRECAUTIONS – Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Administration of RISPERDAL® with Certain Other Medications).

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (Cmax) of lithium (n=13) (see PRECAUTIONS – Drug Interactions).

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three equal doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentrations (C_{max}) after concomitant administration of risperidone (see PRECAUTIONS – Drug Interactions).

There were no significant interactions between risperidone (1 mg QD) and erythromycin (500 mg QD) (see PRECAUTIONS – Drug Interactions).

Cimetidine and ranitidine increased the bioavailability of risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of the active moiety, whereas ranitidine increased the AUC of the active moiety by 20%.

Amitriptyline did not affect the pharmacokinetics of risperidone or the active moiety.

In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of lithium, biperiden, galantamine, which are metabolized by CYP 2D6. RISPERDAL® (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

Excretion

Risperidone and its metabolites are eliminated in the urine and, to a much lesser extent, via the feces. This was demonstrated by a mass balance study of a single 1 mg dose of ^{14}C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity in 7 days was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 22 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=25%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of the active moiety, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Special Populations

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. Dosage of RISPERDAL® doses should be reduced in patients with renal disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of risperidone in patients with liver disease were comparable to those in young healthy

...ates and some ... P2D6 ... α1-acid glycoprotein. ... doses should be reduced in patients with ... (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

...erly subjects, renal clearance of both ... 9-hydroxyrisperidone was decreased, and ... half-lives were prolonged compared to young ... subjects. Dosing should be modified accordingly in ... patients (see DOSAGE AND ADMINISTRATION).

...Gender Effects

...pharmacokinetic study was conducted to investigate ... and gender effects, but a population pharmacokinetic ... analysis did not identify important differences in ... of risperidone due to gender (whether corrected ... body weight or not) or race.

CLINICAL TRIALS

Schizophrenia

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4- to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing active psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall severity of the patient. In addition, the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessment Negative Symptoms (SANS) were employed.

The results of the trials follow:

In a 6-week, placebo-controlled trial (n = 160) involving administration of RISPERDAL® in doses up to 10 mg/day (QD schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

In an 8-week, placebo-controlled trial (n = 513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

In an 8-week, dose comparison trial (n = 1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. Some of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

In a 4-week, placebo-controlled dose comparison trial (n = 246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (≥ 20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2–8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this period compared to those receiving the active comparator.

Bipolar Mania

Monotherapy

The efficacy of RISPERDAL® in the treatment of acute manic or mixed episodes was established in 2 short-term (3-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed features. These trials included patients with or without psychotic features.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) with a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

1. In one 3-week placebo-controlled trial (n = 246), limited to patients with manic episodes, which involved a dose range of RISPERDAL® 1–6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 4.1 mg/day), RISPERDAL® was superior to placebo in the reduction of Y-MRS total score.
2. In another 3-week placebo-controlled trial (n = 286), which involved a dose range of 1–6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 5.6 mg/day), RISPERDAL® was superior to placebo in the reduction of Y-MRS total score.

Combination Therapy

The efficacy of risperidone with concomitant lithium or valproate in the treatment of acute manic or mixed episodes was established in one controlled trial in patients who met the DSM-IV criteria for Bipolar I Disorder. This trial included patients with or without psychotic features and with or without a rapid-cycling course.

1. In this 3-week placebo-controlled combination trial, 148 in- or outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL®, placebo, or an active comparator, in combination with their original therapy. RISPERDAL®, in a dose range of 1–6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.8 mg/day), combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.4 mEq/L or 50 mcg/mL to 120 mcg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.
2. In a second 3-week placebo-controlled combination trial, 142 in- or outpatients on lithium,[1] valproate, or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL® or placebo, in combination with their original therapy. RISPERDAL®, in a dose range of 1–6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.7 mg/day), combined with lithium, valproate, or carbamazepine (in therapeutic ranges of 0.6 mEq/L to 1.4 mEq/L for lithium, 50 mcg/mL to 125 mcg/mL for valproate, or 4–12 mcg/mL for carbamazepine, respectively) was not superior to lithium, valproate, or carbamazepine alone in the reduction of Y-MRS total score. A possible explanation for the failure of this trial was induction of risperidone and 9-hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxyrisperidone.

INDICATIONS AND USAGE

Schizophrenia

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6- to 8-weeks) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see CLINICAL PHARMACOLOGY – Clinical Trials). Nevertheless, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Bipolar Mania

Monotherapy

RISPERDAL® is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL® was established in two placebo-controlled trials (3-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

Combination Therapy

The combination of RISPERDAL® with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL® in combination with lithium or valproate was established in one placebo-controlled (3-week) trial with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

The effectiveness of RISPERDAL® for longer-term use, that is, for more than 3 weeks of treatment of an acute episode, and for prophylactic use in mania, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. RISPERDAL® (risperidone) is not approved for the treatment of dementia-related psychosis (see Boxed Warning).

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that: (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73–97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. (See also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.)

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an in-

Continued on next page

Risperdal®—Cont.

creased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2 and 3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension; e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures

During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL®-treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.)

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see PRECAUTIONS — Carcinogenesis, Mutagenesis, Impairment of Fertility). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high-dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism

Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic Effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

Use In Patients With Concomitant Illness

Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL®, may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²); and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance

Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised not to breast-feed an infant if they are taking RISPERDAL®.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL®.

Phenylketonurics

Phenylalanine is a component of aspartame. Each 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.84 mg phenylalanine; each 3 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.63 mg phenylalanine; each 2 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.42 mg phenylalanine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing [illegible], RISPERDAL® may enhance the hypotensive effect of other therapeutic agents with this potential. [illegible] RISPERDAL® may antagonize the effects of dopamine agonists.

Amitriptyline did not affect the pharmacokinetics of risperidone or the active moiety. Cimetidine [illegible] increased the bioavailability of risperidone by 26%, respectively. However, cimetidine did not affect AUC of the active moiety, whereas ranitidine [illegible] AUC of the active moiety by 20%.

Chronic administration of clozapine with risperidone decrease the clearance of risperidone.

Carbamazepine and Other Enzyme Inducers

In a drug interaction study in schizophrenic subjects received risperidone titrated to 6 [illegible] weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During administration, the plasma concentrations of risperidone and its pharmacologically active 9-hydroxyrisperidone, were decreased by about [illegible]. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be [illegible] accordingly for patients receiving carbamazepine [illegible] larly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known [illegible] ers (e.g., phenytoin, rifampin, and phenobarbital) [illegible] risperidone may cause similar decreases in the plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to [illegible] of risperidone treatment.

Fluoxetine and Paroxetine

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) [illegible] been shown to increase the plasma concentrations of risperidone 2.5–2.8 fold and 3–9 fold, respectively. Fluoxetine did not affect the plasma concentrations of 9-hydroxyrisperidone. Paroxetine lowered the plasma concentrations of 9-hydroxyrisperidone by about 10%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, a physician should re-evaluate the dosing of RISPERDAL®. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Lithium

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13).

Valproate

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three equal doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentrations (C_{max}) after concomitant administration of risperidone.

Digoxin

RISPERDAL® (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies [illegible] a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of efficacy between the two groups has been made.

In vitro studies showed that drugs metabolized by [illegible] CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and [illegible] are only weak inhibitors of risperidone metabolism. There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY).

Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a [illegible] weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In a drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in [illegible] mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are approximately equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis and about 0.75, and 3 times the MRHD (mice) or 0.4, 1.6, and 6 times the MRHD (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The following table summarizes the relationship of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

[See table at top of next page]

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were measured during the risperidone carcinogenicity studies; however, measurements during subchronic studies [illegible] showed that risperidone elevated serum prolactin [illegible]

Tumor Type	Species	Sex	Multiples of Maximum Human Dose, in mg/m² (mg/kg)	
			Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6.0 (37.5)	1.5 (9.4)
Mammary gland neoplasm, Total	rat	male	1.5 (9.4)	0.4 (2.4)

...6 in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactinmediated endocrine tumors in rodents is unknown (see PRECAUTIONS, General - Hyperprolactinemia).

Mutagenesis

No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma in vitro rat hepatocyte DNA-repair assay, *in vivo* micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility

Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m² basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a Segment I study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the MRHD on a mg/m² basis. Dose-related decreases were noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C

The teratogenic potential of risperidone was studied in two Segment II studies in Sprague-Dawley and Wistar rats (0.63–10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m² basis) and in one Segment II study in New Zealand rabbits (0.31–5 mg/kg or 0.1 to 6 times the MRHD on a mg/m² basis). The incidence of malformations was not increased compared to control in the offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16–5 mg/kg or 0.1 to 3 times the MRHD on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In a Segment III study, there was an increase in stillborn pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m² basis. In a cross-fostering study in Wistar rats, toxic effect on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups reared by control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, 5 mg/kg or 3 times the MRHD on a mg/m² basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERDAL® therapy is unknown. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of RISPERDAL® during the last trimester of pregnancy. RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis

In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone when compared to patients treated with risperidone alone or with placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of RISPERDAL® regardless of concomitant use with furosemide. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. (See Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.)

ADVERSE REACTIONS

The following findings are based on the short-term, placebo-controlled, North American, premarketing trials for schizophrenia and acute bipolar mania. In patients with Bipolar I Disorder, treatment-emergent adverse events are presented separately for risperidone as monotherapy and as adjunctive therapy to mood stabilizers.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia. However, this information is also generally applicable to bipolar mania.

Associated With Discontinuation of Treatment

Schizophrenia

Approximately 9% (244/2607) of RISPERDAL® (risperidone)treated patients in Phase 2 and 3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL®-related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients; but 3.8% in active-control patients in the Phase 2 and 3 trials.

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (10/134) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 6% (7/125) of placebo-treated patients. The adverse events associated with discontinuation and considered to be possibly, probably, or very likely drug-related included paroniria, somnolence, dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events occurred in one RISPERDAL®-treated patient (0.7%) and in no placebo-treated patients (0%).

In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, there was no overall difference in the incidence of discontinuation due to adverse events (4% for RISPERDAL® vs. 4% for placebo).

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials

Schizophrenia

In two 6- to 8-week placebo-controlled trials, spontaneously reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events occurred at an incidence of at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observed adverse events associated with the use of RISPERDAL® (incidence of 5% or greater and at least twice that of placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, vision abnormal, and saliva increased. In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, the most commonly observed adverse events associated with the use of RISPERDAL® were somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, and urinary incontinence.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Patients - Schizophrenia

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent among RISPERDAL®-treated patients treated at doses of ≤10 mg/day than among placebo-treated patients in the pooled results of two 6- to 8-week controlled trials. Patients received RISPERDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Table 1. Incidence of Treatment-Emergent Adverse Events in 6- to 8-Week Controlled Clinical Trials[1]

Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Central & peripheral nervous system			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%

Continued on next page

Risperdal—Cont.

Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory system			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a whole - general			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the 10 mg/day group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see ADVERSE REACTIONS—Dose Dependency of Adverse Events).

Adverse Events Occurring at an Incidence of 2% or More Among RISPERDAL®-Treated Patients - Bipolar Mania

Tables 2 and 3 display adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of RISPERDAL® (1–6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms.

Table 2. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Monotherapy in Bipolar Mania[1]

Body System/ Preferred Term	RISPERDAL® (N=134)	Placebo (N=125)
Central & peripheral nervous system		
Dystonia	18%	6%
Akathisia	16%	6%
Dizziness	11%	9%
Parkinsonism	6%	3%
Hypoaesthesia	2%	1%
Psychiatric		
Somnolence	28%	7%
Agitation	8%	6%
Manic reaction	8%	6%
Anxiety	4%	2%
Concentration impaired	2%	1%
Gastrointestinal system		
Dyspepsia	11%	6%
Nausea	11%	2%
Saliva increased	5%	1%
Mouth dry	3%	2%
Body as a whole - general		
Pain	5%	3%
Fatigue	4%	2%
Injury	2%	0%
Respiratory system		
Sinusitis	4%	1%
Rhinitis	3%	2%
Coughing	2%	2%
Skin and appendages		
Acne	2%	0%
Pruritus	2%	1%
Musculo-Skeletal		
Myalgia	5%	2%
Skeletal pain	2%	1%
Metabolic and nutritional		
Weight increase	2%	0%
Vision disorders		
Vision abnormal	6%	2%
Cardiovascular, general		
Hypertension	3%	1%
Hypotension	2%	0%
Heart rate and rhythm		
Tachycardia	3%	2%

[1] Events reported by at least 2% of patients treated with RISPERDAL® are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: headache, tremor, insomnia, constipation, back pain, upper respiratory tract infection, pharyngitis, and arthralgia.

Table 3. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Adjunctive Therapy in Bipolar Mania[1]

Body System/ Preferred Term	RISPERDAL® + Mood Stabilizer (N=52)	Placebo + Mood Stabilizer (N=51)
Gastrointestinal system		
Saliva increased	10%	0%
Diarrhea	8%	4%
Abdominal pain	6%	0%
Constipation	6%	4%
Mouth dry	6%	4%
Toothache	4%	0%
Tooth disorder	4%	0%
Central & peripheral nervous system		
Dizziness	14%	2%
Parkinsonism	14%	4%
Akathisia	8%	0%
Dystonia	6%	4%
Psychiatric		
Somnolence	25%	12%
Anxiety	6%	4%
Confusion	4%	0%
Respiratory system		
Rhinitis	8%	4%
Pharyngitis	6%	4%
Coughing	4%	0%
Body as a whole - general		
Asthenia	4%	2%
Urinary system		
Urinary incontinence	6%	2%
Heart rate and rhythm		
Tachycardia	4%	2%
Metabolic and nutritional		
Weight increase	4%	2%
Skin and appendages		
Rash	4%	2%

[1] Events reported by at least 2% of patients treated with RISPERDAL® are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: dyspepsia, nausea, vomiting, headache, tremor, insomnia, chest pain, fatigue, pain, skeletal pain, hypertension, and vision abnormal.

Dose Dependency of Adverse Events

Extrapyramidal Symptoms

Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatigability, and pigmentation.

Vital Sign Changes

RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Changes

The proportions of RISPERDAL® and placebo patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6- to 8-week controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® compared to placebo (9%).

Laboratory Changes

A between-group comparison for 6- to 8-week controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Changes

Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® dose groups were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8–16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4–6 beats per minute).

Other Events Observed During the Premarketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® were administered to 2607 patients in Phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained as spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In large studies, adverse events were also elicited primarily by UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.).

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following initions: frequent adverse events are those occurring at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders

Frequent: increased dream activity*, diminished libido*; nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, decreased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders

Frequent: increased sleep duration*. *Infrequent:* amnesia, vertigo, stupor, paresthesia, confusion, dysarthria, ataxia, cholinergic syndrome, hypoesthesia, hypokinesia, aphasia, cholinergic syndrome, hypoesthesia, hypokinesia, paralysis, leg cramps, torticollis, hypotonia, coma, hypertonia, hyperreflexia, choreoathetosis.

Gastrointestinal Disorders

Frequent: anorexia, reduced salivation*. *Infrequent:* constipation, diarrhea, increased appetite, stomatitis, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, colitis, esophagitis, tongue discoloration, cholelithiasis, fecal edema, diverticulitis, gingivitis, discolored feces, hemorrhage, hematemesis.

Body as a Whole/General Disorders

Frequent: fatigue. *Infrequent:* edema, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders

Infrequent: hyperventilation, bronchospasm, stridor. *Rare:* asthma, increased sputum,

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Skin and Appendage Disorders
Frequent: increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, hyperkeratosis, pruritus, skin exfoliation. *Rare:* eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, pruritus, urticaria.

Cardiovascular Disorders
Frequent: palpitation, hypertension, hypotension, AV conduction disturbance, myocardial infarction. *Rare:* ventricular tachycardia, bradycardia, angina pectoris, premature atrial contractions, T wave inversion, premature ventricular extrasystoles, ST depression, myocardial ischemia.

Vision Disorders
Frequent: abnormal accommodation, xerophthalmia. *Infrequent:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders
Frequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders
Frequent: polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-Skeletal System Disorders
Frequent: myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female
Frequent: menorrhagia*, orgastic dysfunction*, dry vagina. *Infrequent:* nonpuerperal lactation, amenorrhea, breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders
Frequent: increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding, and Clotting Disorders
Infrequent: epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders
Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders
Infrequent: anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male
Frequent: erectile dysfunction*. *Infrequent:* ejaculation disorder.

White Cell and Resistance Disorders
Rare: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders
Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses
Rare: bitter taste.

Frequencies based on elicited reports.

Postintroduction Reports
Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, benign pituitary adenomas, cerebrovascular disorder, including cerebrovascular accident, diabetes mellitus aggravated, including diabetic ketoacidosis, hyperglycemia, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class
RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychological Dependence
RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience
Postmarketing experience included eight reports of acute overdosage with RISPERDAL® (risperidone) overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, the reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with seizure.

Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® overdose, include torsade de pointes, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage
In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Because of the rapid disintegration of RISPERDAL® M-TAB® Orally Disintegrating Tablets, pill fragments may not appear in gastric contents obtained with lavage.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Schizophrenia
Usual Initial Dose
RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1–2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL®; however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy
While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day, and to a target dose of 4 mg QD on the third day (see CLINICAL PHARMACOLOGY – Clinical Trials). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Reinitiation of Treatment in Patients Previously Discontinued
Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching From Other Antipsychotics
There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

Bipolar Mania
Usual Dose
Risperidone should be administered on a once daily schedule, starting with 2 mg to 3 mg per day. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments/decrements of 1 mg per day, as studied in the short-term, placebo-controlled trials. In these trials, short-term (3-week) antimanic efficacy was demonstrated in a flexible dosage range of 1–6 mg per day (see CLINICAL PHARMACOLOGY – Clinical Trials). RISPERDAL® doses higher than 6 mg per day were not studied.

Maintenance Therapy
There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with risperidone. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of risperidone in such longer-term treatment (i.e., beyond 3 weeks).

Pediatric Use
Safety and effectiveness of RISPERDAL® in pediatric patients with schizophrenia or acute mania associated with Bipolar I Disorder have not been established.

Dosage In Special Populations
The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (see PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2–3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Co-Administration of RISPERDAL® with Certain Other Medications
Co-administration of carbamazepine and other enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with risperidone would be expected to cause decreases in the plasma concentrations of active moiety (the sum of risperidone and 9-hydroxyrisperidone), which could lead to decreased efficacy of risperidone treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5–2.8 fold and 3–9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. The dose of risperidone needs to be titrated accordingly when fluoxetine or paroxetine is co-administered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Directions for Use of RISPERDAL® M-TAB® Orally Disintegrating Tablets
Tablet Accessing
RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are supplied in blister packs of 4 tablets each.

Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg are supplied in a child-resistant pouch containing a blister with 1 tablet each.

The child-resistant pouch should be torn open at the notch to access the blister. Do not open the blister until ready to administer. Peel back foil from the side to expose the tablet.

Continued on next page

Risperdal—Cont.

DO NOT push the tablet through the foil, because this could damage the tablet.

Tablet Administration

Using dry hands, remove the tablet from the blister unit and immediately place the entire RISPERDAL® M-TAB® Orally Disintegrating Tablet on the tongue. The RISPERDAL® M-TAB® Orally Disintegrating Tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. RISPERDAL® M-TAB® Orally Disintegrating Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to split or to chew the tablet.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50, hospital unit dose packs of 100 NDC 50458-301-01.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50, hospital unit dose packs of 100 NDC 50458-302-01.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

RISPERDAL® M-TAB® (risperidone) Orally Disintegrating Tablets are etched on one side with "R0.5", "R1", "R2", "R3", and "R4", respectively. RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are packaged in blister packs of 4 (2 × 2) tablets. RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg are packaged in a child-resistant pouch containing a blister with 1 tablet.

0.5 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-395-28, long-term care packaging of 30 tablets NDC 50458-395-30.

1 mg light coral, square, biconvex tablets: 7 blister packages per box, NDC 50458-315-28, long-term care packaging of 30 tablets NDC 50458-315-30.

2 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-325-28.

3 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-335-28.

4 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-355-28.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.

Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°–25°C (59°–77°F). Protect from light and freezing.

Keep out of reach of children.

RISPERDAL® M-TAB® Orally Disintegrating Tablets should be stored at controlled room temperature 15°–25°C (59°–77°F).

Keep out of reach of children.

Rx Only

7503231

Revised March 2006

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RISPERDAL® tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico or Janssen-Cilag, SpA, Latina, Italy

RISPERDAL® oral solution is manufactured by:
Janssen Pharmaceutica N.V., Beerse, Belgium

RISPERDAL® M-TAB® Orally Disintegrating Tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico

RISPERDAL® tablets, RISPERDAL® M-TAB® Orally Disintegrating Tablets, and oral solution are distributed by:
Janssen, L.P., Titusville, NJ 08560

Shown in Product Identification Guide, page 318

RISPERDAL® CONSTA®

[ris'per dăl kon-stă]

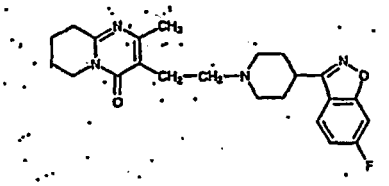
(risperidone) Long-Acting Injection

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. RISPERDAL® CONSTA® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido [1,2-a] pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® CONSTA® (risperidone) Long-Acting Injection is a combination of extended release microspheres for injection and diluent for parenteral use.

The extended release microspheres formulation is a white to off-white, free-flowing powder that is available in dosage strengths of 25, 37.5, or 50 mg risperidone per vial. Risperidone is micro-encapsulated in 7525 polylactide-coglycolide (PLG) at a concentration of 381 mg risperidone per gram of microspheres.

The diluent for parenteral use is a clear, colorless solution. Composition of the diluent includes polysorbate 20, sodium carboxymethyl cellulose, disodium hydrogen phosphate dihydrate, citric acid anhydrous, sodium chloride, sodium hydroxide, and water for injection. The microspheres are suspended in the diluent prior to injection.

RISPERDAL® CONSTA® is provided as a dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a SmartSite® Needle-Free Vial Access Device, and one Needle-Pro® 20 G TW safety needle.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10^{-5} M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Absorption

After a single intramuscular (gluteal) injection of RISPERDAL® CONSTA® (risperidone), there is a small initial release of the drug (<about 1% of the dose), followed by a lag time of 3 weeks. The main release of the drug starts from 3 weeks onward, is maintained from 4 to 6 weeks, and subsides by 7 weeks following the intramuscular (IM) injection. Therefore, oral antipsychotic supplementation should be given during the first 3 weeks of treatment with RISPERDAL® CONSTA® to maintain therapeutic levels until the main release of risperidone from the injection site has begun (see DOSAGE AND ADMINISTRATION).

The combination of the release profile and the dosage regimen (IM injections every 2 weeks) of RISPERDAL® CONSTA® results in sustained therapeutic concentrations. Steady-state plasma concentrations are reached after 4 injections and are maintained for 4 to 6 weeks after the last injection. Plasma concentrations of risperidone, 9-hydroxyrisperidone (the major metabolite), and risperidone plus 9-hydroxyrisperidone are linear over the dosing range of 25 mg to 50 mg.

Distribution

Once absorbed, risperidone is rapidly distributed. The volume of distribution is 1–2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The protein binding of risperidone is approximately 90% that of its major metabolite, 9-hydroxyrisperidone. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10 mcg/mL) caused only a slight increase in the free fraction of risperidone (at 10 ng/mL and of 9-hydroxyrisperidone at 50 ng/mL), changes of unknown clinical significance.

Metabolism and Drug Interactions

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme CYP 2D6. A minor metabolic pathway is N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug (i.e., the moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is an enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and is inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

The interactions of RISPERDAL® CONSTA® with other drugs have not been systematically evaluated in patient subjects. Risperidone could be subject to two kinds of drug interactions (see PRECAUTIONS – Drug Interactions). First, inhibitors of CYP 2D6 interfere with the conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients the risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of both a combination of both risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number of patients with poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, co-administration of carbamazepine and other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone cause a decrease in the combined plasma concentrations of risperidone plus 9-hydroxyrisperidone (see PRECAUTIONS – Drug Interactions). It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to this enzyme suggests this is unlikely.

In a drug interaction study in schizophrenic patients, subjects received oral risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by an average of 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone plus 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment (see PRECAUTIONS – Drug Interactions and DOSAGE AND ADMINISTRATION – Administration of RISPERDAL® CONSTA® with Certain Other Medications).

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentrations of risperidone 2.5–2.8 fold and 3–9 fold, respectively. Fluoxetine did not affect the plasma concentrations of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10% (see PRECAUTIONS – Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Administration of RISPERDAL® CONSTA® with Certain Other Medications).

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations of lithium (n=13) (see PRECAUTIONS – Drug Interactions).

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations of valproate (1000 mg/day in divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone (see PRECAUTIONS – Drug Interactions).

There were no significant interactions between risperidone (1 mg QD) and erythromycin (see PRECAUTIONS – Drug Interactions).

Cimetidine and ranitidine increased the bioavailability of risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of the active moiety, whereas ranitidine increased the AUC of the active moiety by 20%.

Amitriptyline did not affect the pharmacokinetics of risperidone or the active moiety.

OVERDOSAGE

Reports of overdosage with PROPULSID® (cisapride) include an adult who took 540 mg and for 2 hours experienced retching, borborygmi, flatulence, stool frequency and urinary frequency. Treatment should include gastric lavage and/or activated charcoal, close observation and general supportive measures.

Single oral doses of cisapride at 4000 mg/kg, 160 mg/kg, 1280 mg/kg and 640 mg/kg were lethal in adult rats, neonatal rats, mice and dogs, respectively. Symptoms of acute toxicity were ptosis, tremors, convulsions, dyspnea, loss of righting reflex, catalepsy, catatonia, hypotonia and diarrhea.

DOSAGE AND ADMINISTRATION

Adults: Initiate therapy with 10 mg of PROPULSID® (cisapride) 4 times daily at least 15 minutes before meals and at bedtime. In some patients the dosage will need to be increased to 20 mg, given as above, to obtain a satisfactory result.

In elderly patients, steady-state plasma levels are generally higher due to a moderate prolongation of the elimination half-life. Therapeutic doses, however, are similar to those used in younger adults.

HOW SUPPLIED

PROPULSID® (cisapride) is provided as scored white tablets debossed "Janssen" and P/10 containing the equivalent of 10 mg of cisapride in blister packages of 100 (NDC 50458-430-01) and in bottles of 100 (NDC 50458-430-10). PROPULSID® is also provided as blue tablets, debossed "Janssen" and P/20, containing the equivalent of 20 mg cisapride in bottles of 100 (NDC 50458-440-10).

Store at controlled room temperature, 15°-30°C (59°-86°F). Protect from moisture. The 20 mg tablets should also be protected from light.

JANSSEN
PHARMACEUTICA
Titusville, NJ 08560
Revised August 1993, October 1993
U.S. Patent No. 4,962,115

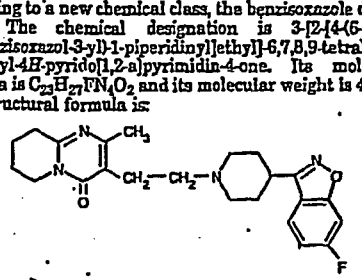
Shown in Product Identification Guide, page 313

RISPERDAL™ R

[ris'per dăl]
(risperidone) Tablets

DESCRIPTION

RISPERDAL™ (risperidone) is an antipsychotic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL™ for oral use is available in tablets of 1 mg (white, scored), 2 mg (orange), 3 mg (yellow), and 4 mg (green). Inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 2, 3, and 4 mg also contain talc and titanium dioxide. The 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL™ (risperidone), as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL™.

RISPERDAL™ is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin type 2 ($5HT_2$), dopamine type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL™ antagonizes other receptors, but with lower potency. RISPERDAL™ has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations > 10^{-5} M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of ^{14}C-risperidone as a solution in three healthy male volunteers. Total recovery of radioactivity at one week was 85%, including 70% in the urine and 15% in the feces.

Risperidone is extensively metabolized in the liver by cytochrome $P_{450}IID_6$ to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating specie, and appears approximately equi-effective with risperidone with respect to receptor binding activity and some effects in animals. (A second minor pathway is *N*-dealkylation). Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hyydroxyrisperidone. Plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) when compared to a solution. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone was 70% (CV=25%).

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is cytochrome $P_{450}IID_6$, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. Cytochrome $P_{450}IID_6$ is subject to genetic polymorphism (about 6-8% of caucasians, and a very low percent of Asians have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers. Following oral administration of solution or tablet, mean peak plasma concentrations occurred at about 1 hour. Peak 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of risperidone was three hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers). Because risperidone and 9-hydroxyrisperidone are approximately equi-effective, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of risperidone and 9-hydroxyrisperidone, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours. In analyses comparing adverse reaction rates in extensive and poor metabolizers in controlled and open studies, no important differences were seen.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of cytochrome $P_{450}IID_6$ could interfere with conversion of risperidone to 9-hydroxyrisperidone. This in fact occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The favorable and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n is approximately equal to 70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by cytochrome $P_{450}IID_6$. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (See PRECAUTIONS and DRUG INTERACTIONS).

The plasma protein binding of risperidone was about 90% over the in vitro concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of α_1-acid glycoprotein. The plasma binding of 9-hydroxyrisperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfamethazine (100 μg/mL), warfarin (10 μg/mL) and carbamazepine (10 μg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Special Populations

Renal Impairment: In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL™ doses should be reduced in patients with renal disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment: While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. RISPERDAL™ doses should be reduced in patients with liver disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly: In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (See DOSAGE AND ADMINISTRATION).

Race and Gender Effects: No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

The efficacy of RISPERDAL™ in the management of the manifestations of psychotic disorders was established in three short-term (5- to 8-week) controlled trials of psychotic inpatients who met DSM III-R criteria for schizophrenia. Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed; these included the Positive and Negative Symptoms Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL™ in doses up to 10 mg/day (BID schedule), RISPERDAL™ was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL™ (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL™ groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL™ dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL™ (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL™ dose groups were generally superior to the 1 mg RISPERDAL™ dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

INDICATIONS AND USAGE

RISPERDAL™ (risperidone) is indicated for the management of the manifestations of psychotic disorders.

The antipsychotic efficacy of RISPERDAL™ was established in short-term (5 to 8 weeks) controlled trials of schizophrenic inpatients (See CLINICAL PHARMACOLOGY).

The effectiveness of RISPERDAL™ in long-term use, that is, more than 6 to 8 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use RISPERDAL™ for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. (See DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL™ (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

Continued on next page

Plaintiff Ex. 643

Janssen Pharmaceutica—Cont.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL™ (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL™, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL™ despite the presence of the syndrome.

Potential for Proarrhythmic Effects: Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12-16 mg/day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrhythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension: RISPERDAL™ (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL™ treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 1 mg BID in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (See DOSAGE AND ADMINISTRATION). A dose reduction should be considered if hypotension occurs. RISPERDAL™ should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizures: During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL™ treated patients, two in association with hyponatremia. RISPERDAL™ should be used cautiously in patients with a history of seizures.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (See CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERDAL™ treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL™ 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL™ 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL™ has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL™ therapy does not affect them adversely.

Priapism: A single case of priapism was reported in a 50-year-old patient receiving RISPERDAL™ in a large, open premarketing experience (approximately 1300 patients). This event occurred after 11 months of treatment with RISPERDAL™ alone, and required surgical intervention. While the relationship of this event to RISPERDAL™ use cannot be established on the basis of a single case, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL™ may share this capacity.

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL™ in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL™ therapy is unknown.

Antiemetic effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Although not reported with risperidone, disruption of body temperature regulation has been attributed to other antipsychotic agents. Caution is advised when prescribing for patients who will be exposed to extreme heat.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for RISPERDAL™ should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with RISPERDAL™ in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL™ in patients with diseases or conditions that could affect metabolism or hemodynamic responses. RISPERDAL™ has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. The electrocardiograms of approximately 380 patients who received RISPERDAL™ and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the data revealed one finding of potential concern, i.e., 8 patients taking RISPERDAL™ whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen in the smaller placebo group. There were 3 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See WARNINGS AND PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²), and an increase in the free fraction of the risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (See DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL™:

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance: Since RISPERDAL™ has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL™ therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed an infant if they are taking RISPERDAL™.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking RISPERDAL™.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL™ and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL™ is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL™ may enhance the effects of certain antihypertensive agents.

RISPERDAL™ may antagonize the effects of levodopa and dopamine agonists. Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Drugs that Inhibit Cytochrome $P_{450}IID_6$ and Other P_{450} Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome $P_{450}IID_6$, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n is approximately equal to 70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other P_{450} isozymes, including 1A1, 1A2, IIC9, MP, and IIIA4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome $P_{450}IID_6$: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome $P_{450}IID_6$. Therefore, RISPERDAL™ is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

TUMOR TYPE	SPECIES	SEX	MULTIPLE OF MAXIMUM HUMAN DOSE in mg/m² (mg/kg)	
			LOWEST EFFECT LEVEL	HIGHEST NO EFFECT LEVEL
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adeno-carcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6 (37.5)	1.5 (9.4)
Mammary gland neoplasms, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (See Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis: No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose on a mg/m² basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the human dose on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C: The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats and in one Segment II study in New Zealand rabbits. The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the human dose on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses 0.1 to 3 times the human dose on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment II study, there was an increase in stillborn rat pups at a dose 5 times higher than the human dose on a mg/m² basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERDAL™ therapy is unknown.

RISPERDAL™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL™ on labor and delivery in humans is unknown.

Nursing Mothers

It is not known whether or not risperidone is excreted in human milk. In animal studies, risperidone and 9-hydroxyrisperidone were excreted in breast milk. Therefore, women receiving RISPERDAL™ should not breast-feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL™ did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and a greater tendency to postural hypotension (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 9% percent (244/2607) of RISPERDAL™ (risperidone)-treated patients in phase 2–3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL™	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL™ treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL™ compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL™ related adverse event (See PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients but 3.8% in active-control patients in the phase 2–3 trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL™ groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL™ at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events were present at at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL™ Treated Patients: The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL™ treated patients treated at doses of ≤10 mg/day than among placebo-treated patients in the pooled results of two 6- to-8-week controlled trials. Patients received RISPERDAL™ doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

[See Table 1 at top of next column.]

Dose Dependency of Adverse Events:

Extrapyramidal symptoms: Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing four fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events: Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL™ (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events: A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile

Table 1: Treatment-Emergent Adverse Experience Incidence in 6- to 8-Week Controlled Clinical Trials[1]

Body System/ Preferred Term	RISPERDAL™ ≤10 mg/day (N=324)	RISPERDAL™ 16 mg/day (N=77)	Placebo (N=142)
Psychiatric Disorders			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	8%	8%	1%
Aggressive reaction	1%	3%	1%
Nervous System			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal System			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory System			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a Whole			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

[1] Events reported by at least 1% of patients with RISPERDAL™ ≤10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL™ 16 mg/day and placebo are provided as well. Events for which the RISPERDAL™ incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '≤10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (See DOSE DEPENDENCY OF ADVERSE EVENTS).

Continued on next page

Plaintiff Ex. 643

Janssen Pharmaceutica—Cont.

dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatigueability, and increased pigmentation.

Vital Sign Changes: RISPERDAL™ is associated with orthostatic hypotension and tachycardia (See PRECAUTIONS).

Weight changes: The proportions of RISPERDAL™ and placebo-treated patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6- to 8-week placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL™ (18%) compared to placebo (9%).

Laboratory Changes: A between group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL™/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL™/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL™ administration was associated with increases in serum prolactin (See PRECAUTIONS).

ECG Changes: The electrocardiograms of approximately 380 patients who received RISPERDAL™ and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL™ whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (See WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL™

During its premarketing assessment, multiple doses of RISPERDAL™ (risperidone) were administered to 2607 patients in phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL™ varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology (Note: These events are marked with an asterisk in the listings that follow).

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL™ who experienced an event of the type cited on at least one occasion while receiving RISPERDAL™. All reported events are included except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL™, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders: Frequent: increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: Frequent: increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-Intestinal Disorders: Frequent: anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: Frequent: fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders: Frequent: increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritis, urticaria.

Cardiovascular Disorders: Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders: Infrequent: abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders: Frequent: polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-skeletal System Disorders: Infrequent: myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female: Frequent: menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain; leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: Infrequent: increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: Infrequent: epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: Infrequent: anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male: Frequent: erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders: Rare: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders: Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: Rare: bitter taste.

* Incidence based on elicited reports.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL™ (risperidone) is not a controlled substance.

Physical and Psychologic Dependence: RISPERDAL™ has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL™ misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Experience with RISPERDAL™ (risperidone) in acute overdosage was limited in the premarketing database (8 reports), with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL™. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose: RISPERDAL™ (risperidone) should be administered on a BID schedule, generally beginning with 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Further dosage adjustments, when indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1 mg BID are recommended.

Antipsychotic efficacy was demonstrated in a dose range of 2 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL™, however, maximal effect was generally seen in a range of 4 to 6 mg/day. Doses above 6 mg/day were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Dosage in Special Populations: The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of 0.5 mg BID. Dosage increases above 1.5 mg BID should generally occur at intervals of no less than 1 week. Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL™ than normal adults. Patients with impaired hepatic function may have increases in the free fraction of the risperidone, possibly resulting in an enhanced effect (See CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (See PRECAUTIONS).

Maintenance Therapy: While there is no body of evidence available to answer the question of how long the patient treated with RISPERDAL™ should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on RISPERDAL™, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL™, the initial 3-day dose titration schedule should be followed.

Switching from Other Antipsychotics: Although there are no data to specifically address switching from other antipsychotics to risperidone, immediate discontinuation of the previous antipsychotic treatment upon initiation of RISPERDAL™ therapy is recommended when medically appropriate. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients from depot antipsychotics, initiate RISPERDAL™ therapy in place of the next scheduled injection. The need for continuing existing EPS medications should be reevaluated periodically.

HOW SUPPLIED

RISPERDAL™ (risperidone) tablets are imprinted "JANSSEN", and "R" and the strength "1", "2", "3", or "4".

1 mg white, scored, tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

Storage and Handling - RISPERDAL™ should be stored at room temperature (59°-86°F/15°-30°C). RISPERDAL™ should be protected from light and moisture.

US Patent 4,804,663.
January 1994, March 1994
JANSSEN
PHARMACEUTICA
Titusville, NJ 08560
Shown in Product Identification Guide, page 313

SPORANOX ℞
[spor'ah-naks]
Itraconazole Capsules

WARNING: Coadministration of terfenadine with itraconazole is contraindicated. Serious cardiovascular adverse events, including death, ventricular tachycardia, and torsades de pointes have occurred in patients taking itraconazole concomitantly with terfenadine. This is due to elevated terfenadine concentrations caused by itraconazole. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections.
Another oral azole antifungal, ketoconazole, inhibits the metabolism of astemizole, resulting in elevated plasma concentrations of astemizole and its active metabolite desmethylastemizole, which may prolong QT intervals. Based on results of an in vitro study and the chemical resemblance of itraconazole and ketoconazole, coadministration of astemizole and itraconazole is contraindicated. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections.

DESCRIPTION

SPORANOX is the brand name for itraconazole, a synthetic triazole antifungal agent. Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers.
(±)-1-[(R*)-sec-Butyl]-4-[p-[4-[p-[[2R*,4S*]-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ²-1,2,4-triazolin-5-one mixture with (±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[2S* 4R*]-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ²-1,2,4-triazolin-5-one

or

(±)-1-[(RS)-sec-Butyl]-4-[p-[4-[p-[(2R, 4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl] phenyl]-Δ²-1,2,4-triazolin-5-one

Itraconazole has a molecular formula of $C_{35}H_{38}Cl_2N_8O_4$ and a molecular weight of 705.64. It is a white to slightly yellowish powder. It is insoluble in water at pH 1–12, very slightly soluble in alcohols, and freely soluble in dichloromethane. It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water partition coefficient) of 5.66 at pH 8.1.
SPORANOX is available in capsules (blue opaque cap/pink transparent body), containing 100 mg of itraconazole coated on sugar spheres for oral administration. Inactive ingredients are gelatin, hydroxypropyl methylcellulose, polyethylene glycol (PEG) 20,000, starch, sucrose, titanium dioxide, FD&C Blue No. 1, FD&C Blue No. 2, D&C Red No. 22 and D&C Red No. 28.

CLINICAL PHARMACOLOGY

Mode of Action: *In vitro* studies have demonstrated that itraconazole inhibits the cytochrome P-450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.
Pharmacokinetics and Metabolism: NOTE: The plasma concentrations reported below were measured by high performance liquid chromatography (HPLC) specific for itraconazole. When itraconazole in plasma is measured by a bioassay, values reported are approximately 3.3 times higher than those obtained by HPLC due to the presence of the bioactive metabolite, hydroxyitraconazole. (See *Microbiology* section.)
The pharmacokinetics of itraconazole after intravenous administration and its absolute oral bioavailability from an oral solution were studied in a randomized cross-over study using six healthy male volunteers. The total plasma clearance averaged 381±95 mL/min and the apparent volume of distribution averaged 795±185 L. The observed absolute oral bioavailability of itraconazole was 55%.
The oral bioavailability of SPORANOX (itraconazole) Capsules is maximal when taken with food. The pharmacokinetics of itraconazole were studied using six healthy male volunteers who received, in a cross-over design, single 100 mg doses of itraconazole as a polyethylene glycol capsule, with or without food. The same six volunteers also received 50 mg or 200 mg with food in a cross-over design. In this study, only itraconazole plasma concentrations were measured. Presented in the table below are the respective pharmacokinetic parameters for itraconazole:

(See table at top of next column.)

	50 mg (fed)	100 mg (fed)	100 mg (fasted)	200 mg (fed)
C_{max} (ng/mL)	45±16	132±67	38±20	289±100
T_{max} (hours)	3.2±1.3	4.0±1.1	3.3±1.0	4.7±1.4
$AUC_{0-\infty}$ (ng.h/mL)	567±264	1899±838	722±289	5211±2116

Values are means ± standard deviation

Doubling the SPORANOX dose results in approximately a three-fold increase in the itraconazole plasma concentrations.
Values given in the table below represent data from a cross-over pharmacokinetics study in which 27 healthy male volunteers each took a single 200 mg dose of SPORANOX with or without food:

	Itraconazole		Hydroxyitraconazole	
	Fed	Fasted	Fed	Fasted
C_{max} (ng/mL)	239±85	140±65	397±103	286±101
T_{max} (hours)	4.5±1.1	3.9±1.0	5.1±1.6	4.5±1.1
$AUC_{0-\infty}$ (ng.h/mL)	3423±1154	2094±905	7978±2648	5191±2489
$t_{1/2}$ (hours)	21±5	21±7	12±3	12±3

Values are means ± standard deviation

Steady-state concentrations were reached within 15 days following oral doses of 50–400 mg daily. Values given in the table below are data at steady-state from a pharmacokinetics study in which 27 healthy male volunteers took 200 mg SPORANOX b.i.d. (with food) for 15 days:

	Itraconazole	Hydroxyitraconazole
C_{max} (ng/mL)	2282±514	3488±742
C_{min} (ng/mL)	1855±535	3349±761
T_{max} (hours)	4.6±1.8	3.4±3.4
AUC_{0-12h} (ng.h/mL)	22569±5375	38572±8450
$t_{1/2}$ (hours)	64±32	66±24

Values are means ± standard deviation

Results of the pharmacokinetics study suggest that itraconazole may undergo saturation metabolism with multiple dosing.
SPORANOX is extensively metabolized by the liver into a large number of metabolites including hydroxyitraconazole, the major metabolite. Fecal excretion of the parent drug varies between 3–18% of the dose. Renal excretion of the parent drug is less than 0.03% of the dose. About 40% of the dose is excreted as inactive metabolites in the urine. No excreted single metabolite represents more than 5% of a dose. The main metabolic pathways are oxidative scission of the dioxolane ring, aliphatic oxidation at the 1-methylpropyl substituent, N-dealkylation of this 1-methylpropyl substituent, oxidative degradation of the piperazine ring and triazole scission.
Plasma concentrations of itraconazole in subjects with renal insufficiency were comparable to those obtained in healthy subjects. The effect of hepatic impairment on the plasma concentration of itraconazole is unknown. It is recommended that plasma concentrations of itraconazole in patients with hepatic impairment be carefully monitored.
The plasma protein binding of itraconazole is 99.8% and that of hydroxyitraconazole is 99.5%. Itraconazole is not removed by hemodialysis.
In animal studies, itraconazole is extensively distributed into lipophilic tissues. Concentrations of itraconazole in fatty tissues, omentum, liver, kidney and skin tissues are 2–20 times the corresponding plasma concentrations. Aqueous fluids such as cerebrospinal fluid and saliva contain negligible amounts of the drug.
Microbiology: Itraconazole exhibits *in vitro* activity against *Blastomyces dermatitidis, Histoplasma capsulatum, Histoplasma duboisii, Aspergillus flavus, Aspergillus fumigatus* and *Cryptococcus neoformans*. Itraconazole also exhibits varying *in vitro* activity against *Sporothrix schenckii*, Trichophyton spp., *Candida albicans* and Candida spp. In addition, the bioactive metabolite, hydroxyitraconazole, was evaluated *in vitro*. Although the activity has not been evaluated against *Histoplasma capsulatum* and *Blastomyces dermatitidis*, the *in vitro* antifungal activity of hydroxyitraconazole against eleven other fungal species was shown to be comparable to that of itraconazole. Correlation between *in vitro* minimum inhibitory concentration (MIC) results and clinical outcome has yet to be established for azole antifungal agents.
Itraconazole administered orally was active in a variety of animal models of fungal infection using standard laboratory strains of fungi. Fungistatic activity has been demonstrated against disseminated fungal infections caused by *Blastomyces dermatitidis, Histoplasma duboisii, Aspergillus fumigatus, Coccidioides immitis, Cryptococcus neoformans, Paracoccidioides brasiliensis, Sporothrix schenckii* and *Trichophyton mentagrophytes*. Itraconazole administered at 2.5 mg/kg and 5.0 mg/kg via the oral and parenteral routes increased survival rates and sterilized organ systems in normal and immunosuppressed guinea pigs with disseminated Aspergillus fumigatus infections. Oral itraconazole administered daily at 40 mg/kg and 80 mg/kg increased survival rates in normal rabbits with disseminated disease and immunosuppressed rats with pulmonary Aspergillus fumigatus infection, respectively. Itraconazole has demonstrated antifungal activity in a variety of animal models infected with *Candida albicans* and other Candida species.
In vivo studies suggest that the activity of amphotericin B may be suppressed by azole antifungal therapy. As with other azoles, ketoconazole and itraconazole inhibit the ^{14}C-demethylation step in the synthesis of ergosterol, a cell wall component of fungi. Ergosterol is the active site for amphotericin B. In one study, the antifungal activity of amphotericin B against *Aspergillus fumigatus* infections in mice was inhibited by ketoconazole therapy. The clinical significance of test results obtained in this study is unknown.

INDICATIONS AND USAGE

SPORANOX (itraconazole) is indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:

1. Blastomycosis, pulmonary and extrapulmonary.
2. Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis; and
3. Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

Specimens for fungal cultures and other relevant laboratory studies (wet mount, histopathology, serology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.
Blastomycosis: Analyses were conducted on data from two open-label, non-concurrently controlled studies (n=73 combined) in patients with normal or abnormal immune status. The median dose was 200 mg/day. A response for most signs and symptoms was observed within the first two weeks, and all cleared between 3 and 6 months. Results of these two studies demonstrated substantial evidence of the effectiveness of itraconazole, for the treatment of blastomycosis, compared to the natural history of untreated cases.
Histoplasmosis: Analyses were conducted on data from two open-label, non-concurrently controlled studies (n=94 combined) in patients with normal or abnormal immune status (not including HIV-infected patients). The median dose was 200 mg/day. A response for most signs and symptoms was observed within the first 2 weeks, and all cleared between 3 and 12 months. Results of these two studies demonstrated substantial evidence of the effectiveness of itraconazone, for the treatment of histoplasmosis, compared to the natural history of untreated cases.
Histoplasmosis in HIV-infected patients: Data from a small number of HIV-infected patients suggested that the response rate of histoplasmosis in HIV-infected patients is similar to non-HIV-infected patients. The clinical course of histoplasmosis in HIV-infected patients is more severe and usually requires maintenance therapy to prevent relapse. Studies to investigate the efficacy and safety of itraconazole, including optimal dosage regimens for treatment and maintenance therapies, in HIV-infected patients are ongoing.
Aspergillosis: Analyses were conducted on data from an open-label, "single-patient-use" protocol designed to make itraconazole available in the U.S. for patients who either failed or were intolerant to amphotericin B therapy (n=190). The findings were corroborated by two smaller

Continued on next page

Plaintiff Ex. 643

RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION

DESCRIPTION

RISPERDAL® (risperidone) is an antipsychotic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49.

Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 1 mg (white, scored), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 2, 3, and 4 mg also contain talc and titanium dioxide. The 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are: tartaric acid, benzoic acid, sodium hydroxide and purified water (formulation F68).

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin type 2 ($5HT_2$), dopamine type 2 (D_2), α_1 and α_2 adrenergic, and H, histaminergic receptors. RISPERDAL® antagonizes other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10^{-4} M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of ^{14}C-risperidone as a solution in three healthy male volunteers. Total recovery of radioactivity at one week was 85%, including 70% in the urine and 15% in the feces.

Risperidone is extensively metabolized in the liver by cytochrome $P_{450}IID_6$ to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating specie, and appears approximately equi-effective with risperidone with respect to receptor binding activity and some effects in animals. (A second minor pathway is *N*-dealkylation). Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. Plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) when compared to a solution. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone was 70% (CV=25%).

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is cytochrome $P_{450}IID_6$, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. Cytochrome $P_{450}IID_6$ is subject to genetic polymorphism (about 6-8% of Caucasians, and a very low percent of Asians have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers. Following oral administration of solution or tablet, mean peak plasma concentrations occurred at about 1 hour. Peak 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of risperidone was three hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Because risperidone and 9-hydroxyrisperidone are approximately equi-effective, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of risperidone and 9-hydroxyrisperidone, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours. In analyses comparing adverse reaction rates in extensive and poor metabolizers in controlled and open studies, no important differences were seen.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of cytochrome $P_{450}IID_6$ could interfere with conversion of risperidone to 9-hydroxyrisperidone. This in fact occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The favorable and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by cytochrome $P_{450}IID_6$. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (See PRECAUTIONS and DRUG INTERACTIONS).

The plasma protein binding of risperidone was about 90% over the in vitro concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of α_1-acid glycoprotein. The plasma binding of 9-hydroxyrisperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfamethazine (100 µg/mL), warfarin (10 µg/mL) and carbamazepine (10 µg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Special Populations

Renal Impairment: In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment: While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly: In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (See DOSAGE AND ADMINISTRATION).

Race and Gender Effects: No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

The efficacy of RISPERDAL® in the management of the manifestations of psychotic disorders was established in four short-term (4- to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed; these included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (> 20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

INDICATIONS AND USAGE

RISPERDAL® (risperidone) is indicated for the management of the manifestations of psychotic disorders.

The antipsychotic efficacy of RISPERDAL® was established in short-term (6 to 8-weeks) controlled trials of schizophrenic inpatients (See CLINICAL PHARMACOLOGY).

The effectiveness of RISPERDAL® in long-term use, that is, more than 6 to 8-weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Potential for Proarrhythmic Effects: Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12-16 mg/day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrhythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL® treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (See DOSAGE AND ADMINISTRATION). A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures: During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL® treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (See CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism: Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the data revealed one finding of potential concern, i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen in the smaller placebo group. There were 3 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²), and an increase in the free fraction of the risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (See DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance: Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed an infant if they are taking RISPERDAL®.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking RISPERDAL®.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Drugs that Inhibit Cytochrome $P_{450}IID_6$ and Other P_{450} Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome $P_{450}IID_6$, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other P_{450} isozymes, including 1A1, 1A2, IIC9, MP, and IIIA4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome $P_{450}IID_6$: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome $P_{450}IID_6$. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

TUMOR TYPE	SPECIES	SEX	MULTIPLE OF MAXIMUM HUMAN DOSE in mg/m² (mg/kg)	
			LOWEST EFFECT LEVEL	HIGHEST NO EFFECT LEVEL
Pituitary adenomas	mouse	female	0.75 *(9.4)*	0.2 *(2.4)*
Endocrine pancreas adenomas	rat	male	1.5 *(9.4)*	0.4 *(2.4)*
Mammary gland adenocarcinomas	mouse	female	0.2 *(2.4)*	none
	rat	female	0.4 *(2.4)*	none
	rat	male	6 *(37.5)*	1.5 *(9.4)*
Mammary gland neoplasms, Total	rat	male	1.5 *(9.4)*	0.4 *(2.4)*

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (See Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis: No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose on a mg/m² basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the human dose on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C: The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats and in one Segment II study in New Zealand rabbits. The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the human dose on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses 0.1 to 3 times the human dose on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose 1.5 times higher than the human dose on a mg/m² basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERDAL® therapy is unknown.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

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Nursing Mothers

It is not known whether or not risperidone is excreted in human milk. In animal studies, risperidone and 9-hydroxyrisperidone were excreted in breast milk. Therefore, women receiving RISPERDAL® should not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and a greater tendency to postural hypotension (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL® related adverse event (See PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients but 3.8% in active-control patients in the phase 2-3 trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events were present at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Patients: The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL®-treated patients treated at doses of ≤ 10 mg/day than among placebo-treated patients in the pooled results of two 6- to 8-week controlled trials. Patients received RISPERDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1: **Treatment-Emergent Adverse Experience Incidence in 6- to 8-Week Controlled Clinical Trials[1]**

Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric Disorders			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Nervous System			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal System			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory System			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a Whole			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '≤ 10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (See DOSE DEPENDENCY OF ADVERSE EVENTS).

Dose Dependency of Adverse Events:

Extrapyramidal symptoms: Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing four fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events: Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatiguability, and increased pigmentation.

Vital Sign Changes: RISPERDAL® is associated with orthostatic hypotension and tachycardia (See PRECAUTIONS).

Weight Changes: The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6- to 8-week placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes: A between group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (See PRECAUTIONS).

ECG Changes: The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (See WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® (risperidone) were administered to 2607 patients in phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology (Note: These events are marked with an asterisk in the listings that follow).

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included except those already listed in Table 1, those events for which a drug cause was remote, and those event

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terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders: *Frequent:* increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: *Frequent:* increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-Intestinal Disorders: *Frequent:* anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: *Frequent:* fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: *Infrequent:* hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders: *Frequent:* increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: *Infrequent:* palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders: *Infrequent:* abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: *Infrequent:* hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders: *Frequent:* polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-skeletal System Disorders: *Infrequent:* myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female: *Frequent:* menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: *Infrequent:* increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: *Infrequent:* epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: *Rare:* tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: *Infrequent:* anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male: *Frequent:* erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders: *Rare:* leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders: *Rare:* gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: *Rare:* bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychologic Dependence: RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Premarketing experience included eight reports of acute RISPERDAL® (risperidone) overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure. Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia and hypotension. Other adverse events reported since market introduction which were temporally, (but not necessarily causally) related to RISPERDAL® overdose, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose: RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Antipsychotic efficacy was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL®, however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Dosage in Special Populations: The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of the risperidone, possibly resulting in an enhanced effect (See CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (See PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Maintenance Therapy: While there is no body of evidence available to answer the question of how long the patient treated with RISPERDAL® should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on RISPERDAL®, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching from Other Antipsychotics: There are no systematically collected data to specifically address switching from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients, more gradual discontinuation may be most appropriate for other patients. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and "R" and the strength "1", "2", "3", or "4".

1 mg white, scored, tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature (59°-77°F/15°-25°C) away from children, and should be protected from light and moisture.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature (59°-77°F/15°-25°C) away from children, and should be protected from light and freezing.

JANSSEN PHARMACEUTICA
Titusville, NJ 08560

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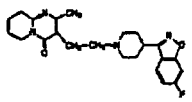
JANSSEN
PHARMACEUTICA

RISPERDAL®

(RISPERIDONE)
TABLETS/ORAL SOLUTION

DESCRIPTION

RISPERDAL® (risperidone) is an antipsychotic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$, and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide, the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide and purified water.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin type 2 ($5HT_2$), dopamine type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® antagonizes other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1A}$, $5HT_{1B}$ and $5HT_{1C}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-4}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of ^{14}C-risperidone as a solution in three healthy male volunteers. Total recovery of radioactivity at one week was 85%, including 70% in the urine and 15% in the feces.

Risperidone is extensively metabolized in the liver by cytochrome $P_{450}IID_6$ to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating specie, and appears approximately equi-effective with risperidone with respect to receptor binding activity and some effects in animals. (A second minor pathway is *N*-dealkylation). Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. Plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) when compared to a solution. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone was 70% (CV=25%).

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is cytochrome $P_{450}IID_6$, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. Cytochrome $P_{450}IID_6$ is subject to genetic polymorphism (about 6-8% of Caucasians, and a very low percent of Asians have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers. Following oral administration of solution or tablet, mean peak plasma concentrations occurred at about 1 hour. Peak 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of risperidone was three hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Because risperidone and 9-hydroxyrisperidone are approximately equi-effective, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of risperidone and 9-hydroxyrisperidone, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours. In analyses comparing adverse reaction rates in extensive and poor metabolizers in controlled and open studies, no important differences were seen.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of cytochrome $P_{450}IID_6$ could interfere with conversion of risperidone to 9-hydroxyrisperidone. This in fact occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The favorable and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by cytochrome $P_{450}IID_6$. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (See PRECAUTIONS and DRUG INTERACTIONS).

The plasma protein binding of risperidone was about 90% over the in vitro concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of α_1-acid glycoprotein. The plasma binding of 9-hydroxyrisperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfamethazine (100 µg/mL), warfarin (10 µg/mL) and carbamazepine (10 µg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Special Populations

Renal Impairment: In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment: While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly: In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (See DOSAGE AND ADMINISTRATION).

Race and Gender Effects: No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

The efficacy of RISPERDAL® in the management of the manifestations of psychotic disorders was established in four short-term (4 to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed; these included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (> 20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

INDICATIONS AND USAGE

RISPERDAL® (risperidone) is indicated for the management of the manifestations of psychotic disorders.

The antipsychotic efficacy of RISPERDAL® was established in short-term (6 to 8-weeks) controlled trials of schizophrenic inpatients (See CLINICAL PHARMACOLOGY).

The effectiveness of RISPERDAL® in long-term use, that is, more than 6 to 8-weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Potential for Proarrhythmic Effects: Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12-16 mg/day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrhythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL® treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either OD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (See DOSAGE AND ADMINISTRATION).

Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures: During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL® treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

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Hyperprolactinemia: As with other drugs that antagonize dopamine D$_2$ receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (See CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism: Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the data revealed one finding of potential concern, i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen in the smaller placebo group. There were 3 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2), and an increase in the free fraction of the risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (See DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance: Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed an infant if they are taking RISPERDAL®.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking RISPERDAL®.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Fluoxetine may increase the plasma concentration of the anti-psychotic fraction (risperidone plus 9-hydroxyrisperidone) by raising the concentration of risperidone, although not the active metabolite, 9-hydroxyrisperidone.

Drugs that Inhibit Cytochrome P$_{450}$IID$_6$ and Other P$_{450}$ Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome P$_{450}$IID$_6$, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other P$_{450}$ isozymes, including 1A1, 1A2, IIC9, MP, and IIA4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome P$_{450}$IID$_6$: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome P$_{450}$IID$_6$. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a *mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum* human dose (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m^2 (mg/kg) basis at which these tumors occurred.

TUMOR TYPE	SPECIES	SEX	MULTIPLE OF MAXIMUM HUMAN DOSE in mg/m^2 (mg/kg)	
			LOWEST EFFECT LEVEL	HIGHEST NO EFFECT LEVEL
Pituitary adenomas	mouse	female	0.75 *(9.4)*	0.2 *(2.4)*
Endocrine pancreas adenomas	rat	male	1.5 *(9.4)*	0.4 *(2.4)*
Mammary gland adenocarcinomas	mouse	female	0.2 *(2.4)*	none
	rat	female	0.4 *(2.4)*	none
	rat	male	6 *(37.5)*	1.5 *(9.4)*
Mammary gland neoplasms, Total	rat	male	1.5 *(9.4)*	0.4 *(2.4)*

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (See Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis: No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose on a *mg/m^2* basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the human dose on a mg/m^2 basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C: The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats and in one Segment II study in New Zealand rabbits. The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the human dose on a mg/m^2 basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses 0.1 to 3 times the human dose on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose 1.5 times higher than the human dose on a mg/m^2 basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERDAL® therapy is unknown.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

Nursing Mothers

It is not known whether or not risperidone is excreted in human milk. In animal studies, risperidone and 9-hydroxyrisperidone were excreted in breast milk. Therefore, women receiving RISPERDAL® should not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (See PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 9% (244/2507) of RISPERDAL® (risperidone)-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL® related adverse event (See PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients but 3.8% in active-control patients in the phase 2-3 trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: In two 6 to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events were present at at least 5% and twice the rate of placebo: increased dream activity, increased *duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain,* menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Patients: The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL®-treated patients treated at doses of ≤ 10 mg/day than among placebo-treated patients in the pooled results of two 6 to 8-week controlled trials. Patients received RISPERDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1: Treatment-Emergent Adverse Experience Incidence in 6 to 8-Week Controlled Clinical Trials[1]

Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric Disorders			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	8%	8%	1%
Aggressive reaction	1%	3%	1%
Nervous System			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal System			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%

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Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory System			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a Whole			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '≤ 10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (See. DOSE DEPENDENCY OF ADVERSE EVENTS).

Dose Dependency of Adverse Events:

Extrapyramidal symptoms: Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing four fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.8
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events: Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: *sleepiness, increased duration of sleep,* accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatiguability, and increased pigmentation.

Vital Sign Changes: RISPERDAL® is associated with orthostatic hypotension and tachycardia (See PRECAUTIONS).

Weight Changes: The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6 to 8-week placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes: A between group comparison for 6 to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (See PRECAUTIONS).

ECG Changes: The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (See WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/125).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® (risperidone) were administered to 2607 patients in phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology (Note: These events are marked with an asterisk in the listings that follow).

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders: Frequent: increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: Frequent: increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-Intestinal Disorders: Frequent: anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: Frequent: fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders: Frequent: increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis fichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST decression, myocarditis.

Vision Disorders: Infrequent: abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders: Frequent: polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-skeletal System Disorders: Infrequent: myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female: Frequent: menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: Infrequent: increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: Infrequent: epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: Infrequent: anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male: Frequent: erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders: Rare: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders: Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: Rare: bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychologic Dependence: RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Premarketing experience included eight reports of acute RISPERDAL® (risperidone) overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure. Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia and hypotension. Other adverse events reported since market introduction which were temporally, (but not necessarily causally) related to RISPERDAL® overdose, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose: RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

*Antipsychotic efficacy was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL®, however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 8 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Dosage in Special Populations: The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of the risperidone, possibly resulting in an enhanced effect (See CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (See PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Maintenance Therapy: While there is no body of evidence available to answer the question of how long the patient treated with RISPERDAL® should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on RISPERDAL®, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

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einitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching from Other Antipsychotics: There are no systematically collected data to specifically address switching from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients, more gradual discontinuation may be most appropriate for other patients. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature (59°-77°F/15°-25°C) away from children, and should be protected from light and moisture.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature (59°-77°F/15°-25°C) away from children, and should be protected from light and freezing.

JANSSEN PHARMACEUTICA
Titusville, NJ 08560

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RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION

DESCRIPTION

RISPERDAL® (risperidone) is an antipsychotic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49.

Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide, the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide and purified water.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin type 2 ($5HT_2$), dopamine type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® antagonizes other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of ^{14}C-risperidone as a solution in three healthy male volunteers. Total recovery of radioactivity at one week was 85%, including 70% in the urine and 15% in the feces.

Risperidone is extensively metabolized in the liver by cytochrome $P_{450}IID_6$ to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating specie, and appears approximately equi-effective with risperidone with respect to receptor binding activity and some effects in animals. (A second minor pathway is *N*-dealkylation). Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. Plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) when compared to a solution. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone was 70% (CV=25%).

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is cytochrome $P_{450}IID_6$, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. Cytochrome $P_{450}IID_6$ is subject to genetic polymorphism (about 6-8% of Caucasians, and a very low percent of Asians have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers. Following oral administration of solution or tablet, mean peak plasma concentrations occurred at about 1 hour. Peak 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of risperidone was three hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Because risperidone and 9-hydroxyrisperidone are approximately equi-effective, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of risperidone and 9-hydroxyrisperidone, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours. In analyses comparing adverse reaction rates in extensive and poor metabolizers in controlled and open studies, no important differences were seen.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of cytochrome $P_{450}IID_6$ could interfere with conversion of risperidone to 9-hydroxyrisperidone. This in fact occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The favorable and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by cytochrome $P_{450}IID_6$. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (See PRECAUTIONS and DRUG INTERACTIONS).

The plasma protein binding of risperidone was about 90% over the in vitro concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of α_1-acid glycoprotein. The plasma binding of 9-hydroxyrisperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfamethazine (100 µg/mL), warfarin (10 µg/mL) and carbamazepine (10 µg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Special Populations

Renal Impairment: In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment: While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly: In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (See DOSAGE AND ADMINISTRATION).

Race and Gender Effects: No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

The efficacy of RISPERDAL® in the management of the manifestations of psychotic disorders was established in four short-term (4 to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing activity schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed; these included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (> 20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

INDICATIONS AND USAGE

RISPERDAL® (risperidone) is indicated for the management of the manifestations of psychotic disorders.

The antipsychotic efficacy of RISPERDAL® was established in short-term (6 to 8-weeks) controlled trials of schizophrenic inpatients (See CLINICAL PHARMACOLOGY).

The effectiveness of RISPERDAL® in long-term use, that is, more than 6 to 8-weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Potential for Proarrhythmic Effects: Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12-16 mg/day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrhythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL® treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (See DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures: During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL® treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (See CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism: Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the data revealed one finding of potential concern, i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen in the smaller placebo group. There were 3 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²), and an increase in the free fraction of the risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (See DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance: Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed an infant if they are taking RISPERDAL®.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking RISPERDAL®.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Fluoxetine may increase the plasma concentration of the anti-psychotic fraction (risperidone plus 9-hydroxyrisperidone) by raising the concentration of risperidone, although not the active metabolite, 9-hydroxyrisperidone.

Drugs that Inhibit Cytochrome $P_{450}IID_6$ and Other P_{450} Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome $P_{450}IID_6$, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers ($n \approx 70$) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other P_{450} isozymes, including 1A1, 1A2, IIC9, MP, and IIIA4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome $P_{450}IID_6$: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome $P_{450}IID_6$. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

TUMOR TYPE	SPECIES	SEX	MULTIPLE OF MAXIMUM HUMAN DOSE in mg/m² (mg/kg)	
			LOWEST EFFECT LEVEL	HIGHEST NO EFFECT LEVEL
Pituitary adenomas	mouse	female	0.75 *(9.4)*	0.2 *(2.4)*
Endocrine pancreas adenomas	rat	male	1.5 *(9.4)*	0.4 *(2.4)*
Mammary gland adenocarcinomas	mouse	female	0.2 *(2.4)*	none
	rat	female	0.4 *(2.4)*	none
	rat	male	6 *(37.5)*	1.5 *(9.4)*
Mammary gland neoplasms, Total	rat	male	1.5 *(9.4)*	0.4 *(2.4)*

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (See Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis: No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose on a mg/m² basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the human dose on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C: The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats and in one Segment II study in New Zealand rabbits. The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the human dose on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses 0.1 to 3 times the human dose on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose 1.5 times higher than the human dose on a mg/m² basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERDAL® therapy is unknown.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

Nursing Mothers

It is not known whether or not risperidone is excreted in human milk. In animal studies, risperidone and 9-hydroxyrisperidone were excreted in breast milk. Therefore, women receiving RISPERDAL® should not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

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Geriatric Use

Clinical studies of RISPERDAL® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (See PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL® related adverse event (See PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients but 3.8% in active-control patients in the phase 2-3 trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: In two 6 to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events were present at at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Patients: The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL®-treated patients treated at doses of ≤ 10 mg/day than among placebo-treated patients in the pooled results of two 6 to 8-week controlled trials. Patients received RISPERDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1: **Treatment-Emergent Adverse Experience Incidence in 6 to 8-Week Controlled Clinical Trials[1]**

Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric Disorders			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Nervous System			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal System			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory System			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a Whole			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '≤ 10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (See DOSE DEPENDENCY OF ADVERSE EVENTS).

Dose Dependency of Adverse Events:

Extrapyramidal symptoms: Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing four fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events: Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatiguability, and increased pigmentation.

Vital Sign Changes: RISPERDAL® is associated with orthostatic hypotension and tachycardia (See PRECAUTIONS).

Weight Changes: The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6 to 8-week placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes: A between group comparison for 6 to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (See PRECAUTIONS).

ECG Changes: The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (See WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® (risperidone) were administered to 2607 patients in phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology (Note: These events are marked with an asterisk in the listings that follow).

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

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Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders: *Frequent:* increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: *Frequent:* increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-intestinal Disorders: *Frequent:* anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: *Frequent:* fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: *Infrequent:* hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders: *Frequent:* increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: *Infrequent:* palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders: *Infrequent:* abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: *Infrequent:* hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders: *Frequent:* polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-skeletal System Disorders: *Infrequent:* myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female: *Frequent:* menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: *Infrequent:* increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: *Infrequent:* epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: *Rare:* tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: *Infrequent:* anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male: *Frequent:* erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders: *Rare:* leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders: *Rare:* gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: *Rare:* bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychologic Dependence: RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Premarketing experience included eight reports of acute RISPERDAL® (risperidone) overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure. Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia and hypotension. Other adverse events reported since market introduction which were temporally, (but not necessarily causally) related to RISPERDAL® overdose, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose: RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Antipsychotic efficacy was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL®, however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Dosage in Special Populations: The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of the risperidone, possibly resulting in an enhanced effect (See CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (See PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Maintenance Therapy: While there is no body of evidence available to answer the question of how long the patient treated with RISPERDAL® should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on RISPERDAL®, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching from Other Antipsychotics: There are no systematically collected data to specifically address switching from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients, more gradual discontinuation may be most appropriate for other patients. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.

Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.

Keep out of reach of children.

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US Patent 4,804,663

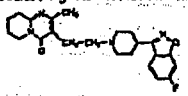
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RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is *practically* insoluble in water, freely soluble in *methylene chloride*, and soluble in methanol and 0.1 *N* HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, *hydroxypropyl* methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide, the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide and purified water.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that this drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin type 2 ($5HT_2$), dopamine type 2 (D_2), α$_1$ and α$_2$ adrenergic, and H$_1$ histaminergic receptors. RISPERDAL® antagonizes other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10^{-4} M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of ^{14}C-risperidone as a solution in three healthy male volunteers. Total recovery of radioactivity at one week was 85%, including 70% in the urine and 15% in the feces.

Risperidone is extensively metabolized in the liver by CYP 2D6 to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating species, and appears approximately equi-effective with risperidone with respect to receptor binding activity and some effects in animals. (A second minor pathway is *N*-dealkylation.) Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. Plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) when compared to a solution. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone was 70% (CV=25%).

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is CYP 2D6, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6-8% of Caucasians, and a very low percent of Asians have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers. Following oral administration of solution or tablet, mean peak plasma concentrations occurred at about 1 hour. Peak 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of risperidone was three hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Because risperidone and 9-hydroxyrisperidone are approximately equi-effective, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of risperidone and 9-hydroxyrisperidone, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours. In analyses comparing adverse reaction rates in extensive and poor metabolizers in controlled and open studies, no important differences were seen.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of CYP 2D6 could interfere with conversion of risperidone to 9-hydroxyrisperidone. This in fact occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The favorable and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (see PRECAUTIONS and DRUG INTERACTIONS).

The plasma protein binding of risperidone was about 90% over the in vivo concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of α$_1$-acid glycoprotein. The plasma binding of 9-hydroxyrisperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfamethazine (100 µg/mL), warfarin (10 µg/mL) and carbamazepine (10 µg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Special Populations

Renal Impairment: In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with *renal* disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment: While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the *mean free fraction* of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α$_1$-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly: In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (see DOSAGE AND ADMINISTRATION).

Race and Gender Effects: No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4 to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales were employed; these included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (> 20% reduction in PANSS (total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

INDICATIONS AND USAGE

RISPERDAL® (*risperidone*) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6 to 8 weeks) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to this product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (*rhabdomyolysis*), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious *medical* illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially *elderly women*, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that *symptomatic suppression* has upon the *long-term course* of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be *reserved* for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less *harmful* treatments are not available or *appropriate*. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed *periodically*.

If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Potential for Proarrhythmic Effects: Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients,

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even at 12-16 mg/day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrhythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL® treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures: During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL® treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinaemia: As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism: Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic Effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness: Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the data revealed one finding of potential concern, i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen in the smaller placebo group. There were 3 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (see WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2), and an increase in the free fraction of the risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance: Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed an infant if they are taking RISPERDAL®.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking RISPERDAL®.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of carbamazepine with risperidone may increase the clearance risperidone.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone

Fluoxetine may increase the plasma concentration of the anti-psychotic fraction (risperidone plu hydroxyrisperidone) by raising the concentration of risperidone, although not the active metabo 9-hydroxyrisperidone.

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes: Risperidone is metabolized to 9-hydr risperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhit by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interact that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plas concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysi clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that and extensive metabolizers have different rates of adverse effects. No comparison of effectiver in the two groups has been made.

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, I MP, and IIIA4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by CYP 2D6: In vitro studies indicate that risperidone is a relatively w inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the cleara of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in Swiss albino mice and Wistar r Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to r and for 25 months in rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maxim human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human d (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m^2 basis. A maxin tolerated dose was not achieved in male mice. There were statistically significant increase pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinon The following table summarizes the multiples of the human dose on a mg/m^2 (mg/kg) basis at wi these tumors occurred.

TUMOR TYPE	SPECIES	SEX	MULTIPLE OF MAXIMUM HUMAN DOS in mg/m^2 (mg/kg)	
			LOWEST EFFECT LEVEL	HIGHEST NO EFFECT LEVEL
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6 (37.5)	1.5 (9.4)
Mammary gland neoplasms, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Ser prolactin levels were not measured during the risperidone carcinogenicity studies; howe measurements during subchronic toxicity studies showed that risperidone elevated serum prola levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. Increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rod after chronic administration of other antipsychotic drugs and is considered to be prolactin media The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodent unknown (see Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis: No evidence of mutagenic potential for risperidone was found in the Ames rev mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or the chromoso aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fert in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at do 0.1 to 3 times the maximum recommended human dose on a mg/m^2 basis. The effect appears to be in females since impaired mating behavior was not noted in the Segment I study in which ma only were treated. In a subchronic study in Beagle dogs in which risperidone was administere doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 t the human dose on a mg/m^2 basis. Dose-related decreases were also noted in serum testoster at the same doses. Serum testosterone and sperm parameters partially recovered but remai decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C: The teratogenic potential of risperidone was studied in three Segme studies in Sprague-Dawley and Wistar rats and in one Segment II study in New Zealand rabt The incidence of malformations was not increased compared to control in offspring of rat rabbits given 0.4 to 6 times the human dose on a mg/m^2 basis. In three reproductive studie rats (two Segment III and a multigenerational study), there was an increase in pup deaths du the first 4 days of lactation at doses 0.1 to 3 times the human dose on a mg/m^2 basis. It is known whether these deaths were due to a direct effect on the fetuses or pups or to effects the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III st there was an increase in stillborn rat pups at a dose 1.5 times higher than the human dose c mg/m^2 basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-contro studies in pregnant women. However, there was one report of a case of agenesis of the cor callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERD therapy is unknown.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the poter risk to the fetus.

Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone were excreted in breast milk. It has b demonstrated that risperidone and 9-hydroxyrisperidone are also excreted in human breast m Therefore, women receiving RISPERDAL® should not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL® did not include sufficient numbers of patients aged 65 and ove determine whether they respond differently from younger patients. Other reported clin experience has not identified differences in responses between elderly and younger patients general, a lower starting dose is recommended for an elderly patient, reflecting a decreas pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepa renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINIC PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhib greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitorin orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to drug may be greater in patients with impaired renal function. Because elderly patients are m likely to have decreased renal function, care should be taken in dose selection, and it may be us to monitor renal function (see DOSAGE AND ADMINISTRATION).

Plaintiff Ex. 656

R. 3296

JJRIS 00001798

ADVERSE REACTIONS

Associated With Discontinuation of Treatment

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL® related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients but 3.6% in active-control patients in the phase 2-3 trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: In two 6 to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 18 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events were present in at least 5% and twice the rate of placebo: *increased* dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Patients: The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL®-treated patients treated at doses of ≤ 10 mg/day than among placebo-treated patients in the pooled results of two 6 to 8-week controlled trials. Patients received RISPERDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. *Reported* adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1: Treatment-Emergent Adverse Experience Incidence in 6 to 8-Week Controlled Clinical Trials*

Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric Disorders			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	22%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Nervous System			
Extrapyramidal symptoms†	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal System			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory System			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a Whole			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Sebornhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

* Events reported by at least 1% of patients treated with RISPERDAL® ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

† Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of *'extrapyramidal symptoms'* does not appear to differ for the ≤ 10 mg/day group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see DOSE DEPENDENCY OF ADVERSE EVENTS).

Dose Dependency of Adverse Events

Extrapyramidal Symptoms: Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing four fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	RIS 2	RIS 6	RIS 10	RIS 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	RIS 1	RIS 4	RIS 8	RIS 12	RIS 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events: Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatiguability, and increased pigmentation.

Vital Sign Changes: RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Changes: The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6 to 8-week placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes: A between group comparison for 6 to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Changes: The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (see WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® (risperidone) were administered to 2607 patients in phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders: Frequent: increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, *delirium*, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: Frequent: increased sleep duration*, *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, tonicitis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-Intestinal Disorders: Frequent: anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: Frequent: fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders: Frequent: increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders: Infrequent: abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hypercalcemia, hypoglycemia.

Urinary System Disorders: Frequent: polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-Skeletal System Disorders: Infrequent: myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Plaintiff Ex. 656

R. 3297

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Reproductive Disorders, Female: Frequent: menorrhagia*, orgasmic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: Infrequent: increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: Infrequent: epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: Infrequent: anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male: Frequent: erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance-Disorders: Rare: leukocytosis, lymphadenopathy, leucopenia, Felger-Huot anomaly.

Endocrine Disorders: Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: Rare: bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, hyperglycemia, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychologic Dependence: RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Premarketing experience included eight reports of acute RISPERDAL® (risperidone) overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure. Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia and hypotension. Other adverse events reported since market introduction which were temporally, (but not necessarily causally) related to RISPERDAL® overdose, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with *appropriate* measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose: RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early short-term clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent short-term controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. In a long-term controlled trial in stable patients, RISPERDAL® was administered on a QD schedule at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in short-term clinical trials supporting effectiveness of RISPERDAL®, however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 8 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy: While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Dosage in Special Populations: The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of the risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (see PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching From Other Antipsychotics: There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or concurring concomitant administration with other antipsychotics. While *immediate discontinuation* of the previous antipsychotic treatment may be acceptable for *some schizophrenic patients, more* gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "1" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with other cola or tea, however.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.

Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.

Keep out of reach of children.

7500221
US Patent 4,804,663
Revised July 2002
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RISPERDAL® tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico or
Janssen-Cilag, SpA, Latina, Italy

RISPERDAL® oral solution is manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium

RISPERDAL® tablets and oral solution are distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

JANSSEN CILAG PHARMACEUTICA PRODUCTS, L.P.

Plaintiff Ex. 656

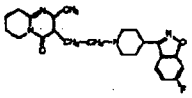
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JJRIS 00001796

RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro- 2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, *microcrystalline* cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide, the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide and purified water.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that this drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin type 2 ($5HT_2$), dopamine type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® antagonizes other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-4}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of ^{14}C-risperidone as a solution in three healthy male volunteers. Total recovery of radioactivity at one week was 85%, including 70% in the urine and 15% in the feces.

Risperidone is extensively metabolized in the liver by CYP 2D6 to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating specie, and appears approximately equi-effective with risperidone with respect to receptor binding activity and some effects in animals. (A second minor pathway is *N*-deafkylation.) Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. Plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) when compared to a solution. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone was 70% (CV=25%).

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is CYP 2D6, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6-8% of Caucasians, and a very low percent of Asians have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers. Following oral administration of solution or tablet, mean peak plasma concentrations occurred at about 1 hour. Peak 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of risperidone was three hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Because risperidone and 9-hydroxyrisperidone are approximately equi-effective, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of risperidone and 9-hydroxyrisperidone, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours. In analyses comparing adverse reaction rates in extensive and poor metabolizers in controlled and open studies, no important differences were seen.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of CYP 2D6 could interfere with conversion of risperidone to 9-hydroxyrisperidone. This in fact occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The favorable and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (see PRECAUTIONS and DRUG INTERACTIONS).

The plasma protein binding of risperidone was about 90% over the in vitro concentration range of 0.5 to 200 ng/mL, and increased with increasing concentrations of α_1-acid glycoprotein. The plasma binding of 9-hydroxyrisperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfamethazine (100 µg/mL), warfarin (10 µg/mL) and carbamazepine (10 µg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Special Populations

Renal Impairment: In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment: While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly: In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (see DOSAGE AND ADMINISTRATION).

Race and Gender Effects: No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4 to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed; these included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (> 20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

INDICATIONS AND USAGE

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6 to 8 weeks) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with

Plaintiff Ex. 657

R. 3299

JJRP 006609

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dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® has not been shown to be safe or effective in the treatment of patients with dementia-related psychosis.

Potential for Proarrhythmic Effects: Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12-16 mg/day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrhythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL® treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures: During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL® treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism: Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic Effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness: Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the data revealed one finding of potential concern, i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen in the smaller placebo group. There were 3 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (see WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²), and an increase in the free fraction of the risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance: Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed an infant if they are taking RISPERDAL®.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking RISPERDAL®.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Fluoxetine may increase the plasma concentration of the anti-psychotic fraction (risperidone plus 9-hydroxyrisperidone) by raising the concentration of risperidone, although not the active metabolite, 9-hydroxyrisperidone.

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, IIC9, MP, and IIIA4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by CYP 2D6 : In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

TUMOR TYPE	SPECIES	SEX	MULTIPLE OF MAXIMUM HUMAN DOSE in mg/m² (mg/kg)	
			LOWEST EFFECT LEVEL	HIGHEST NO EFFECT LEVEL
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6 (37.5)	1.5 (9.4)
Mammary gland neoplasms, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis: No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose on a mg/m² basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.8 to 10 times the human dose on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C: The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats and in one Segment II study in New Zealand rabbits. The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the human dose on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses 0.1 to 3 times the human dose on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose 1.5 times higher than the human dose on a mg/m² basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERDAL® therapy is unknown.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone were excreted in breast milk. It has been demonstrated that risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving RISPERDAL® should not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the

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initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated With Discontinuation of Treatment

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL® related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients but 3.8% in active-control patients in the phase 2-3 trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: In two 6 to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events were present in at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Patients: The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL®-treated patients treated at doses of ≤ 10 mg/day than among placebo-treated patients in the pooled results of two 6 to 8-week controlled trials. Patients received RISPERDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1: Treatment-Emergent Adverse Experience Incidence in 6 to 8-Week Controlled Clinical Trials[1]

Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric Disorders			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Nervous System			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal System			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory System			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a Whole			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '≤ 10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see DOSE DEPENDENCY OF ADVERSE EVENTS).

Dose Dependency of Adverse Events:

Extrapyramidal Symptoms: Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing four fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events: Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatiguability, and increased pigmentation.

Vital Sign Changes: RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Changes: The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6 to 8-week placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes: A between group comparison for 6 to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Changes: The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (see WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® (risperidone) were administered to 2607 patients in phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders: Frequent: increased dream activity*, diminished sexual desire*, nervousness. ***Infrequent:*** impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. ***Rare:*** emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: Frequent: increased sleep duration*. ***Infrequent:*** dysarthria, vertigo, stupor, paraesthesia, confusion. ***Rare:*** aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-Intestinal Disorders: Frequent: anorexia, reduced salivation*. ***Infrequent:*** flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. ***Rare:*** fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: Frequent: fatigue. ***Infrequent:*** edema, rigors, malaise, influenza-like symptoms. ***Rare:*** pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. ***Rare:*** asthma, increased sputum, aspiration.

Skin and Appendage Disorders: Frequent: increased pigmentation*, photosensitivity*. ***Infrequent:*** increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. ***Rare:*** bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. ***Rare:*** ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders: Infrequent: abnormal accommodation, xerophthalmia. ***Rare:*** diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. ***Rare:*** decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

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Urinary System Disorders: *Frequent:* polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-Skeletal System Disorders: *Infrequent:* myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female: *Frequent:* menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: *Infrequent:* increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: *Infrequent:* epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: *Rare:* tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: *Infrequent:* anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male: *Frequent:* erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders: *Rare:* leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders: *Rare:* gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: *Rare:* bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, hyperglycemia, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychologic Dependence: RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Premarketing experience included eight reports of acute RISPERDAL® (risperidone) overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure. Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia and hypotension. Other adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® overdose, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose: RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early short-term clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent short-term controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. In a long-term controlled trial in stable patients, RISPERDAL® was administered on a QD schedule at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in short-term clinical trials supporting effectiveness of RISPERDAL®, however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 8 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy: While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Dosage in Special Populations: The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of the risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (see PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching From Other Antipsychotics: There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.

Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.

Keep out of reach of children.

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US Patent 4,804,663
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RISPERDAL® tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico or
Janssen-Cilag, SpA, Latina, Italy

RISPERDAL® oral solution is manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium

RISPERDAL® tablets and oral solution are distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

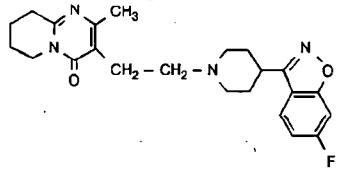
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RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION
RISPERDAL® M-TAB™
(RISPERIDONE)
ORALLY DISINTEGRATING TABLETS

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL® M-TAB™ Orally Disintegrating Tablets are available in 0.5 mg, 1 mg, and 2 mg strengths and are light coral in color.

RISPERDAL® M-TAB™ Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Pharmacokinetic studies showed that RISPERDAL® M-TAB™ Orally Disintegrating Tablets and RISPERDAL® Oral Solution are bioequivalent to RISPERDAL® Tablets.

Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through *N*-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug (e.g., the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions (see PRECAUTIONS – Drug Interactions). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n≅70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment (see PRECAUTIONS – Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Administration of RISPERDAL® with Certain Other Medications).

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13% (see PRECAUTIONS – Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Administration of RISPERDAL® with Certain Other Medications).

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13) (see PRECAUTIONS – Drug Interactions).

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone (see PRECAUTIONS – Drug Interactions).

There were no significant interactions between risperidone (1 mg QD) and erythromycin (500 mg QID) (see PRECAUTIONS – Drug Interactions).

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of ^{14}C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of the active moiety, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Special Populations

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly

In healthy elderly subjects, renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (see DOSAGE AND ADMINISTRATION).

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

Schizophrenia

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4- to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia,

Plaintiff Ex. 661

R. 3303

LIRF 00739324

about the overall clinical state of the patient. In addition, the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS) were employed.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (>20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

Bipolar Mania

Monotherapy

The efficacy of RISPERDAL® in the treatment of acute manic or mixed episodes was established in 2 short-term (3-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=246), limited to patients with manic episodes, which involved a dose range of RISPERDAL® 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 4.1 mg/day), RISPERDAL® was superior to placebo in the reduction of Y-MRS total score.

(2) In another 3-week placebo-controlled trial (n=286), which involved a dose range of 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 5.6 mg/day), RISPERDAL® was superior to placebo in the reduction of Y-MRS total score.

Combination Therapy

The efficacy of risperidone with concomitant lithium or valproate in the treatment of acute manic or mixed episodes was established in one controlled trial in patients who met the DSM-IV criteria for Bipolar I Disorder. This trial included patients with or without psychotic features and with or without a rapid-cycling course.

(1) In this 3-week placebo-controlled combination trial, 148 in- or outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL®, placebo, or an active comparator, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.8 mg/day), combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.4 mEq/L or 50 mcg/mL to 120 mcg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 3-week placebo-controlled combination trial, 142 in- or outpatients on lithium, valproate, or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL® or placebo, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.7 mg/day), combined with lithium, valproate, or carbamazepine (in therapeutic ranges of 0.6 mEq/L to 1.4 mEq/L for lithium, 50 mcg/mL to 125 mcg/mL for valproate, or 4-12 mcg/mL for carbamazepine, respectively) was not superior to lithium, valproate, or carbamazepine alone in the reduction of Y-MRS total score. A possible explanation for the failure of this trial was induction of risperidone and 9-hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxyrisperidone.

INDICATIONS AND USAGE

Schizophrenia

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6- to 8-weeks) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see CLINICAL PHARMACOLOGY – Clinical Trials). Nevertheless, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Bipolar Mania

Monotherapy

RISPERDAL® is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL® was established in two placebo-controlled trials (3-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

Combination Therapy

The combination of RISPERDAL® with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL® in combination with lithium or valproate was established in one placebo-controlled (3-week) trial with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

The effectiveness of RISPERDAL® for longer-term use, that is, for more than 3 weeks of treatment of an acute episode, and for prophylactic use in mania, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk

factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2 and 3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures

During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL®-treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see PRECAUTIONS – Carcinogenesis, Mutagenesis, Impairment of Fertility). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high-dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism

Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic Effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness

Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²), and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance

Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised not to breast-feed an infant if they are taking RISPERDAL®.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL®.

Phenylketonurics

Phenylalanine is a component of aspartame. Each 2 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.56 mg phenylalanine; each 1 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Amytriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increased the bioavailability of risperidone, but only marginally increased the plasma concentration of the active antipsychotic fraction.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Carbamazepine and Other Enzyme Inducers

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment.

Fluoxetine and Paroxetine

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Lithium

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13).

Valproate

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone.

Digoxin

RISPERDAL® (0.25 mg BID) does not show a clinically relevant effect on the pharmacokinetics of digoxin.

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

R. 3305

LIRF 00739326

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism.

There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY).

Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m² (mg/kg) Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6.0 (37.5)	1.5 (9.4)
Mammary gland neoplasm, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5-6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS, General - Hyperprolactinemia).

Mutagenesis

No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, *in vitro* rat hepatocyte DNA-repair assay, *in vivo* micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility

Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m² basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the MRHD on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C

The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m² basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m² basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m² basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m² basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to RISPERDAL® therapy is unknown.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL® did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The following findings are based on the short-term, placebo-controlled, North American, premarketing trials for schizophrenia and acute bipolar mania. In patients with Bipolar I Disorder, treatment-emergent adverse events are presented separately for risperidone as monotherapy and as adjunctive therapy to mood stabilizers.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia. However, this information is also generally applicable to bipolar mania.

Associated With Discontinuation of Treatment

Schizophrenia

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in Phase 2 and 3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL®-related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients, but 3.8% in active-control patients in the Phase 2 and 3 trials.

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (10/134) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 6% (7/125) of placebo-treated patients. The adverse events associated with discontinuation and considered to be possibly, probably, or very likely drug-related included paroniria, somnolence, dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events occurred in one RISPERDAL®-treated patient (0.7%) and in no placebo-treated patients (0%).

In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, there was no overall difference in the incidence of discontinuation due to adverse events (4% for RISPERDAL® vs. 4% for placebo).

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials

Schizophrenia

In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events occurred at an incidence of at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observed adverse events associated with the use of RISPERDAL® (incidence of 5% or greater and at least twice that of placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism,

LIRF 00739327

vision abnormal, and saliva increased. In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, the most commonly observed adverse events associated with the use of RISPERDAL® were somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, and urinary incontinence.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Patients - Schizophrenia

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent among RISPERDAL®-treated patients treated at doses of ≤10 mg/day than among placebo-treated patients in the pooled results of two 6- to 8-week controlled trials. Patients received RISPERDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Table 1. Incidence of Treatment-Emergent Adverse Events in 6- to 8-Week Controlled Clinical Trials[1]

Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Central & peripheral nervous system			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory system			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a whole - general			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see ADVERSE REACTIONS – Dose Dependency of Adverse Events).

Adverse Events Occurring at an Incidence of 2% or More Among RISPERDAL®-Treated Patients - Bipolar Mania

Tables 2 and 3 display adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of RISPERDAL® (1-6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms.

Table 2. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Monotherapy in Bipolar Mania[1]

Body System/ Preferred Term	RISPERDAL® (N=134)	Placebo (N=125)
Central & peripheral nervous system		
Dystonia	18%	6%
Akathisia	16%	6%
Dizziness	11%	9%
Parkinsonism	6%	3%
Hypoaesthesia	2%	1%
Psychiatric		
Somnolence	28%	7%
Agitation	8%	6%
Manic reaction	8%	6%
Anxiety	4%	2%
Concentration impaired	2%	1%
Gastrointestinal system		
Dyspepsia	11%	6%
Nausea	11%	2%
Saliva increased	5%	1%
Mouth dry	3%	2%
Body as a whole - general		
Pain	5%	3%
Fatigue	4%	2%
Injury	2%	0%
Respiratory system		
Sinusitis	4%	1%
Rhinitis	3%	2%
Coughing	2%	2%
Skin and appendage		
Acne	2%	0%
Pruritus	2%	1%
Musculo-Skeletal		
Myalgia	5%	2%
Skeletal pain	2%	1%
Metabolic and nutritional		
Weight increase	2%	0%
Vision disorders		
Vision abnormal	6%	2%
Cardiovascular, general		
Hypertension	3%	1%
Hypotension	2%	0%
Heart rate and rhythm		
Tachycardia	3%	2%

[1] Events reported by at least 2% of patients treated with RISPERDAL® are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: headache, tremor, insomnia, constipation, back pain, upper respiratory tract infection, pharyngitis, and arthralgia.

Table 3. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Adjunctive Therapy in Bipolar Mania[1]

Body System/Preferred Term	RISPERDAL® + Mood Stabilizer (N=52)	Placebo + Mood Stabilizer (N=51)
Gastrointestinal system		
Saliva increased	10%	0%
Diarrhea	8%	4%
Abdominal pain	6%	0%
Constipation	6%	4%
Mouth dry	6%	4%
Tooth ache	4%	0%
Tooth disorder	4%	0%
Central & peripheral nervous system		
Dizziness	14%	2%
Parkinsonism	14%	4%
Akathisia	8%	0%
Dystonia	6%	4%
Psychiatric		
Somnolence	25%	12%
Anxiety	6%	4%
Confusion	4%	0%
Respiratory system		
Rhinitis	8%	4%
Pharyngitis	6%	4%
Coughing	4%	0%
Body as a whole - general		
Asthenia	4%	2%

LIRF 00739328

Table 3. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Adjunctive Therapy in Bipolar Mania[1] (continued)

Body System/Preferred Term	RISPERDAL® + Mood Stabilizer (N=52)	Placebo + Mood Stabilizer (N=51)
Urinary system		
Urinary incontinence	6%	2%
Heart rate and rhythm		
Tachycardia	4%	2%
Metabolic and nutritional		
Weight increase	4%	2%
Skin and appendages		
Rash	4%	2%

[1] Events reported by at least 2% of patients treated with RISPERDAL® are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: dyspepsia, nausea, vomiting, headache, tremor, insomnia, chest pain, fatigue, pain, skeletal pain, hypertension, and vision abnormal.

Dose Dependency of Adverse Events

Extrapyramidal Symptoms

Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

Vital Sign Changes

RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Changes

The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes

A between-group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Changes

Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute).

Other Events Observed During the Premarketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® were administered to 2607 patients in Phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included, except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders

Frequent: increased dream activity*, diminished sexual desire*, nervousness.
Infrequent: impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia.
Rare: emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders

Frequent: increased sleep duration*.
Infrequent: dysarthria, vertigo, stupor, paraesthesia, confusion.
Rare: aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastrointestinal Disorders

Frequent: anorexia, reduced salivation*.
Infrequent: flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis.
Rare: fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders

Frequent: fatigue.
Infrequent: edema, rigors, malaise, influenza-like symptoms.
Rare: pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders

Infrequent: hyperventilation, bronchospasm, pneumonia, stridor.
Rare: asthma, increased sputum, aspiration.

Skin and Appendage Disorders

Frequent: increased pigmentation*, photosensitivity*.
Infrequent: increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation.
Rare: bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders

Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction.
Rare: ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders

Infrequent: abnormal accommodation, xerophthalmia.
Rare: diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders

Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus.
Rare: decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders

Frequent: polyuria/polydipsia*.
Infrequent: urinary incontinence, hematuria, dysuria.
Rare: urinary retention, cystitis, renal insufficiency.

Musculo-Skeletal System Disorders

Infrequent: myalgia.
Rare: arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female

Frequent: menorrhagia*, orgastic dysfunction*, dry vagina*.
Infrequent: nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders

Infrequent: increased SGOT, increased SGPT.
Rare: hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding, and Clotting Disorders

Infrequent: epistaxis, purpura.
Rare: hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders

Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders

Infrequent: anemia, hypochromic anemia.
Rare: normocytic anemia.

Reproductive Disorders, Male

Frequent: erectile dysfunction*.
Infrequent: ejaculation failure.

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LIRF 00739320

White Cell and Resistance Disorders

Rare: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders

Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses

Rare: bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, hyperglycemia, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychological Dependence

RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Premarketing experience included eight reports of acute RISPERDAL® (risperidone) overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. Other adverse events reported since market introduction which were temporally, (but not necessarily causally) related to RISPERDAL® overdose, include torsade de pointes, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Because of the rapid disintegration of RISPERDAL® M-TAB™ Orally Disintegrating Tablets, pill fragments may not appear in gastric contents obtained with lavage.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Schizophrenia

Usual Initial Dose

RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL®; however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day, and to a target dose of 4 mg QD on the third day (see CLINICAL PHARMACOLOGY – Clinical Trials). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching From Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

Bipolar Mania

Usual Dose

Risperidone should be administered on a once daily schedule, starting with 2 mg to 3 mg per day. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments/decrements of 1 mg per day, as studied in the short-term, placebo-controlled trials. In these trials, short-term (3 week) anti-manic efficacy was demonstrated in a flexible dosage range of 1-6 mg per day (see CLINICAL PHARMACOLOGY – Clinical Trials). RISPERDAL® doses higher than 6 mg per day were not studied.

Maintenance Therapy

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with risperidone. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of risperidone in such longer-term treatment (e.g., beyond 3 weeks).

Pediatric Use

Safety and effectiveness of RISPERDAL® in pediatric patients with schizophrenia or acute mania associated with Bipolar I Disorder have not been established.

Dosage in Special Populations

The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (see PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Co-Administration of RISPERDAL® with Certain Other Medications

Co-administration of carbamazepine and other enzyme inducers (e.g., phenytoin; rifampin, phenobarbital) with risperidone would be expected to cause decreases in the plasma concentrations of active moiety (the sum of risperidone and 9-hydroxyrisperidone), which could lead to decreased efficacy of risperidone treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13%. The dose of risperidone needs to be titrated accordingly when fluoxetine or paroxetine is co-administered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Directions for Use of RISPERDAL® M-TAB™ Orally Disintegrating Tablets

RISPERDAL® M-TAB™ Orally Disintegrating Tablets are supplied in blister packs of 4 tablet units each.

Tablet Accessing

Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

Tablet Administration

Using dry hands, remove the tablet from the blister unit and immediately place the entire RISPERDAL® M-TAB™ Orally Disintegrating Tablet on the tongue. The RISPERDAL® M-TAB™ Orally Disintegrating Tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. RISPERDAL® M-TAB™ Orally Disintegrating Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to split or to chew the tablet.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

URF 00739336

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50, hospital unit dose packs of 100 NDC 50458-301-01.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50, hospital unit dose packs of 100 NDC 50458-302-01.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and millilliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

RISPERDAL® M-TAB™ (risperidone) Orally Disintegrating Tablets are etched on one side with "R0.5", "R1", and "R2", respectively, and are packaged in blister packs of 4 (2 X 2) tablets.

0.5 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-395-28, long-term care packaging of 30 tablets NDC 50458-395-30.

1 mg light coral, square, biconvex tablets: 7 blister packages per box, NDC 50458-315-28, long-term care packaging of 30 tablets NDC 50458-315-30.

2 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-325-28.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.
Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.
Keep out of reach of children.

RISPERDAL® M-TAB™ Orally Disintegrating Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F).
Keep out of reach of children.

JANSSEN PHARMACEUTICA PRODUCTS, L.P.

RISPERDAL® tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico or Janssen-Cilag, SpA, Latina, Italy

RISPERDAL® oral solution is manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium

RISPERDAL® M-TAB™ Orally Disintegrating Tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico

RISPERDAL® tablets, RISPERDAL® M-TAB™ Orally Disintegrating Tablets, and oral solution are distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

7513908
US Patent 4,804,663
Revised: December 2003
©Janssen 2004
260648

USING YOUR RISPERDAL® (RISPERIDONE) DISPENSING-PIPETTE AND BOTTLE

Use this product as indicated below, unless directed otherwise by your Physician.

IMPORTANT: Please read these instructions before using RISPERDAL® (risperidone) oral solution.

1. Push the plastic screw-cap on the bottle down while turning it counter-clockwise. Remove the unscrewed cap (see Figure 1).
2. Insert the dispensing-pipette fully into the bottle (see Figure 2).
3. While holding the outer barrel of the pipette, pull the plunger up to the level (see markings on side) that equals the dosage prescribed by your physician (see Figure 3).
4. Holding the outer barrel of the pipette, remove the entire pipette from the bottle, being careful not to depress the plunger prematurely (see Figure 4).
5. Empty the entire contents of the pipette into 3-4 ounces (100mL) of a beverage by pushing the plunger down inside the pipette barrel. Stir the mixture thoroughly before consuming. RISPERDAL® is compatible with water, coffee, orange juice, or low-fat milk: IT IS NOT COMPATIBLE with cola or tea.
6. Replace the plastic cap on the bottle by screwing it clockwise; rinse the empty dispensing-pipette with water.
7. Peel the adhesive backing off the pipette holder and attach holder directly onto all-GLASS area of the bottle (see Figure 5). Attach the holder such that the adhesive strip is at the top end of the pipette holder. Press firmly against the bottle for a few seconds. Note: Adhesive will not stick to label area.
8. Insert pipette into holder.

DOSAGE: For information about the use of **RISPERDAL®** (risperidone), please see accompanying **Package Insert.**

STORAGE: Store bottle at controlled room temperature 15° –25°C (59°-77°F/) away from children; avoid freezing and protect from light.

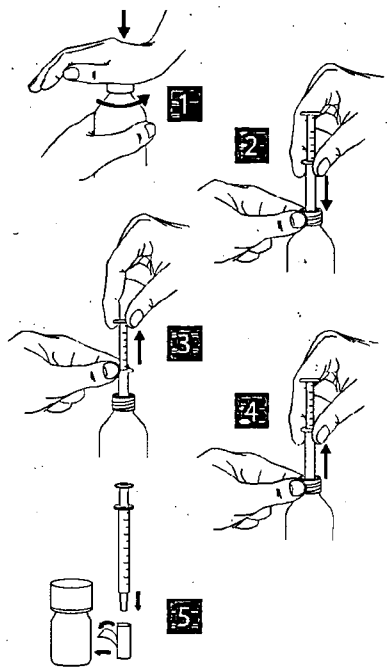
Each 1mL contains: 1mg of risperidone in an aqueous solution.

NDC 50458-305-03 30mL
RISPERDAL®
(RISPERIDONE)
ORAL SOLUTION
1mg/mL

Manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium

Distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ, United States 08560

Dispensing Diagram / Diagram del dispensación



CÓMO USAR SU PIPETA DISPENSADORA Y FRASCO DE RISPERDAL® (RISPERIDONA)

Utilice este producto según lo indicado a continuación, salvo instrucción contraria de su medico.

IMPORTANTE: Sírvase leer estas indicaciones antes de utilizar la solución oral de RISPERDAL® (risperidona).

1. Empujar la tapa plástica a rosca del frasco hacia abajo girándola al mismo tiempo en el sentido contrario a las manecillas del reloj. Quitar la tapa desenroscada (ver la Figura 1).
2. Introducir la pipeta dispensadora completamente en el frasco (ver la Figura 2).
3. Sosteniendo el barril externo de la pipeta, tirar del émbolo hasta el nivel (ver las marcas de costado) que representa la dosis recetada por su médico (ver la Figura 3).
4. Sosteniendo el barril externo de la pipeta, quitar la pipeta entera del frasco, cuidándose de no oprimir el émbolo prematuramente (ver la Figura 4).
5. Vaciar el contenido completo de la pipeta en 3-4 onzas (100mL) de una bebida oprimiendo el émbolo dentro del barril de la pipeta. Agitar la mezcla minuciosamente antes de tomarla. RISPERDAL® es compatible con agua, café, jugo de naranja o leche de bajo tenor graso. NO ES COMPATIBLE con bebidas gaseosas ni té.
6. Reemplazar la tapa de plástico en el frasco enroscándola en el sentido de las manecillas del reloj; enjuagar la pipeta surtidora vacia con agua.
7. Pelar el protector del adhesivo del portapipeta y fijarlo directamente en un área del frasco que sea sólo de VIDRIO (ver la Figura 5). Fijar el portapipeta. Apretar firmemente contra el frasco durante varios segundos. Nota: El adhesivo no se pegará al área del rótulo.
8. Introducir la pipeta en el portapipeta.

Posología: Para información acerca del uso de **RISPERDAL®** (risperidona), sírvase leer **el prospecto adjunto en el paquete.**

Almacenamiento: Almacene el frasco a temperatura ambiente controlada (59°-77°F/15° -25°C) lejos de los niños; evite que se congele y protéjalo de la luz.

Cada 1 mL contiene: 1 mg de risperidona en solución acuosa.

NDC 50458-305-03 30mL
RISPERDAL®
(RISPERIDONE)
ORAL SOLUTION
1mg/mL

Manufacturado por:
Janssen Pharmaceutica N.V.
Beerse, Bélgica

Distribuido por:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ, Estados Unidos 08560

R. 3310

LIRF 00739331

JANSSEN
PHARMACEUTICA
PRODUCTS, L.P.

RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION

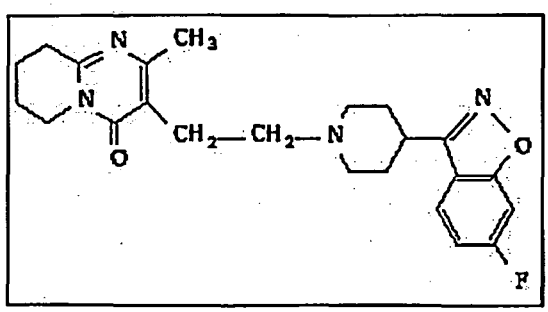
RISPERDAL® M-TAB®
(RISPERIDONE)
ORALLY DISINTEGRATING TABLETS

Increased Mortality in Elderly Patients with Dementia–Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. RISPERDAL® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is C23H27FN4O2 and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

Plaintiff Ex. 662

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL® M-TAB® Orally Disintegrating Tablets are available in 0.5 mg, 1 mg, and 2 mg strengths and are light coral in color.

RISPERDAL® M-TAB® Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Plaintiff Ex. 662

R. 3312

Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Pharmacokinetic studies showed that RISPERDAL® M-TAB® Orally Disintegrating Tablets and RISPERDAL® Oral Solution are bioequivalent to RISPERDAL® Tablets.

Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and a1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug (e.g., the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

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CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions (see PRECAUTIONS – Drug Interactions). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n@70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment (see PRECAUTIONS – Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Administration of RISPERDAL® with Certain Other Medications).

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Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13% (see PRECAUTIONS -Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Administration of RISPERDAL® with Certain Other Medications).

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13) (see PRECAUTIONS – Drug Interactions).

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone (see PRECAUTIONS – Drug Interactions).

There were no significant interactions between risperidone (1 mg QD) and erythromycin (500 mg QID) (see PRECAUTIONS – Drug Interactions).

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of 14C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of the active moiety, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Special Populations

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Plaintiff Ex. 662

Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and a1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly

In healthy elderly subjects, renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (see DOSAGE AND ADMINISTRATION).

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

CLINICAL TRIALS

Schizophrenia

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4- to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS) were employed.

Plaintiff Ex. 662

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (>20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

Bipolar Mania

Monotherapy

The efficacy of RISPERDAL® in the treatment of acute manic or mixed episodes was established in 2 short-term (3-week) placebo-controlled trials in patients who met the

Plaintiff Ex. 662

R. 3317

DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=246), limited to patients with manic episodes, which involved a dose range of RISPERDAL® 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 4.1 mg/day), RISPERDAL® was superior to placebo in the reduction of Y-MRS total score.

(2) In another 3-week placebo-controlled trial (n=286), which involved a dose range of 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 5.6 mg/day), RISPERDAL® was superior to placebo in the reduction of Y-MRS total score.

Combination Therapy

The efficacy of risperidone with concomitant lithium or valproate in the treatment of acute manic or mixed episodes was established in one controlled trial in patients who met the DSM-IV criteria for Bipolar I Disorder. This trial included patients with or without psychotic features and with or without a rapid-cycling course.

(1) In this 3-week placebo-controlled combination trial, 148 in- or outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL®, placebo, or an active comparator, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.8 mg/day), combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.4 mEq/L or 50 mcg/mL to 120 mcg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 3-week placebo-controlled combination trial, 142 in- or outpatients on lithium, valproate, or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive

Plaintiff Ex. 662

RISPERDAL® or placebo, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.7 mg/day), combined with lithium, valproate, or carbamazepine (in therapeutic ranges of 0.6 mEq/L to 1.4 mEq/L for lithium, 50 mcg/mL to 125 mcg/mL for valproate, or 4-12 mcg/mL for carbamazepine, respectively) was not superior to lithium, valproate, or carbamazepine alone in the reduction of Y-MRS total score. A possible explanation for the failure of this trial was induction of risperidone and 9-hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxyrisperidone.

INDICATIONS AND USAGE

Schizophrenia

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6- to 8-weeks) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see CLINICAL PHARMACOLOGY -Clinical Trials). Nevertheless, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Bipolar Mania

Monotherapy

RISPERDAL® is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL® was established in two placebo-controlled trials (3-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

Combination Therapy

The combination of RISPERDAL® with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

Plaintiff Ex. 662

The efficacy of RISPERDAL® in combination with lithium or valproate was established in one placebo-controlled (3-week) trial with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

The effectiveness of RISPERDAL® for longer-term use, that is, for more than 3 weeks of treatment of an acute episode, and for prophylactic use in mania, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. RISPERDAL®(risperidone) is not approved for the treatment of dementia-related psychosis (see Boxed Warning).

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

Plaintiff Ex. 662

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

Plaintiff Ex. 662

If signs and symptoms of tardive dyskinesia appear in a patient treated on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.)**

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued;

Plaintiff Ex. 662

however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2 and 3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures

During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL®-treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.)**

Hyperprolactinemia

As with other drugs that antagonize dopamine D2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of

Plaintiff Ex. 662

these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see PRECAUTIONS – Carcinogenesis, Mutagenesis, Impairment of Fertility). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high-dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism

Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Plaintiff Ex. 662

R. 3324

Antiemetic Effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness

Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL®, may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m2), and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

Plaintiff Ex. 662

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance

Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised not to breast-feed an infant if they are taking RISPERDAL®.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL®.

Phenylketonurics

Phenylalanine is a component of aspartame. Each 2 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.56 mg phenylalanine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Plaintiff Ex. 662

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Amytriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increased the bioavailability of risperidone, but only marginally increased the plasma concentration of the active antipsychotic fraction.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Carbamazepine and Other Enzyme Inducers

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment.

Fluoxetine and Paroxetine

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Lithium

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13).

Plaintiff Ex. 662

R. 3327

Valproate

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone.

Digoxin

RISPERDAL® (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n@70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism.

There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY).

Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or

Plaintiff Ex. 662

R. 3328

0.4, 1.5, and 6 times the MRHD (rats) on a mg/m2 basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m2 (mg/kg) basis at which these tumors occurred.

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m^2 (mg/kg)	
			Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	None
	rat	female	0.4 (2.4)	none
	rat	male	6.0 (37.5)	1.5 (9.4)
Mammary gland neoplasm, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5-6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS, General -Hyperprolactinemia).

Mutagenesis

No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility

Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the MRHD on a mg/m^2 basis. Dose-related decreases were also noted in

Plaintiff Ex. 662

R. 3329

serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C

The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m^2 basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m^2 basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERDAL® therapy is unknown.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

Plaintiff Ex. 662

R. 3330

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination should be considered prior to

Plaintiff Ex. 662

the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant medication with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia-related psychosis. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis (See also Boxed WARNING, WARNINGS: **Increased Mortality in Elderly Patients with Dementia-Related Psychosis.)**

ADVERSE REACTIONS

The following findings are based on the short-term, placebo-controlled, North American, premarketing trials for schizophrenia and acute bipolar mania. In patients with Bipolar I Disorder, treatment-emergent adverse events are presented separately for risperidone as monotherapy and as adjunctive therapy to mood stabilizers.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia. However, this information is also generally applicable to bipolar mania.

Associated With Discontinuation of Treatment

Schizophrenia

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in Phase 2 and 3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL®-related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients, but 3.8% in active-control patients in the Phase 2 and 3 trials.

Plaintiff Ex. 662

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (10/134) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 6% (7/125) of placebo-treated patients. The adverse events associated with discontinuation and considered to be possibly, probably, or very likely drug-related included paroniria, somnolence, dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events occurred in one RISPERDAL®-treated patient (0.7%) and in no placebo-treated patients (0%).

In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, there was no overall difference in the incidence of discontinuation due to adverse events (4% for RISPERDAL® vs. 4% for placebo).

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials

Schizophrenia

In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events occurred at an incidence of at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observed adverse events associated with the use of RISPERDAL® (incidence of 5% or greater and at least twice that of placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, vision abnormal, and saliva increased. In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, the most commonly observed adverse events associated with the use

Plaintiff Ex. 662

of RISPERDAL® were somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, and urinary incontinence.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Patients - Schizophrenia

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent among RISPERDAL®-treated patients treated at doses of ≤10 mg/day than among placebo-treated patients in the pooled results of two 6- to 8-week controlled trials. Patients received RISPERDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Plaintiff Ex. 662

Table 1. Incidence of Treatment-Emergent Adverse Events in 6- to 8-Week Controlled Clinical Trials[1]

Body System/ Preferred Term	≤10mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Central & peripheral nervous system			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory system			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a whole - general			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%

(continued)

Plaintiff Ex. 662

Table 1. Incidence of Treatment-Emergent Adverse Events in 6- to 8-Week Controlled Clinical Trials[1]

Body System/ Preferred Term	RISPERDAL® ≤10mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Cardiovascular			
Tachycardia	3%	5%	0%

[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see ADVERSE REACTIONS – Dose Dependency of Adverse Events).

Adverse Events Occurring at an Incidence of 2% or More Among RISPERDAL®-Treated Patients - Bipolar Mania

Tables 2 and 3 display adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of RISPERDAL® (1-6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms.

Table 2. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Monotherapy in Bipolar Mania[1]

Body System/ Preferred Term	RISPERDAL® (N=134)	Placebo (N=125)
Central & peripheral nervous system		
Dystonia	18%	6%
Akathisia	16%	6%
Dizziness	11%	9%
Parkinsonism	6%	3%
Hypoaesthesia	2%	1%
Psychiatric		
Somnolence	28%	7%
Agitation	8%	6%
Manic reaction	8%	6%
Anxiety	4%	2%
Concentration impaired	2%	1%
Gastrointestinal system		
Dyspepsia	11%	6%

(continued)

Plaintiff Ex. 662

R. 3336

Table 2. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Monotherapy in Bipolar Mania[1]

Body System/ Preferred Term	RISPERDAL® (N=134)	Placebo (N=125)
Nausea	11%	2%
Saliva increased	5%	1%
Mouth dry	3%	2%
Body as a whole - general		
Pain	5%	3%
Fatigue	4%	2%
Injury	2%	0%
Respiratory system		
Sinusitis	4%	1%
Rhinitis	3%	2%
Coughing	2%	2%
Skin and appendages		
Acne	2%	0%
Pruritus	2%	1%
Musculo-Skeletal		
Myalgia	5%	2%
Skeletal pain	2%	1%
Metabolic and nutritional		
Weight increase	2%	0%
Vision disorders		
Vision abnormal	6%	2%
Cardiovascular, general		
Hypertension	3%	1%
Hypotension	2%	0%
Heart rate and rhythm		
Tachycardia	3%	2%

[1]Events reported by at least 2% of patients treated with RISPERDAL® are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: headache, tremor, insomnia, constipation, back pain, upper respiratory tract infection, pharyngitis, and arthralgia.

Plaintiff Ex. 662

R. 3337

Table 3. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Adjunctive Therapy in Bipolar Mania[1]

Body System/ Preferred Term	RISPERDAL® + Mood Stabilizer (N=52)	Placebo Mood Stabilizer (N=51)
Gastrointestinal system		
Saliva increased	10%	0%
Diarrhea	8%	4%
Abdominal pain	6%	0%
Constipation	6%	4%
Mouth dry	6%	4%
Tooth ache	4%	0%
Tooth disorder	4%	0%
Central & peripheral nervous system		
Dizziness	14%	2%
Parkinsonism	14%	4%
Akathisia	8%	0%
Dystonia	6%	4%
Psychiatric		
Somnolence	25%	12%
Anxiety	6%	4%
Confusion	4%	0%
Respiratory system		
Rhinitis	8%	4%
Pharyngitis	6%	4%
Coughing	4%	0%
Body as a whole - general		
Asthenia	4%	2%
Urinary system		
Urinary incontinence	6%	2%
Heart rate and rhythm		
Tachycardia	4%	2%
Metabolic and nutritional		
Weight increase	4%	2%
Skin and appendages		
Rash	4%	2%

[1]Events reported by at least 2% of patients treated with RISPERDAL® are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: dyspepsia, nausea, vomiting, headache, tremor, insomnia, chest pain, fatigue, pain, skeletal pain, hypertension, and vision abnormal.

Dose Dependency of Adverse Events

Extrapyramidal Symptoms

Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

Plaintiff Ex. 662

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

Vital Sign Changes

RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Changes

The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes

A between-group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Changes

Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes

Plaintiff Ex. 662

from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute).

Other Events Observed During the Premarketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® were administered to 2607 patients in Phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included, except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Plaintiff Ex. 662

Psychiatric Disorders

Frequent: increased dream activity*, diminished sexual desire*, nervousness. Infrequent: impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare*: emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders

Frequent: increased sleep duration*. *Infrequent*: dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare*: aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastrointestinal Disorders

Frequent: anorexia, reduced salivation*. *Infrequent*: flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders

Frequent: fatigue. *Infrequent*: edema, rigors, malaise, influenza-like symptoms. *Rare*: pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders

Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. *Rare*: asthma, increased sputum, aspiration.

Skin and Appendage Disorders

Frequent: increased pigmentation*, photosensitivity* *Infrequent*: increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare*: bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders

Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare*: ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders

Infrequent: abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Plaintiff Ex. 662

R. 3341

Metabolic and Nutritional Disorders

Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare*: decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders

Frequent: polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare*: urinary retention, cystitis, renal insufficiency.

Musculo-Skeletal System Disorders

Infrequent: myalgia. *Rare*: arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female

Frequent: menorrhagia*, orgastic dysfunction*, dry vagina* Infrequent: nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders

Infrequent: increased SGOT, increased SGPT. *Rare*: hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding, and Clotting Disorders

Infrequent: epistaxis, purpura. *Rare*: hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders

Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders

Infrequent: anemia, hypochromic anemia. *Rare*: normocytic anemia.

Reproductive Disorders, Male

Frequent: erectile dysfunction* Infrequent: ejaculation failure.

White Cell and Resistance Disorders

Rare: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders

Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Plaintiff Ex. 662

Special Senses
Rare: bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, hyperglycemia, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychological Dependence

RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Premarketing experience included eight reports of acute RISPERDAL® (risperidone) overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT,

Plaintiff Ex. 662

and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® overdose, include torsade de pointes, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Because of the rapid disintegration of RISPERDAL® M-TAB® Orally Disintegrating Tablets, pill fragments may not appear in gastric contents obtained with lavage.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

Plaintiff Ex. 662

DOSAGE AND ADMINISTRATION

Schizophrenia

Usual Initial Dose

RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL®; however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day, and to a target dose of 4 mg QD on the third day (see CLINICAL PHARMACOLOGY – Clinical Trials). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Plaintiff Ex. 662

Switching From Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

Bipolar Mania

Usual Dose

Risperidone should be administered on a once daily schedule, starting with 2 mg to 3 mg per day. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments/decrements of 1 mg per day, as studied in the short-term, placebo-controlled trials. In these trials, short-term (3 week) anti-manic efficacy was demonstrated in a flexible dosage range of 1-6 mg per day (see CLINICAL PHARMACOLOGY – Clinical Trials). RISPERDAL® doses higher than 6 mg per day were not studied.

Maintenance Therapy

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with risperidone. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of risperidone in such longer-term treatment (i.e., beyond 3 weeks).

Pediatric Use

Safety and effectiveness of RISPERDAL® in pediatric patients with schizophrenia or acute mania associated with Bipolar I Disorder have not been established.

Dosage in Special Populations

The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID.

Plaintiff Ex. 662

Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (see PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Co-Administration of RISPERDAL® with Certain Other Medications

Co-administration of carbamazepine and other enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with risperidone would be expected to cause decreases in the plasma concentrations of active moiety (the sum of risperidone and 9-hydroxyrisperidone), which could lead to decreased efficacy of risperidone treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13%. The dose of risperidone needs to be titrated accordingly when fluoxetine or paroxetine is co-administered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Directions for Use of RISPERDAL® M-TAB® Orally Disintegrating Tablets

RISPERDAL® M-TAB® Orally Disintegrating Tablets are supplied in blister packs of 4 tablet units each.

Tablet Accessing

Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

Plaintiff Ex. 662

Tablet Administration

Using dry hands, remove the tablet from the blister unit and immediately place the entire RISPERDAL® M-TAB® Orally Disintegrating Tablet on the tongue. The RISPERDAL® M-TAB® Orally Disintegrating Tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. RISPERDAL® M-TAB® Orally Disintegrating Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to split or to chew the tablet.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50, hospital unit dose packs of 100 NDC 50458-301-01.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50, hospital unit dose packs of 100 NDC 50458-302-01.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

RISPERDAL® M-TAB® (risperidone) Orally Disintegrating Tablets are etched on one side with "R0.5", "R1", and "R2", respectively, and are packaged in blister packs of 4 (2 X 2) tablets.

Plaintiff Ex. 662

0.5 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-395-28, long-term care packaging of 30 tablets NDC 50458-395-30.

1 mg light coral, square, biconvex tablets: 7 blister packages per box, NDC 50458-315-28, long-term care packaging of 30 tablets NDC 50458-315-30.

2 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-325-28.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature 15o-25oC (59o-77oF). Protect from light and moisture.

Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15o-25oC (59o-77oF). Protect from light and freezing.

Keep out of reach of children.

RISPERDAL® M-TAB® Orally Disintegrating Tablets should be stored at controlled room temperature 15o-25oC (59o-77oF).

Keep out of reach of children.

7503228
US Patent 4,804,663

Revised February 2005
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RISPERDAL® tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico or
Janssen-Cilag, SpA, Latina, Italy
RISPERDAL® oral solution is manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium

RISPERDAL® M-TAB® Orally Disintegrating Tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico

Plaintiff Ex. 662

RISPERDAL® tablets, RISPERDAL® M-TAB® Orally Disintegrating Tablets, and oral solution are distributed by:

Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

Plaintiff Ex. 662

JANSSEN, L.P.

RISPERDAL®
(risperidone)
TABLETS/ORAL SOLUTION

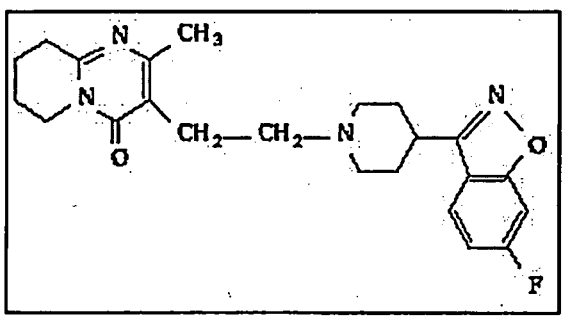
RISPERDAL® M-TAB®
(risperidone)
ORALLY DISINTEGRATING TABLETS

Increased Mortality in Elderly Patients with Dementia –Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. RISPERDAL® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

Plaintiff Ex. 665

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL® M-TAB® Orally Disintegrating Tablets are available in 0.5 mg (light coral), 1 mg (light coral), 2 mg (light coral), 3 mg (coral), and 4 mg (coral) strengths.

RISPERDAL® M-TAB® Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil. In addition, the 3 mg and 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablets contain xanthan gum.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Plaintiff Ex. 665

Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Pharmacokinetic studies showed that RISPERDAL® M-TAB® Orally Disintegrating Tablets and RISPERDAL® Oral Solution are bioequivalent to RISPERDAL® Tablets.

Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism and Drug Interactions

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through *N*-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug

Plaintiff Ex. 665

R. 3353

(e.g., the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions (see PRECAUTIONS – Drug Interactions). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number ($n \cong 70$) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment (see PRECAUTIONS – Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Administration of RISPERDAL® with Certain Other Medications).

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the

Plaintiff Ex. 665

R. 3354

plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10% (see PRECAUTIONS -Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Administration of RISPERDAL® with Certain Other Medications).

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13) (see PRECAUTIONS – Drug Interactions).

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone (see PRECAUTIONS – Drug Interactions).

There were no significant interactions between risperidone (1 mg QD) and erythromycin (500 mg QID) (see PRECAUTIONS – Drug Interactions).

Cimetidine and ranitidine increased the bioavailability of risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of the active moiety, whereas ranitidine increased the AUC of the active moiety by 20%.

Amitriptyline did not affect the pharmacokinetics of risperidone or the active moiety.

In drug-interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

RISPERDAL® (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of 14C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of the active moiety, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Plaintiff Ex. 665

Special Populations

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly

In healthy elderly subjects, renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (see DOSAGE AND ADMINISTRATION).

Pediatric

The pharmacokinetics of risperidone and 9-hydroxyrisperidone in children were similar to those in adults after correcting for the difference in body weight.

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

CLINICAL TRIALS SCHIZOPHRENIA

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4- to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness,

Plaintiff Ex. 665

and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS) were employed.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (>20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic

Plaintiff Ex. 665

medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

Bipolar Mania

Monotherapy

The efficacy of RISPERDAL® in the treatment of acute manic or mixed episodes was established in 2 short-term (3-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=246), limited to patients with manic episodes, which involved a dose range of RISPERDAL® 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 4.1 mg/day), RISPERDAL® was superior to placebo in the reduction of Y-MRS total score.

(2) In another 3-week placebo-controlled trial (n=286), which involved a dose range of 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 5.6 mg/day), RISPERDAL® was superior to placebo in the reduction of Y-MRS total score.

Combination Therapy

The efficacy of risperidone with concomitant lithium or valproate in the treatment of acute manic or mixed episodes was established in one controlled trial in patients who met the DSM-IV criteria for Bipolar I Disorder. This trial included patients with or without psychotic features and with or without a rapid-cycling course.

(1) In this 3-week placebo-controlled combination trial, 148 in- or outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL®, placebo, or an active comparator, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2

Plaintiff Ex. 665

mg/day (mean modal dose of 3.8 mg/day), combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.4 mEq/L or 50 mcg/mL to 120 mcg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 3-week placebo-controlled combination trial, 142 in- or outpatients on lithium, valproate, or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL® or placebo, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.7 mg/day), combined with lithium, valproate, or carbamazepine (in therapeutic ranges of 0.6 mEq/L to 1.4 mEq/L for lithium, 50 mcg/mL to 125 mcg/mL for valproate, or 4-12 mcg/mL for carbamazepine, respectively) was not superior to lithium, valproate, or carbamazepine alone in the reduction of Y-MRS total score. A possible explanation for the failure of this trial was induction of risperidone and 9-hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxyrisperidone.

Irritability Associated with Autistic Disorder

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of irritability associated with autistic disorder was established in two 8-week, placebo-controlled trials in children and adolescents (aged 5 to 16 years) who met the DSM-IV criteria for autistic disorder. Over 90% of these subjects were under 12 years of age and most weighed over 20 kg (16-104.3 kg).

Efficacy was evaluated using two assessment scales: the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression - Change (CGI-C) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I). The ABC-I subscale measured the emotional and behavioral symptoms of autism, including aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. The CGI-C rating at endpoint was a co-primary outcome measure in one of the studies.

The results of these trials are as follows:

(1) In one of the 8-week, placebo-controlled trials, children and adolescents with autistic disorder (n=101), aged 5 to 16 years, received twice daily doses of placebo or RISPERDAL® 0.5-3.5 mg/day on a weight-adjusted basis. RISPERDAL®, starting at 0.25 mg/day or 0.5 mg/day depending on baseline weight (< 20 kg and ≥ 20 kg, respectively) and titrated to clinical response (mean modal dose of 1.9 mg/day, equivalent to 0.06 mg/kg/day),

Plaintiff Ex. 665

significantly improved scores on the ABC-I subscale and on the CGI-C scale compared with placebo.

(2) In the other 8-week, placebo-controlled trial in children with autistic disorder (n=55), aged 5 to 12 years, RISPERDAL® 0.02 to 0.06 mg/kg/day given once or twice daily, starting at 0.01 mg/kg/day and titrated to clinical response (mean modal dose of 0.05 mg/kg/day, equivalent to 1.4 mg/day), significantly improved scores on the ABC-I subscale compared with placebo.

Long-Term Efficacy

Following completion of the first 8-week double-blind study, 63 patients entered an open-label study extension where they were treated with RISPERDAL® for 4 or 6 months (depending on whether they received RISPERDAL® or placebo in the double-blind study). During this open-label treatment period, patients were maintained on a mean modal dose of RISPERDAL® of 1.8-2.1 mg/day (equivalent to 0.05 - 0.07 mg/kg/day).

Patients who maintained their positive response to RISPERDAL® (response was defined as ≥ 25% improvement on the ABC-I subscale and a CGI-C rating of 'much improved' or 'very much improved') during the 4-6 month open-label treatment phase for about 140 days, on average, were randomized to receive RISPERDAL® or placebo during an 8-week, double-blind withdrawal study (n=39 of the 63 patients). A pre-planned interim analysis of data from patients who completed the withdrawal study (n=32), undertaken by an independent Data Safety Monitoring Board, demonstrated a significantly lower relapse rate in the RISPERDAL® group compared with the placebo group. Based on the interim analysis results, the study was terminated due to demonstration of a statistically significant effect on relapse prevention. Relapse was defined as ≥ 25% worsening on the most recent assessment of the ABC-I subscale (in relation to baseline of the randomized withdrawal phase).

INDICATIONS AND USAGE

Schizophrenia

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6- to 8-weeks) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see CLINICAL PHARMACOLOGY -Clinical Trials). Nevertheless, the

Plaintiff Ex. 665

physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Bipolar Mania

Monotherapy

RISPERDAL® is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL® was established in two placebo-controlled trials (3-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

Combination Therapy

The combination of RISPERDAL® with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL® in combination with lithium or valproate was established in one placebo-controlled (3-week) trial with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

The effectiveness of RISPERDAL® for longer-term use, that is, for more than 3 weeks of treatment of an acute episode, and for prophylactic use in mania, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Irritability Associated with Autistic Disorder

RISPERDAL® is indicated for the treatment of irritability associated with autistic disorder in children and adolescents, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods.

The efficacy of RISPERDAL® was established in two 8-week, placebo-controlled trials in children and adolescents (aged 5 to 16 years) who met the DSM-IV criteria for autistic disorder. The benefit of maintaining patients with irritability associated with autistic disorder on therapy with RISPERDAL® after achieving a responder status for an average duration of about 140 days was demonstrated in a controlled trial (see CLINICAL PHARMACOLOGY - Clinical Trials.)

Plaintiff Ex. 665

Physicians who elect to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. RISPERDAL®(risperidone) is not approved for the treatment of dementia-related psychosis (see Boxed Warning).

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

Plaintiff Ex. 665

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that: (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis

Plaintiff Ex. 665

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis (See also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.)

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period,

Plaintiff Ex. 665

probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2 and 3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures

During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL®-treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also **Boxed WARNING**, **WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**.)

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Plaintiff Ex. 665

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. An increase in pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats (see PRECAUTIONS – Carcinogenesis, Mutagenesis, Impairment of Fertility). Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high-dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism

Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic Effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Plaintiff Ex. 665

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide

The possibility of a suicide attempt is inherent in patients with schizophrenia and bipolar mania, including children and adolescent patients, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness

Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL®, are reported to have an increased sensitivity to antipsychotic medications. Manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2), and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Plaintiff Ex. 665

Interference With Cognitive and Motor Performance

Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised not to breast-feed an infant if they are taking RISPERDAL®.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL®.

Phenylketonurics

Phenylalanine is a component of aspartame. Each 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.84 mg phenylalanine; each 3 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.63 mg phenylalanine; each 2 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.42 mg phenylalanine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Plaintiff Ex. 665

Amitriptyline did not affect the pharmacokinetics of risperidone or the active moiety. Cimetidine and ranitidine increased the bioavailability of risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of the active moiety, whereas ranitidine increased the AUC of the active moiety by 20%.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Carbamazepine and Other Enzyme Inducers

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment.

Fluoxetine and Paroxetine

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Lithium

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13).

Valproate

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone.

Digoxin

Plaintiff Ex. 665

RISPERDAL® (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers ($n \cong 70$) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism.

There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY).

Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) for schizophrenia (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m^2 (mg/kg) basis at which these tumors occurred.

Plaintiff Ex. 665

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m^2 (mg/kg)	
			Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6.0 (37.5)	1.5 (9.4)
Mammary gland neoplasm, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5-6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS, General -Hyperprolactinemia).

Mutagenesis

No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility

Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the MRHD on a mg/m^2 basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Plaintiff Ex. 665

Pregnancy Category C

The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m^2 basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m^2 basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to RISPERDAL® therapy is unknown. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed.

Plaintiff Ex. 665

Pediatric Use

The safety and effectiveness of RISPERDAL® in pediatric patients with schizophrenia or bipolar mania have not been established.

The efficacy and safety of RISPERDAL® in the treatment of irritability associated with autistic disorder were established in two 8-week, placebo-controlled trials in 156 children and adolescent patients, aged 5 to 16 years (see CLINICAL PHARMACOLOGY - Clinical Trials, INDICATIONS AND USAGE, and ADVERSE REACTIONS). Additional safety information was also assessed in a long-term study in patients with autistic disorder, or in short- and long-term studies in more than 1200 pediatric patients with other psychiatric disorders who were of similar age and weight, and who received similar dosages of RISPERDAL® as patients who were treated for irritability associated with autistic disorder.

The safety and effectiveness of RISPERDAL® in pediatric patients with autistic disorder less than 5 years of age have not been established.

Tardive Dyskinesia

In clinical trials in 1885 children and adolescents with autistic disorder or other psychiatric disorders treated with risperidone, 2 (0.1%) patients were reported to have tardive dyskinesia, which resolved on discontinuation of risperidone treatment (see WARNINGS – Tardive Dyskinesia).

Weight Gain

In long-term, open-label trials (studies in patients with autistic disorder or other psychiatric disorders), a mean increase of 7.5 kg after 12 months of RISPERDAL® treatment was observed, which was higher than the expected normal weight gain (approximately 3 to 3.5 kg per year adjusted for age, based on Centers for Disease Control and Prevention normative data). The majority of that increase occurred within the first 6 months of exposure to RISPERDAL®. The average percentiles at baseline and 12 months, respectively, were 49 and 60 for weight, 48 and 53 for height, and 50 and 62 for body mass index. When treating patients with RISPERDAL®, weight gain should be assessed against that expected with normal growth. (See also ADVERSE REACTIONS.)

Somnolence

Somnolence was frequently observed in placebo-controlled clinical trials of pediatric patients with autistic disorder. Most cases were mild or moderate in severity. These events were most often of early onset with peak incidence occurring during the first two weeks of treatment, and transient with a median duration of 16 days. (See also ADVERSE REACTIONS.) Patients

Plaintiff Ex. 665

experiencing persistent somnolence may benefit from a change in dosing regimen (see DOSAGE AND ADMINISTRATION – Irritability Associated with Autistic Disorder).

Hyperprolactinemia, Growth, and Sexual Maturation

Risperidone has been shown to elevate prolactin levels in children and adolescents as well as in adults (see PRECAUTIONS - Hyperprolactinemia). In double-blind, placebo-controlled studies of up to 8 weeks duration in children and adolescents (aged 5 to 17 years) 49% of patients who received risperidone had elevated prolactin levels compared to 2% of patients who received placebo.

In clinical trials in 1885 children and adolescents with autistic disorder or other psychiatric disorders treated with risperidone, galactorrhea was reported in 0.8% of risperidone-treated patients and gynecomastia was reported in 2.3% of risperidone-treated patients.

The long-term effects of risperidone on growth and sexual maturation have not been fully evaluated.

Geriatric Use

Clinical studies of RISPERDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis

In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone

Plaintiff Ex. 665

when compared to patients treated with risperidone alone or with placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of RISPERDAL® regardless of concomitant use with furosemide. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. (See Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.)

ADVERSE REACTIONS

The following findings are based on the short-term, placebo-controlled, North American, premarketing trials for schizophrenia and acute bipolar mania, and are followed by a description of adverse events and other safety measures in short-term, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder. In patients with Bipolar I Disorder, treatment-emergent adverse events are presented separately for risperidone as monotherapy and as adjunctive therapy to mood stabilizers.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia. However, this information is also generally applicable to bipolar mania and pediatric patients with autistic disorder.

Associated With Discontinuation of Treatment

Schizophrenia

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in Phase 2 and 3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL®-related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal

symptoms was 0% in placebo patients, but 3.8% in active-control patients in the Phase 2 and 3 trials.

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (10/134) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 6% (7/125) of placebo-treated patients. The adverse events associated with discontinuation and considered to be possibly, probably, or very likely drug-related included paroniria, somnolence, dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events occurred in one RISPERDAL®-treated patient (0.7%) and in no placebo-treated patients (0%).

In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, there was no overall difference in the incidence of discontinuation due to adverse events (4% for RISPERDAL® vs. 4% for placebo).

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials

Schizophrenia

In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events occurred at an incidence of at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Plaintiff Ex. 665

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observed adverse events associated with the use of RISPERDAL® (incidence of 5% or greater and at least twice that of placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, vision abnormal, and saliva increased. In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, the most commonly observed adverse events associated with the use of RISPERDAL® were somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, and urinary incontinence.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Patients - Schizophrenia

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent among RISPERDAL®-treated patients treated at doses of ≤10 mg/day than among placebo-treated patients in the pooled results of two 6- to 8-week controlled trials. Patients received RISPERDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Table 1: Incidence of Treatment-Emergent Adverse Events in 6- to 8-Week Controlled Clinical Trials in Schizophrenia[1]

Body System/ Preferred Term	RISPERDAL® <10mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric.			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Central & peripheral nervous system			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory system			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a whole – general			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see ADVERSE REACTIONS – Dose Dependency of Adverse Events).

Adverse Events Occurring at an Incidence of 2% or More Among RISPERDAL®-Treated Patients - Bipolar Mania

Tables 2 and 3 display adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of RISPERDAL® (1-6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms.

Plaintiff Ex. 665

Table 2: Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Monotherapy in Bipolar Mania[1]

Body System/ Preferred Term	RISPERDAL® (N=134)	Placebo (N=125)
Central & peripheral nervous system		
Dystonia	18%	6%
Akathisia	16%	6%
Dizziness	11%	9%
Parkinsonism	6%	3%
Hypoaesthesia	2%	1%
Psychiatric		
Somnolence	28%	7%
Agitation	8%	6%
Manic reaction	8%	6%
Anxiety	4%	2%
Concentration impaired	2%	1%
Gastrointestinal system		
Dyspepsia	11%	6%
Nausea	11%	2%
Saliva increased	5%	1%
Mouth dry	3%	2%
Body as a whole - general		
Pain	5%	3%
Fatigue	4%	2%
Injury	2%	0%
Respiratory system		
Sinusitis	4%	1%
Rhinitis	3%	2%
Coughing	2%	2%
Skin and appendages		
Acne	2%	0%
Pruritus	2%	1%
Musculo-Skeletal		
Myalgia	5%	2%
Skeletal pain	2%	1%
Metabolic and nutritional		
Weight increase	2%	0%
Vision disorders		
Vision abnormal	6%	2%
Cardiovascular, general		
Hypertension	3%	1%
Hypotension	2%	0%
Heart rate and rhythm		
Tachycardia	3%	2%

[1] Events reported by at least 2% of patients treated with RISPERDAL® are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: headache, tremor, insomnia, constipation, back pain, upper respiratory tract infection, pharyngitis, and arthralgia.

Table 3: Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Adjunctive Therapy in Bipolar Mania[1]

Body System/ Preferred Term	RISPERDAL® + Mood Stabilizer (N=52)	Placebo + Mood Stabilizer (N=51)
Gastrointestinal system		
Saliva increased	10%	0%
Diarrhea	8%	4%
Abdominal pain	6%	0%
Constipation	6%	4%
Mouth dry	6%	4%
Tooth ache	4%	0%
Tooth disorder	4%	0%
Central & peripheral nervous system		
Dizziness	14%	2%
Parkinsonism	14%	4%
Akathisia	8%	0%
Dystonia	6%	4%
Psychiatric		
Somnolence	25%	12%
Anxiety	6%	4%
Confusion	4%	0%
Respiratory system		
Rhinitis	8%	4%
Pharyngitis	6%	4%
Coughing	4%	0%
Body as a whole - general		
Asthenia	4%	2%
Urinary system		
Urinary incontinence	6%	2%
Heart rate and rhythm		
Tachycardia	4%	2%
Metabolic and nutritional		
Weight increase	4%	2%
Skin and appendages		
Rash	4%	2%

[1] Events reported by at least 2% of patients treated with RISPERDAL® are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: dyspepsia, nausea, vomiting, headache, tremor, insomnia, chest pain, fatigue, pain, skeletal pain, hypertension, and vision abnormal.

Dose Dependency of Adverse Events

Extrapyramidal Symptoms

Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism

Plaintiff Ex. 665

score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

Vital Sign Changes

RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Changes

The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of $\geq 7\%$ of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes

A between-group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Changes

Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute).

Adverse Events and Other Safety Measures in Pediatric Patients With Autistic Disorder

In the two 8-week, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder (n=156), two patients (one treated with RISPERDAL® and one treated with placebo) discontinued treatment due to an adverse event.

In addition to spontaneous reporting, in one of the studies, adverse events were also elicited from a checklist for detecting selected events, a method that is more sensitive than spontaneous reporting.

The most common adverse events with RISPERDAL® that occurred at an incidence equal to or greater than 5% and at a rate of at least twice that of placebo are shown in Table 4.

Table 4 Incidence of Treatment-Emergent Adverse Events in Two 8-Week, Placebo-Controlled Trials in Pediatric Patients with Autistic Disorder

Body System Preferred Term	RISPERDAL® (n=76)	Placebo (n=80)
Psychiatric		
Somnolence	67%	23%
Appetite increased	49%	19%
Confusion	5%	0%
Gastrointestinal		
Saliva increased	22%	6%
Constipation	21%	8%

Dry mouth	13%	6%
Body as a whole - general		
Fatigue	42%	13%
Central & peripheral nervous system		
Tremor	12%	1%
Dystonia	12%	6%
Dizziness	9%	3%
Automatism	7%	1%
Dyskinesia	7%	0%
Parkinsonism	8%	0%
Respiratory		
Upper respiratory tract infection	34%	15%
Metabolic and nutritional		
Weight increase	5%	0%
Heart rate and rhythm		
Tachycardia	7%	0%

Weight increase was reported more frequently with RISPERDAL® than with placebo. The average weight increase over 8 weeks was 2.6 kg in patients treated with RISPERDAL® compared with 0.9 kg in patients treated with placebo. (See also PRECAUTIONS – Pediatric Use – Weight Gain.)

There was a higher incidence of adverse events reflecting extrapyramidal symptoms (EPS) in the RISPERDAL® group (27.6%) compared with the placebo group (10.0%). In addition, between-group comparison of the severity of EPS were assessed objectively by the following rating instruments: the Simpson-Angus Rating Scale (SARS) and the Abnormal Involuntary Movement Scale (AIMS) in one study, and the Extrapyramidal Symptom Rating Scale (ESRS) in the other study. The mean changes between baseline and endpoint in the total ESRS score were –0.3 in the RISPERDAL® group and –0.4 in the placebo group. The median change from baseline to endpoint was 0 in both treatment groups for each EPS rating scale.

Somnolence was the most frequent adverse event, and was reported at a higher incidence in the RISPERDAL® group compared with the placebo group. The vast majority of cases (96%) were either mild or moderate in severity. These events were most often of early onset with peak incidence occurring during the first 2 weeks of treatment, and median duration was 16 days. Patients experiencing persistent somnolence may benefit from a change in dosing regimen (see DOSAGE AND ADMINISTRATION – Irritability Associated with Autistic Disorder – Pediatrics [Children and Adolescents]).

Other Events Observed During the Premarketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® were administered to 2607 adult patients with schizophrenia and 1923 pediatric patients in Phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 adult or 1923 pediatric patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included, except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it. Serious adverse reactions experienced by the pediatric population were similar to those seen in the adult population (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS).

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders

Frequent: increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare*: emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Plaintiff Ex. 665

Central and Peripheral Nervous System Disorders

Frequent: increased sleep duration*. *Infrequent*: dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare*: aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastrointestinal Disorders

Frequent: anorexia, reduced salivation*. *Infrequent*: flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders

Frequent: fatigue. *Infrequent*: edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders

Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. *Rare*: asthma, increased sputum, aspiration.

Skin and Appendage Disorders

Frequent: increased pigmentation*, photosensitivity* *Infrequent*: increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare*: bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders

Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare*: ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders

Infrequent: abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders

Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare*: decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Plaintiff Ex. 665

Urinary System Disorders

Frequent: polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare*: urinary retention, cystitis, renal insufficiency.

Musculo-Skeletal System Disorders

Infrequent: myalgia. *Rare*: arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female

Frequent: menorrhagia*, orgastic dysfunction*, dry vagina* *Infrequent*: nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders

Infrequent: increased SGOT, increased SGPT. *Rare*: hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding, and Clotting Disorders

Infrequent: epistaxis, purpura. *Rare*: hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders

Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders

Infrequent: anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male

Frequent: erectile dysfunction* Infrequent: ejaculation failure.

White Cell and Resistance Disorders

Infrequent: granulocytopenia. *Rare*: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders

Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses

Rare: bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, diabetes mellitus aggravated, including diabetic ketoacidosis, hyperglycemia, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pituitary adenomas, pulmonary embolism, and precocious puberty. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychological Dependence

RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Premarketing experience included eight reports of acute RISPERDAL® (risperidone) overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Plaintiff Ex. 665

Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® overdose, include torsade de pointes, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Because of the rapid disintegration of RISPERDAL® M-TAB®Orally Disintegrating Tablets, pill fragments may not appear in gastric contents obtained with lavage.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

Plaintiff Ex. 665

DOSAGE AND ADMINISTRATION

Schizophrenia

Usual Initial Dose

RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL®; however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day, and to a target dose of 4 mg QD on the third day (see CLINICAL PHARMACOLOGY – Clinical Trials). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Plaintiff Ex. 665

Switching From Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

Pediatric Use

The safety and effectiveness of RISPERDAL® in pediatric patients with schizophrenia have not been established.

Bipolar Mania

Usual Dose

Risperidone should be administered on a once daily schedule, starting with 2 mg to 3 mg per day. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments/decrements of 1 mg per day, as studied in the short-term, placebo-controlled trials. In these trials, short-term (3 week) anti-manic efficacy was demonstrated in a flexible dosage range of 1-6 mg per day (see CLINICAL PHARMACOLOGY – Clinical Trials). RISPERDAL® doses higher than 6 mg per day were not studied.

Maintenance Therapy

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with risperidone. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of risperidone in such longer-term treatment (i.e., beyond 3 weeks).

Pediatric Use

The safety and effectiveness of RISPERDAL® in pediatric patients with bipolar mania have not been established.

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Irritability Associated with Autistic Disorder – Pediatrics (Children and Adolescents)

The safety and effectiveness of RISPERDAL® in pediatric patients with autistic disorder less than 5 years of age have not been established.

The dosage of RISPERDAL® should be individualized according to the response and tolerability of the patient. The total daily dose of RISPERDAL® can be administered once daily, or half the total daily dose can be administered twice daily.

Dosing should be initiated at 0.25 mg per day for patients < 20 kg and 0.5 mg per day for patients ≥ 20 kg. After a minimum of four days from treatment initiation, the dose may be increased to the recommended dose of 0.5 mg per day for patients < 20 kg and 1 mg per day for patients ≥ 20 kg. This dose should be maintained for a minimum of 14 days. In patients not achieving sufficient clinical response, dose increases may be considered at ≥ 2-week intervals in increments of 0.25 mg per day for patients < 20 kg or 0.5 mg per day for patients ≥ 20 kg. Caution should be exercised with dosage for smaller children who weighed less than 15 kg.

In clinical trials, 90% of patients who showed a response (based on at least 25% improvement on ABC-I, see CLINICAL PHARMACOLOGY – Clinical Trials) received doses of RISPERDAL® between 0.5 mg and 2.5 mg per day. The maximum daily dose of RISPERDAL® in one of the pivotal trials, when the therapeutic effect reached plateau, was 1.0 mg in patients < 20 kg, 2.5 mg in patients ≥ 20 kg, or 3.0 mg in patients > 45 kg. No dosing data are available for children who weigh less than 15 kg.

Once sufficient clinical response has been achieved and maintained, consideration should be given to gradually lowering the dose to achieve the optimal balance of efficacy and safety.

Patients experiencing persistent somnolence may benefit from a once-daily dose administered at bedtime or administering half the daily dose twice daily, or a reduction of the dose.

Dosage in Special Populations

The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have

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increases in the free fraction of risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (see PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Co-Administration of RISPERDAL® with Certain Other Medications

Co-administration of carbamazepine and other enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with risperidone would be expected to cause decreases in the plasma concentrations of active moiety (the sum of risperidone and 9-hydroxyrisperidone), which could lead to decreased efficacy of risperidone treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. The dose of risperidone needs to be titrated accordingly when fluoxetine or paroxetine is co-administered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Directions for Use of RISPERDAL® M-TAB® Orally Disintegrating Tablets

Tablet Accessing

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are supplied in blister packs of 4 tablets each.

Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg are supplied in a child-resistant pouch containing a blister with 1 tablet each.

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The child-resistant pouch should be torn open at the notch to access the blister. Do not open the blister until ready to administer. Peel back foil from the side to expose the tablet. DO NOT push the tablet through the foil, because this could damage the tablet.

Tablet Administration

Using dry hands, remove the tablet from the blister unit and immediately place the entire RISPERDAL® M-TAB® Orally Disintegrating Tablet on the tongue. The RISPERDAL® M-TAB® Orally Disintegrating Tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. RISPERDAL® M-TAB® Orally Disintegrating Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to split or to chew the tablet.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50, hospital unit dose packs of 100 NDC 50458-301-01.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50, hospital unit dose packs of 100 NDC 50458-302-01.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

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RISPERDAL® M-TAB® (risperidone) Orally Disintegrating Tablets are etched on one side with "R0.5", "R1", "R2", "R3", and "R4", respectively. RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are packaged in blister packs of 4 (2 X 2) tablets. Orally Disintegrating Tablets 3 mg and 4 mg are packaged in a child-resistant pouch containing a blister with 1 tablet.

0.5 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-395-28, long-term care packaging of 30 tablets NDC 50458-395-30.

1 mg light coral, square, biconvex tablets: 7 blister packages per box, NDC 50458-315-28, long-term care packaging of 30 tablets NDC 50458-315-30.

2 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-325-28.

3 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-335-28.

4 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-355-28.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.

Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.

Keep out of reach of children.

RISPERDAL® M-TAB® Orally Disintegrating Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F).

Keep out of reach of children.

[INSERT NEW COMPONENT CODE]

Revised October 2006
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RISPERDAL® tablets are manufactured by:

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JOLLC, Gurabo, Puerto Rico or
Janssen-Cilag, SpA, Latina, Italy
RISPERDAL® oral solution is manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium

RISPERDAL® M-TAB® Orally Disintegrating Tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico

RISPERDAL® tablets, RISPERDAL® M-TAB® Orally Disintegrating Tablets, and oral solution are distributed by:
Janssen, L.P.
Titusville, NJ 08560

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

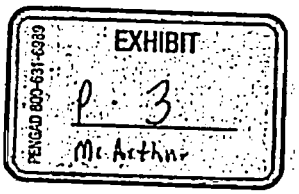
Food and Drug Administration
Rockville MD 20857

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R. A. WASSERMAN

FEB - 9 1994

NDA 20-272



Ms. Ruth Wasserman
Director, Regulatory Affairs
Janssen Pharmaceutica Research Foundation
Janssen at Washington Crossing
1125 Trenton-Harbourton Road
PO Box 200
Titusville, NJ 08560-0200

Re: Risperdal (risperidone) Tablets introductory campaign

Dear Ms. Wasserman:

The Division of Drug Marketing, Advertising and Communications (DDMAC) in consultation with the Division of Neuropharmacological Drug Products has reviewed Janssen's proposed introductory campaign for Risperdal (risperidone) Tablets.

Since the layout copies are tentative, our comments are restricted to the layouts as submitted and do not imply preclearance of the final promotional materials. Many variables, in addition to text, must be taken into consideration, such as size, placement, prominence, graphs, etc. Therefore, final comments cannot be provided until review of the final materials.

We will refer to the Sales Aid as a reference document for our review. Since many claims and presentations are similar or closely related, the following comments on a particular claim or presentation apply to all such claims and presentations, whether they appear now or in the future.

We offer the following comments:

Page 2

(1) **"Introducing a first-line antipsychotic for both positive and negative symptoms of schizophrenia."**

There are three issues:

(a) The phrase "first-line" is misleading. First, it implies that there are two classes of antipsychotics, first-line and second-line. Since all antipsychotics are technically considered first-line therapies, with the exception of clozapine, which was developed specifically for the treatment of refractory schizophrenia, this distinction would be misleading. Thus, all

references to "first-line" should be deleted.

(b) The efficacy claim, "for both positive and negative symptoms of schizophrenia" is false and/or misleading. Risperdal is indicated for the management of the manifestations of psychotic disorders, and all efficacy claims should be limited to this indication. Furthermore, any suggestion or implication that Risperdal treats the negative symptoms of schizophrenia, and that other antipsychotic drugs do not, is unacceptable.

(c) The tone of this headline suggests that Janssen may be attempting to position risperidone as a safer alternative to clozapine. We strongly object to this strategy on the basis that it would be false and/or misleading.

Page 3

(2) Introduction to PANSS scale

An introductory paragraph describing the "Positive and Negative Symptoms Scale (PANSS)" scale should be added prior to the discussion of efficacy. This discussion should include the methodology of symptom classification (positive, negative or general), the assessment criteria and the evaluation methodology.

(3) "Effective treatment for positive symptoms of schizophrenia."

As discussed in Comment 1, all efficacy claims must be limited to the indication in the approved product labeling. The scope of discussions about specific outcomes in the Clinical Trials section of the labeling should be limited to the parameters of the measuring scale, i.e., PANSS, Brief Psychiatric Rating Scale (BPRS), or Clinical Global Impression (CGI). The results from the clinical trials may not be presented as broad efficacy statements about the treatment of positive and negative symptoms. An appropriate headline for this discussion, therefore, would be, "Improvement in the PANSS positive symptom scores."

(4) "Significant improvement of positive symptoms" chart

There are three issues:

(a) The word, "significant," is misleading in this headline. The improvement of positive symptoms was determined to be statistically significant, but not necessarily clinically significant. A more accurate headline would specify, "Statistically significant improvement of positive symptoms."

(b) The relevant p-value in this trial is between the risperidone and placebo arms, not the within group p-value between the baseline and endpoint of the risperidone arm. The within group p-value should be replaced with the relevant p-value.

(c) The scale of this chart is misleading. In order to accurately present these outcomes, the full PANSS scale should be used as the x-axis for the chart.

(5) "Significant improvement in all 7 PANSS positive symptoms" chart.

Presentation of the seven PANSS positive symptoms as line item efficacy outcomes is misleading. The PANSS scale was intended to be used in its entirety to derive efficacy outcomes by cluster, i.e. positive symptoms, negative symptoms or general symptoms. It was not intended to be used as a means of evaluating line item efficacy outcomes, i.e. efficacy in treating delusions. Presentation of line item efficacy outcomes is therefore a misuse of the scale and creates misleading implications.

Page 4

(6) "Effective treatment for negative symptoms of schizophrenia."

This headline should be revised to read, "Improvement in the PANSS negative symptom scores." See Comment 3.

(7) "Significant improvement of negative symptoms."

This headline should be revised to read, "Statistically significant improvement of negative symptoms." Additionally, the "p-value" should be re-calculated to

compare the risperidone and placebo arms of the study. See Comment 4.

(8) **Significant improvement in all 7 PANSS negative symptoms."**

Presentation of the seven PANSS negative symptoms as line item efficacy outcomes is misleading. The PANSS scale was intended to be used in its entirety to derive efficacy outcomes by cluster, i.e. positive symptoms, negative symptoms or general symptoms. It was not intended to be used as a means of evaluating line item efficacy outcomes, i.e. efficacy in treating delusions. Presentation of line item efficacy outcomes is therefore a misuse of the scale and creates misleading implications.

Page 5

(9) **"Significant rate of response" chart**

The rates of response presented in this chart are misleading. The definition of a responder is a patient showing a 20% or greater reduction in total PANSS score at endpoint. This reduction in PANSS score is calculated with the following expression:

$$\text{Percent change} = \frac{\text{Total PANSS} - \text{Total PANSS at baseline}}{\text{Total PANSS at baseline} - 30}$$

Subtracting 30 from the denominator corrects for the fact that 30 is the lowest possible PANSS score. The effect of this correction is to reduce the denominator and magnify the percent change for a given pair of PANSS scores. Although the placebo rates are calculated with the same expression, the overall effect is to magnify the response rates, thereby creating a misleading impression of efficacy.

This information should be presented as a cumulative distribution curve of the change in total PANSS scores from baseline. The curve for a particular dose of risperidone and the corresponding placebo curve should be included on the graph.

(10) **"Dropout rate due to insufficient response" chart**

This chart is misleading because it suggests that the total completion rates are a reflection of risperidone's

tolerability. A more accurate presentation of risperidone's tolerability is the rate of premature discontinuation due to adverse events. The rates which should be presented are 10.5% and 3.4% for risperidone (6 mg) and placebo respectively.

Page 6

(11) Comparisons to haloperidol

All comparisons to haloperidol are unacceptable. Comments on this page are based upon the "EPS" (extrapyramidal symptoms) page which does not refer to haloperidol. The alternate page is acceptable.

(12) "Low incidence of EPS (at doses ≤ 10 mg/day)."

This claim is misleading. The word "low" is not consistent with a 17% incidence. All references to the incidence of EPS should include the dose-related incidence of EPS for risperidone and placebo.

Page 7

(13) "Well tolerated in clinical trials worldwide."

This headline is misleading. The phrase "well-tolerated" is not consistent with the treatment-emergent adverse experience incidence.

(14) "Percentage of patients reporting common side effects" chart.

The treatment-emergent side effect rates for extrapyramidal symptoms, dizziness, coughing, rash, dyspepsia and nausea should be added to this chart. Additionally, the risperidone 16 mg results, sample size for sub-groups (N) and data source should be added to this presentation.

(15) "excellent safety profile."

"An outstanding safety profile that offers excellent potential for compliance."

These claims are misleading. The adverse event rates of risperidone are not consistent with claims for an outstanding or excellent safety profile.

Page 8

(16) "A new class of antipsychotic."

This claim is misleading. Risperidone represents a new chemical class, but not a new therapeutic class of antipsychotic. A more accurate headline would be, "A new chemical class of antipsychotic."

(17) "with unique pathways of action."

This claim is misleading. Since the exact mechanism of action of risperidone is unknown, the uniqueness of this mechanism is also unknown.

(18) Positron Emission Tomography (PET) scan

These images are misleading because they imply clinical significance. A prominent statement should be added to this page which clarifies that there is no known clinical significance to these images.

Page 9

(19) "Clinical studies have demonstrated..."

This claim is misleading. The results in these charts were derived from one of the pivotal studies. Therefore, this bullet point should be revised to read, "One clinical study demonstrated..."

(20) "Optimal efficacy for positive symptoms...and negative symptoms..."

There are four issues:

(a) The headlines should be revised in accordance with Comment 2.

(b) The placebo rates should be included in these charts.

(c) The standard error should be added to the presentation of the point results.

(d) The scale of this chart is misleading. In order to accurately present these outcomes, the full PANSS scale should be used as the x-axis for the chart.

Page 11

(21) "Appropriate patient types."

These patient descriptions are misleading. Although some sub-group analysis were performed, the clinical trials were not designed to specifically study patients solely with negative symptoms. Similarly, sub-group analysis was not performed on patients determined to be prone to EPS. These descriptions should be deleted.

(22) "The most common side effects..."

This list of side effects is misleading because it does not represent the most common side effects of risperidone therapy. This list should include all of the side effects which will appear on the revised chart on Page 6. The rates of incidence of risperidone should be included in this discussion. See Comment 14.

(23) Graphic: Prescription pad, "Risperdal 3 mg, #60"

This graphic is misleading. A prescription for 60 capsules of risperidone will usually be a 30 day supply. This prescription contradicts the Precautions section of the approved product labeling which recommends, "Prescription for Risperdal should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose." A prominent and readable footnote would be an acceptable format for this disclosure.

(24) Warnings and Precautions

A page discussing the Warnings and Precautions section of the approved product labeling should be added to all promotional material. There are many serious warnings, such as neuroleptic malignant syndrome, tardive dyskinesia and potential for proarrhythmic effects which should be disclosed. Additionally, there are many serious precautions, including orthostatic hypotension, seizures, hyperprolactinemia and potential for cognitive and motor impairment which should be disclosed.

The presentation and discussion of the Warnings and Precautions must be compliance with 21 CFR § 202.1(e)(7)(viii). This regulation requires risk information to be presented with a prominence and readability reasonably comparable to the presentation of information about drug effectiveness. The presentation

should take into account typography, layout, contrast, headlines, paragraphing, white space, etc.

There should be a prominent notice on all other pages to refer to this page and to the full prescribing information.

(25) Short term efficacy

The efficacy of risperidone has been established in short-term (6-8 week) trials only. The effectiveness of risperidone in long-term use has not been systematically evaluated in controlled trials. Therefore, the following disclosure should be made:

> The physician who elects to use Risperdal for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

This disclosure should be presented in compliance with 21 CFR § 202.1(e)(7)(viii).

Journal ad

"The sedation rate was approximately 3% with risperidone (≤10 mg/day) and 1% with placebo (p=NS).

This claim is false and/or misleading. There are two issues:

(a) The finding that the p-value was not statistically significant is most likely a Type II error, and not evidence that risperidone is non-sedating. The Cochran-Armitage trend test showed a statistically significant dose dependency for the checklist item "sleepiness" in study 024.

(b) There is a Precaution in the approved product labeling regarding risperidone's sedative properties:

> Somnolence was a commonly reported adverse event associated with Risperdal treatment, especially when ascertained by direct questioning of patients.

All implications that risperidone is a non-sedating drug are therefore unacceptable.

If you have questions, or would like additional clarification, please contact the undersigned at (301) 594-6824, or write to:

Food and Drug Administration
Division of Drug Marketing,
Advertising and Communications
HFD-240, Rm. 17-B-17
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Sherry Danese

Sherry Danese, MBA
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications