

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 VIII

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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 <i>in Limine</i> , 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

<u>Hearing Transcript, February 2, 2011</u>	143
MOTIONS	143
<u>Transcript of Trial, March 7-22, 2011</u>	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)

<u>Transcript of Penalty Hearing, April 18-19, 2011</u>	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 Pharmaceutica Inc. to Healthcare Providers, dated November 2003.....	3788
P2353 Draft letter from Janssen Pharmaceutica Inc. to Healthcare Providers, dated November 2003.....	3790
P2354 Draft letter from Janssen Pharmaceutica 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 Pharmaceutica 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 <i>in Limine</i> 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 <i>in Limine</i> 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

RISPERDAL® Oral Brand
2003 Business Plan Summary

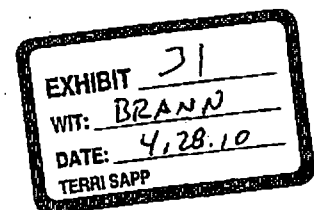


Table of Contents

RISPERDAL Oral

- I. Executive Summary
- II. Situation Diagnostic/Analysis
- III. 2002 Product Performance Summary
- IV. SWOT Analysis, Key Issues
- V. 2003 Strategic Objectives
- VI. Key Business Strategies
- VII. Key Programs and Tactics
- VIII. Success Predictors

Appendices

1. Brand Summary
2. Competitive Overview
3. Competitive Spending
4. Sales Force Coverage
5. Strategic Customer Segments
6. Life Cycle Plan
7. Market Research Plan
8. Tactical Plan
9. RISPERDAL Lifecycle Development Plans:
 - Bipolar Pre-Launch Plan
 - QuickSolv Launch Plan
 - Child & Adolescent Market Segment

RISPERDAL® Oral 2003 Business Plan Summary

I. EXECUTIVE SUMMARY:

The critical contingencies shaping today's competitive landscape of the antipsychotic (APS) market scarcely resemble the APS market environment when RISPERDAL was launched over eight years ago. The shift in market dynamics continues to benefit the atypicals, which contribute over 84% of the total market prescriptions and are used to treat a myriad of psychiatric disorders. Although antipsychotics have routinely been used off label, the approval of olanzapine for the treatment of acute mania associated with bipolar disorder in March of 2000 has greatly expanded the utilization of atypicals. It was the catalyst behind a two fold increase of the growth rate in the APS market between 1999 and 2000 (9.5% vs. 19.1%). These trends continued throughout 2001 and, in 2002, nearly 75% of atypical usage falls outside schizophrenia - driven by the Mood and Anxiety segment at roughly 42% of total prescriptions.

The overall market continues to churn out double-digit TRx growth - 13% for the APS market and 18% for the atypicals - and is expected to generate sales exceeding \$6.0 billion in 2002. This robust growth is primarily driven by new labeling (acute mania in bipolar, psychotropic), expanded uses of these medications across a spectrum of psychiatric disorders and increased promotional activities/share of voice to all customer segments including primary care.

In 2003, growth is projected to continue at a double digit pace (12% in 2003) due to:

- Further penetration of atypical use across the spectrum of mood and anxiety disorders (publication of key data sets in Treatment Resistant Depression);
- New product formulations (RISPERDAL CONSTA, RISPERDAL QuickSolv and Zyprexa IM);
- New indications for existing products (Zyprexa for Bipolar Maintenance); and
- The launch of a new atypical, Abilify (ariprazole) by Bristol Myers Squibb (BMS).

In one of the most fiercely competitive markets in the pharmaceutical industry, RISPERDAL remains the #1 prescribed product in its class and has maintained a relatively flat market share over the past two years. However in 2002, the share gap between RISPERDAL and its nearest competitor has been compressed and competitor gains have stemmed from all customer segments:

- LTC (64% of competitor gains);
- PCP (19% of competitor gains); and
- Psych (17% of competitor gains).

The largest gains have been achieved by Seroquel. In 2002, Seroquel entered the year with a 14.4% TRx market share and, as of September 2002, their TRx market share has climbed to 16.8%; growing in all business segments. The competitive NRx market share within the psychiatry/ PCP markets and TRx values for all products (month ending September 2002) are:

	RISPERDAL	Zyprexa	Seroquel	Geodon
Psychiatry (NRx)	29.2%	27.5%	20.5%	5.1%
PCP (NRx)	27.1%	37.1%	13.9%	2%
TRx	29.6%	28.2%	16.8%	3.1%

The market share gains by Seroquel and Zyprexa are a result of physicians' perception that these agents' product profiles are more suitable for treating the growth areas of the business, specifically mood and anxiety symptoms. Interestingly, RISPERDAL performance in our area of focus (schizophrenia) has been solid but has been unable to compensate for the loss experienced in the growth segments. The following chart shows the market growth of atypicals across indications in 2002 and RISPERDAL product performance in each segment:

	Schizophrenia	Mood and Anxiety	Dementia
Total Market	17%	30%	28%
RISPERDAL	4%	-7%	-5%

The growth engine in the market place has clearly shifted from schizophrenia to Mood & Anxiety and this shift is expected to accelerate over the next few years. Clinicians have clearly discovered the broad-spectrum utility of atypicals. This behavior change has been hastened by Lilly's aggressive promotion of Zyprexa in bipolar mania and AstraZeneca's push for Seroquel use in anxiety disorders.

The mood segment is comprised of bipolar, depressive and anxiety disorders. These disorders are comprised of symptoms that are implicated in many disease states, including Schizophrenia. Consequently, RISPERDAL's stout heritage as an efficacious agent across a broad range of symptoms associated with schizophrenia will enable RISPERDAL to effectively compete along this new paradigm.

A major shift in focus from positive and negative symptoms of schizophrenia to mood and anxiety symptoms of schizophrenia will result from a determined, concentrated effort from the RISPERDAL Brand team, the CNS and Primary Care Sales Forces and other internal partners to change customer perceptions of RISPERDAL. Initially, mood and anxiety symptoms in schizophrenia will be the focal area of promotion and firmly establish the efficacy platform of RISPERDAL in the mood and anxiety segment. A new message campaign will begin in early 2003. It will be rolled out to all sales forces prior to the second cycle (2003). Upon receiving FDA approval for the treatment of bipolar disorder (1Q 2004), the efficacy platform established in mood and anxiety symptoms will serve as a springboard to migrate the RISPERDAL promotional message from efficacy in mood and anxiety symptoms to efficacy of mood and anxiety symptoms across a spectrum of psychiatric disorders (including mood disorders).

RISPERDAL's main indication and core business, schizophrenia, will continue to be an important disease state, and RISPERDAL CONSTA will be positioned as the new treatment of choice in schizophrenia.

Focus will be critical and the Brand Team will be structured to ensure that messages are consistent and focused across all sales forces. The new positioning of the brand will help to differentiate RISPERDAL from the competition and ensure that RISPERDAL not only remains the #1 product in its class, but also increases the gap between RISPERDAL and the nearest competitor.

The year 2003 will find the RISPERDAL brand reaching new heights. The CNS sales force will grow to 570 reps, an increase of 50% over 2002. Recognizing the growing importance of the Primary Care audience, 500 additional sales representatives will be added to the 876 representatives already focusing on selling RISPERDAL to Primary Care Physicians. We will use

this competitive share of voice to leverage our market leadership and deliver focused, high impact sales messages and materials to targeted prescribers and environments, including:

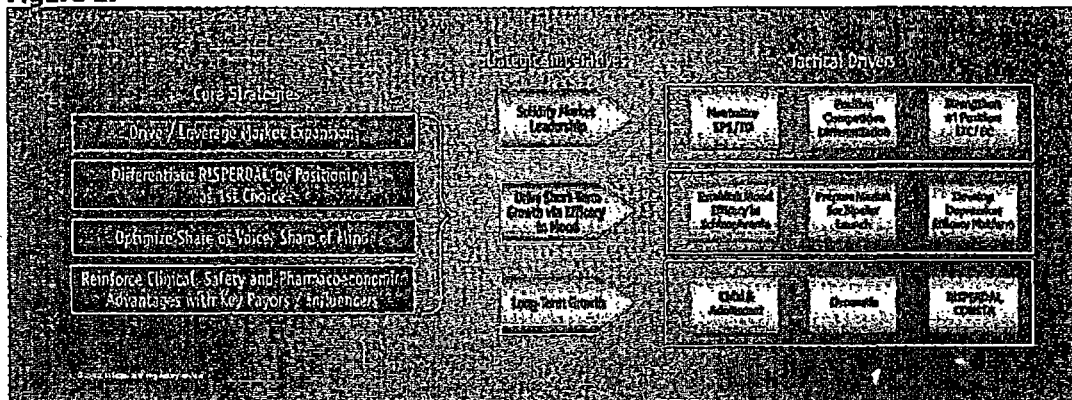
- Psychiatrists (CNS);
- Geriatric psychiatrists (ElderCare);
- Training Directors/Residents (HSR and I-Reps); and
- Primary Care Physicians (500 Blue & Gold).

Approximately 80% of the core messages will be shared across all sales forces, ensuring a more consistent, focused RISPERDAL message. These messages will support the RISPERDAL product position as delivering superior efficacy for the treatment of mood and anxiety symptoms uncompromised by long-term safety considerations like diabetes.

The 2003 business goal is to attain RISPERDAL sales of \$1.52 MM and achieve an exit share TRx of 28.0%. The 2003 strategic objective for RISPERDAL is establishing RISPERDAL Oral as the first choice for Mood & Anxiety symptoms and RISPERDAL CONSTA as first choice in schizophrenia. The franchise will realize these goals through the unwavering pursuit of excellence and flawless execution.

The following graphic outlines our core strategies, strategic imperatives, and tactical clusters for 2003 and will serve as our guiding light:

Figure 1:



II. SITUATION DIAGNOSTIC/ANALYSIS:

Market Overview:

It is estimated that the antipsychotic market in 2002 will exceed \$6.0 billion. The total market dollars for 2003 are projected to increase by 25%. The 4 drivers of market growth are:

1. The market continues to convert use from conventionals to newer atypical options. Conventionals continue to lose share to atypicals due primarily to the preferred side effect profile of the newer agents and efficacy against negative symptoms. This conversion will slow as the conventional share declines.
2. Due to the continued competitive focus on expanding the use of atypical antipsychotics, 2002 brought two significant shifts to the market. The growth rates of bipolar depression and mood and anxiety combined (30%) and Dementia (28%) outpaced the growth of schizophrenia (17%). Continued growth is anticipated with the impending launch of Zyprexa IM for use in agitation associated with bipolar depression and dementia, and bipolar indications for Zyprexa and RISPERDAL.

In addition, while psychiatry continues to offer the greatest dollar opportunity, the percentage growth of NRx within PCP (27%) outpaced the rate seen in psychiatry (15%).

3. During 2003, Janssen is expected to receive approval for the long-acting injectable formulation RISPERDAL CONSTA, a formulation that will assist in reducing partial compliance, along with the RISPERDAL fast dissolving tablet formulation, a formulation that will enhance compliance and ease of use.
4. Abilify, the new atypical antipsychotic from Bristol Myers Squibb, is expected to launch in late 2002. Its positioning is anticipated to be as new next generation atypical that offers comparable efficacy and fewer side effects when compared to current agents.

RISPERDAL continues to be the #1 prescribed antipsychotic in the United States, with current overall NRx share of 30.0% (YTD 10-02).

To capitalize on the powerful base within psychiatry and the growing influence of primary care, Janssen expanded the psychiatry sales force by 201 representatives in late 2002 and will introduce RISPERDAL to the 500 Blue in 2003. These expansions will ensure that RISPERDAL is positioned to expand within both key segments with its competitive share of voice.

Competitive Overview:

Over the past eight years, the antipsychotic market has experienced significant change and growth due to the introduction of RISPERDAL, Zyprexa, Seroquel, and Geodon into the marketplace. In general, clinicians perceive all atypicals to be similar in efficacy; although there is a common belief that RISPERDAL has superior efficacy in treating positive symptoms whereas Zyprexa [and Seroquel] have a broader application in depressive and anxiety symptom domains. Competitors are continuing to focus their promotional efforts on differentiation via safety and tolerability weaknesses of their competitors. With our competitors trying to differentiate themselves on safety and tolerability issues, RISPERDAL must continue to focus on its uncompromised safety profile and superior efficacy across a broad spectrum of symptoms.

Zyprexa (olanzapine):

Zyprexa, marketed by Eli Lilly, is the #2 prescribed antipsychotic based on prescription volume and #1 based on dollar share (due to its higher price versus RISPERDAL). While Zyprexa continued to experience a slight share decline in psychiatry (-.7) in 2002, share growth within the PCP segment was significant (+3.9). Zyprexa put significant resources behind their primary care mood & anxiety message. Although share has been relatively flat for both Zyprexa and RISPERDAL, Zyprexa's share within the mood markets of bipolar disorder (37.7%, 11-02) and depression (35.9%, 11-02) appears to be strengthening, while its share of schizophrenia declines (20.4%, 11-02). Despite a slow initial uptake for Zyprexa Zydls orally disintegrating tablet, this line extension has been steadily increasing market share. Zydls currently represents approximately 3% of Zyprexa total prescriptions and is projected to achieve \$100 million in sales in 2002. Lilly has been shifting its focus with Zydls to the long-term care/elderly segment.

The current positioning for Zyprexa focuses on established efficacy that enables patients to be reintegrated into life. Lilly has also recently launched a DTC campaign for Bipolar Disorder as they attempt to expand this important market segment.

Significant weight gain continues to be Zyprexa's primary side effect liability. However, there is a growing body of evidence demonstrating that Zyprexa (like Clozapine) has a propensity to cause new onset diabetes and DKA. This evidence has caused health authorities in Japan and UK to introduce warnings into the Zyprexa prescribing information. It is unclear whether or not similar changes to Zyprexa's package insert will occur in the US. Since the launch of Zyprexa, Lilly continues to focus on RISPERDAL's potential to cause EPS, as well as raising concerns around elevated prolactin. More recently, Lilly is aggressively driving a message that RISPERDAL has a greater propensity for TD, which they link to EPS.

While 2002 was expected to be a big year for Zyprexa, the year was full of challenges. In particular, there has been the continued delay of Zyprexa IM due to significant manufacturing issues and the negative publications/press regarding its association with new onset diabetes and DKA. However, from a clinical development perspective, Lilly is prepared to file two sNDA's by end of 2002. These indications include bipolar maintenance as monotherapy and bipolar depression in combination with fluoxetine. The projected launch for these two new indications is 1Q04 for bipolar maintenance and 2Q04 for bipolar depression. The treatment-resistant depression program consisting of (Zyp-Zac) has been delayed due to a failed trial with revised expected launch of 2005. Zyprexa is expected to receive its dementia claim in 2005.

In previous years, support and resources for psychiatry outweighed primary care. However, in the first quarter of 2002, Eli Lilly spent approximately 70% of their resources on the primary care

market. While the spend has equalized between psychiatry and primary care, Eli Lilly continues to outspend the market.

Seroquel (quetiapine):

Over the past year, AstraZeneca, marketer of Seroquel, has aggressively gained market share within this category. Seroquel is the fastest growing antipsychotic increasing NRxs by 44.8% (YTD 11-01 vs. YTD 11-02). Similar to the other competitors in the market, AstraZeneca is also positioning its product against RISPERDAL by focusing on increased potential for EPS and TD. Although physicians generally agree that Seroquel does not exhibit the efficacy of other atypicals, its use is driven by a perceived superior side effect profile and attractive sedative properties. Consequently, physicians tend to co-prescribe Seroquel – "a mild antipsychotic" - with other antipsychotics. In schizophrenia, Seroquel is co-prescribed with other antipsychotics 45% of the time. Overall Seroquel is co-prescribed with other APS 18% of the time. The key liability for Seroquel is their confusing dosing and titration – "Go to 4, then explore" and their relative lack of data. Based on their significant growth trends, Seroquel will continue to be a key focus for the RISPERDAL brand in 2003.

Geodon (ziprasidone):

Geodon, marketed by Pfizer, was launched in March of 2001. As anticipated, Geodon's share has grown as physicians gain experience with the product. Currently, the overall NRx share is 3.4% (YTD 11-02) with an October NRx share of 3.8%.

Geodon continues to face challenges due to QTc concerns that surfaced during the FDA's review of the product. With the addition of 9 more drugs to Geodon's contraindication section in 2002, there are now 19 contraindicated products listed in the package insert. Cardiac concerns have prevented Geodon from achieving any significant penetration in the 65+ population. Additionally, Pfizer received a Notice of Violation from DDMAC associated with their promotional activities at the 2002 APA conference in Philadelphia, PA. Specifically, DDMAC objected to:

- A promotional piece;
- Oral comments from representatives that minimized the QTc issue associated with Geodon; and
- Oral comments from representatives on Geodon's similarity to selective serotonin reuptake inhibitors on depression.

Pfizer has entered the side effect war waged within the antipsychotic market focusing on:

- Weight gain, lipid profiles and glucose concerns in Zyprexa; and
- EPS/TD in RISPERDAL.

Following initial delays, Geodon IM received approval in June 2002 and was launched in September. With the introduction of Geodon IM, Pfizer is expected to re-launch Geodon. However, it is too soon to determine if the new product introduction will have a significant impact.

In contrast to Lilly, Pfizer is pursuing only a few additional indications. In 2004, it is expected that Geodon will receive an indication for acute mania. In addition, Pfizer has a pediatric bipolar program ongoing.

Abilify (Aripiprazole):

Bristol-Meyers Squibb and Otsuka America Pharmaceuticals are expected to launch Abilify 4Q02. Described as a dopamine-system stabilizer, it is being positioned as a next generation psychotropic because of its agonistic and antagonistic activity balancing dopamine and serotonin levels. Current available data suggest that Abilify has a modest efficacy profile with a favorable side effect profile. It is expected that BMS will focus on:

- Zyprexa's weight gain, diabetes and DKA potential;
- RISPERDAL's EPS/TD and prolactin; and
- Seroquel's sedative properties.

Other New Entrants:

Novartis and Titan Pharmaceuticals were jointly developing Zomaril, a new atypical antipsychotic for the treatment of schizophrenia. A decision has been made to stop further development due to safety concerns.

Customer Segment Overview:

In 2003, focus will be on the following four customer segments:

- Physicians;
- Nurses;
- LTC Providers; and
- Institutions.

In order to effectively reach key influencers, Janssen will deploy additional sales representatives in both primary care and specialty physician markets. By 1st cycle 2003, an additional 1,000 Primary Care sales representatives and 201 CNS M & L sales representatives will be calling on our targeted audience to augment the existing 488 Gold, 285 Eldercare, 107 on the HSR team, 310 CNS M & L and 65 I-Reps sales forces. The new increase will put Janssen in a competitive selling position with Lilly who currently has 1,400 sales representatives calling on psychiatrists and primary care physicians.

Physicians:

The physicians are placed in two groups, primary care and specialist. Primary care physicians are made up of geriatricians, internist, family practice, general practice and D.O.'s. The primary care physician has become increasingly more important because they are fueling the fastest growing segment of the antipsychotic market. The specialty physicians are made up of psychiatrists (general and geriatric), neurologists, and endocrinologists. Psychiatrists continue to be the greatest users of antipsychotic medications and account for approximately two thirds of all new prescriptions. Neurologist will be a key focus group as we look to develop broader market awareness of the low risk of movement disorders associated with RISPERDAL. Endocrinologists will be a new target segment in 2003 as we continue to differentiate RISPERDAL from the competition with regards to diabetes/DKA.

U.S. practitioners include approximately:

- 40,000 psychiatrists;
- 60,000 primary care physicians; and
- 11,823 neurologists.

Janssen targets approximately:

- 18,300 psychiatrists;
- 34,000 primary care physicians; and
- 4,500 neurologists.

Figure 2: Customer Segment by Specialty:

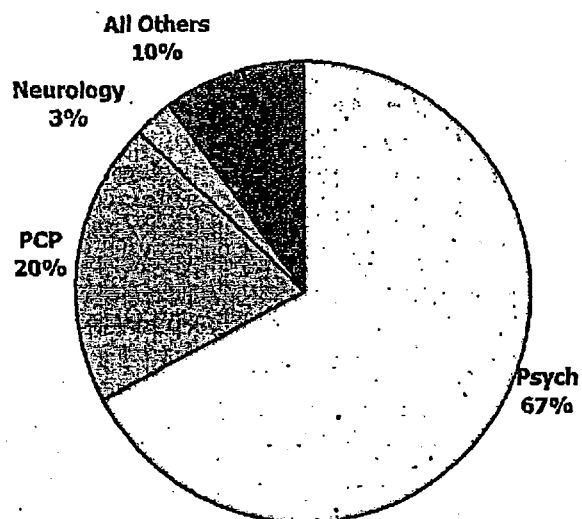


Figure 3: Distribution by Diagnosis – RISPERDAL:

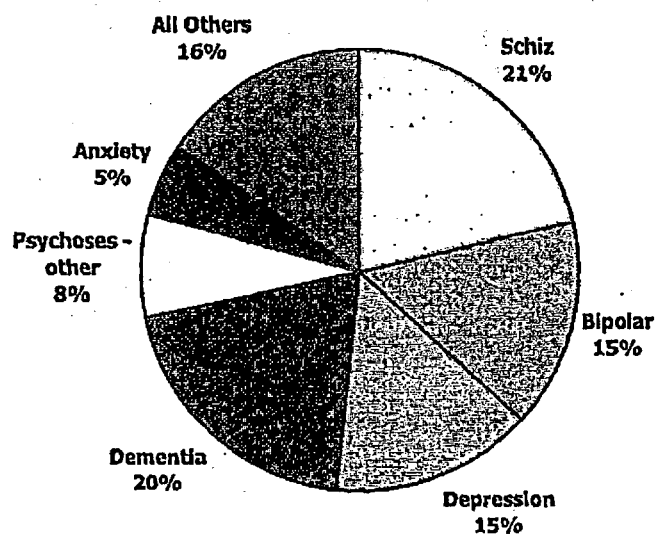
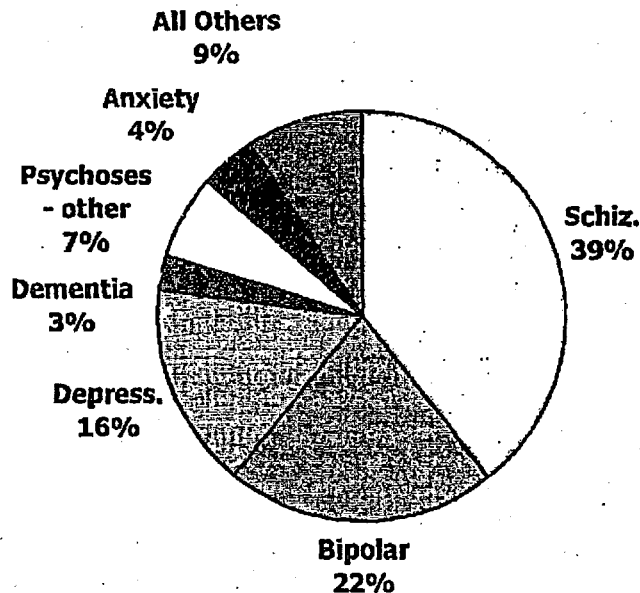


Figure 4: Distribution by Diagnosis – Antipsychotics:**Nurses:**

Nurse Practitioners (NPs) have been recognized as a very important segment of the business for Janssen. NPs have prescribing privileges in 49 states and therefore they have the ability to help drive the RISPERDAL business. NPs can be broken out into two important groups: geriatric NPs and psychiatric NPs. Based on the growing importance of these two groups Janssen Sales and Marketing will be incorporating specific tactics focused on educating them on the appropriate use of atypicals. In many cases, these individuals are the front line in the assessment of patient symptoms and have a great influence on the initiation of treatment.

Institutions:

Key institutions that we focus on are state, public and private hospitals along with VA system. Our target customers in these institutions are Psychiatrists, Psychiatry Residents, Primary Care Residents, Primary Care clinics and Pharmacists. The Psychiatrist and the Psychiatry Resident are the two most important target groups. Many hospital based Psychiatrists are either local, regional or national Key Opinion Leader's (KOLs). They have extended influence beyond their own prescribing. There are 220 accredited psychiatry residency programs in the United States each training between 10 – 40 residents. Fostering relationships with this group is critical for future RISPERDAL success. These relationships create the groundwork that enable appropriate

RISPERDAL message dissemination and ensure successful use of the brand in their training initiatives. For the past three years, Janssen has sponsored the "Janssen Psychiatry Resident Award of Excellence" that allows residents to participate in a full day of educational lectures, followed by interaction with key thought leaders in the field. A more focused effort to ensure RISPERDAL growth within the VA system will be based on the rollout of a blanket purchase agreement that must be completed in 2003. Our most significant opportunity is to ensure that new patients are started on RISPERDAL over Seroquel.

Long-term Care:

One of Janssen's five key strategic objectives is to be #1 in EC/LTC. The LTC market continues to grow, however, it will continue to struggle to provide effective treatment with increased cost pressures and restricted budgets. LTC pharmacy providers, Nursing Home chains and Skilled Nursing Facilities (SNF) all impact the availability and reimbursement of atypicals. Contracting and innovative partnerships will ensure a profitable relationship with these important customers.

A key customer that has a direct impact on our growth within this segment is the Consultant Pharmacist (CP). A greater knowledge of the product profile of RISPERDAL – superior efficacy, protective effect from falls, enhanced sleep, low risk of movement disorders and a low potential to increase the anticholinergic load, will allow the CP to make data driven recommendations for the use of RISPERDAL over other atypicals. CPs impact prescribing patterns of consultant psychiatrists, attending physicians and nurse practitioners.

Within the nursing home setting, the important targets are the consulting psychiatrists, medical directors, attending physicians, consultant pharmacists and nurse practitioners. Other influencers include Directors of Nursing and the nursing staff. In addition, Assisted Living Facilities, Community Mental Health Centers and even home-based care are emerging as alternatives to nursing homes and will remain important segments for RISPERDAL. Representatives are responsible for establishing solid relationships with the on-site staff. Consultant pharmacists will conduct chart reviews and recommend switch's when appropriate.

III. 2002 PRODUCT PERFORMANCE SUMMARY:**2002 Quantitative Goals:**

Goal: Business Sales: \$1,123 MM Psych, \$290 MM PCP (original)
 \$1,037 MM Psych, \$268 MM PCP (updated)
 December exit share: 27.8% Psych, 27.6% PCP

2002 Qualitative Goals:

Goal: To drive the position of RISPERDAL as the FIRST CHOICE antipsychotic. This will be done by protecting our core business of schizophrenia with the launch of RISPERDAL CONSTA, while refocusing our message to increase usage in the mood related symptoms of schizophrenia.

<u>Lessons Learned</u>	<u>Implications</u>
☐ Seroquel has capitalized on market expansion in mood and anxiety; Sedation is a smoke screen	☐ Seroquel's use needs to be displaced if RISPERDAL is to grow in mood & anxiety symptoms
☐ Market is currently focused on short-term vs. long-term efficacy and safety	☐ RISPERDAL's long-term benefit message has not yet resonated with prescribers
☐ PCP growth starting to outpace Psychiatry	☐ Validates a fast follower strategy in PCP
☐ Mood & Anxiety have higher growth rate because of lower penetration of APS class	☐ Drugs with the indications are driving the business
☐ Clinical data, SOV, SOM and indications are key drivers	☐ Competitive SOV and SOM are required for RISPERDAL to impact market growth
☐ Emergence of other health care professionals as influencers (NPs, PAs, psychologists, RPh & PharmD)	☐ For 2003, no change in fundamental market mix. Significant changes in how customers are viewed is a longer term concern

IV. SWOT ANALYSIS, KEY ISSUES:

Strengths	Weaknesses
☐ RISPERDAL =#1 Prescribed with dominance in LTC, EC and C&A ☐ Increasing focus on M&A, task forces, RISPERDAL CONSTA vs. Oral ☐ Only LAI in market (RISPERDAL CONSTA) ☐ Trust/market longevity/reliability ☐ Superior cost-effectiveness ☐ Strong data on long-term efficacy & safety ☐ Only APS approved to delay relapse vs. active comparator ☐ Minimal metabolic risk profile/ superior cost-effectiveness ☐ Dosing flexibility ☐ Focused field presence ☐ Field Sales Force expansion	☐ Limited Indications ☐ Market perceives EPS, TD & Prolactin as liabilities ☐ Decreasing share of Voice, Share of Mind ☐ Publications from existing data ☐ Perceived as "older agent" ☐ Patent expiration interfering with life-cycle management
Opportunities	Threats
☐ Diabetes/DKA ☐ Expansion of customer base & usage ☐ New Indications & formulations ☐ Leverage guidelines ☐ Expanded usage in existing indications (dual diagnosis, prodromal schizophrenia) ☐ Together Rx ☐ QTc & Lipid AE's with other atypicals ☐ Field Sales Force Expansion	☐ New product entries ☐ Increasing budget constraints of payors (Medicaid/Managed Care/LTC/State controls) ☐ Diabetes class effect ☐ Differential RISPERDAL CVA labeling ☐ Current and future competitor messages focused on adverse events with efficacy as a class effect ☐ Non-approvable letter and PR surrounding RISPERDAL CONSTA spillover on oral ☐ TD liability/claims

KEY ISSUES:

- LTC share loss
- Seroquel Growth
- Abilify (Aripiprazole) Launch
- Zyprexa diabetes/DKA
- EPS/TD roadblock for growth
- Our focus has been in schizophrenia, however, highest growth opportunity is mood and anxiety symptoms

V. 2003 STRATEGIC OBJECTIVES:

Qualitative:

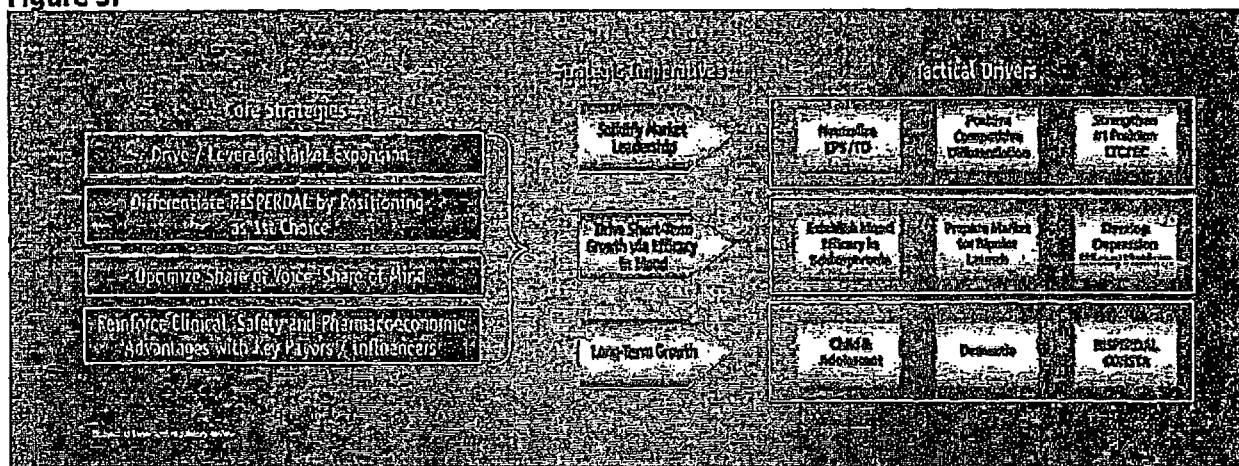
- Establish RISPERDAL as first choice in treating mood and anxiety symptoms in schizophrenia
- Blunt growth of Seroquel
- Defend against Abilify
- Minimize impact of Geodon IM/Zyprexa IM
- Drive metabolic/lipids as a differentiator
- Introduce RISPERDAL QuickSolv
- Message alignment across field forces

Quantitative:

- NTS = \$1.540 Billion: This is a base case scenario which assumes the following:
 - Market growth = 12.5%
 - Market share = 28.0%
 - GTN = 73.0%
 - CNS Sales Force expansion (50% increase by January 1)
 - RISPERDAL QS launch in 1Q03
 - Abilify (Aripiprazole) launch 4Q02
 - Geodon IM 4Q02
 - Zyprexa IM launch 2Q03
- Share of Voice Target = 2,159,133 Total contacts (26% share); Comparable to Zyprexa
 - In Primary Care = xx contacts (x% share)
 - In Psychiatry = yy contacts (y% share)
- Improve perceptions of RISPERDAL - mood and anxiety symptoms, EPS/TD

VI. KEY BUSINESS STRATEGIES:

KEY BUSINESS STRATEGIES	TACTICAL CLUSTERS
☐ Solidify Market Leadership	☐ Neutralize EPS/TD ☐ Positive Competitive Differentiation ☐ Strengthen #1 Position LTC/EC
☐ Drive Short-Term Growth via Efficacy in Mood	☐ Establish Mood Efficacy in Schizophrenia ☐ Prepare Market for Bipolar Launch ☐ Develop Depression Efficacy Platform
☐ Long-Term Growth	☐ Child & Adolescent ☐ Dementia ☐ RISPERDAL CONSTA

Figure 5:**Solidify Market Leadership:**

RISPERDAL continues to be the market leader in terms of prescriptions and has a trusted heritage amongst the customer base. Over the past two years our growth has been flat or declining. We have not made many significant changes to our overall brand strategy. We need to use our leadership position to make some substantial shifts in our direction and "act like a market leader."

It is critical that each and every member of our Sales & Marketing organization act like a market leader by focusing on excellence and innovation. We truly have the best product and the best people. We need to be passionate about RISPERDAL and communicate this passion to our customers in all interactions. Three tactical clusters will help us to solidify and expand our leadership position:

- **Neutralize EPS/TD:**

We know that extrapyramidal side effects are RISPERDAL's biggest liability. Physicians routinely bring up this issue in all the market research we conduct. Additionally, our competitors focus on this liability and suggest a strong association with tardive dyskinesia. We have presented messages and data to support EPS as comparable to placebo and/or other atypicals. However, this message has met with much skepticism and resistance.

We must realize that we have become the number one product in the class with all of these EPS issues, and that physicians need to look at our product over the long-term with the proper risk/benefit mentality.

We will be learning how our highest share physicians think about and deal with EPS. We will be educating all physicians on drug-induced movement disorders. We will teach them proper recognition and management. Most importantly, we will be putting this short-term manageable side effect (that is more associated with risperidone) into the context of other more problematic long-term safety issues associated with other atypicals.

It is important to note that we cannot be as successful moving into mood symptoms without neutralizing this liability. Mood patients tend to be higher functioning and this issue is even more prohibitive to a physician. By meeting it head on and educating on recognition & management, we can be on par with our competition from a safety/tolerability standpoint.

- **Positive Competitive Differentiation:**

We compete in a somewhat crowded market with very strong competitors. We need to make sure that we positively distinguish RISPERDAL from key agents like Zyprexa, Seroquel, and Abilify. We need to do this by noting those products' liabilities. Most importantly, however, we need to sell the benefits of RISPERDAL. As the market leader, we do not need to be overly reactionary, but we do need to face significant competitive challenges head on.

We have numerous tactics that address individual competitors as well as some that cross the set. The specific tactics will cross Medical Affairs, Sales and Marketing but will ensure that, while we are pointing out competitors weaknesses, we are selling RISPERDAL's strengths.

- **Strengthen #1 Position in LTC/EC:**

RISPERDAL's share of use in dementia is over 40% and is well recognized as an effective treatment option in the elderly population. However, over the past 12 - 18 months, our competitors have made significant inroads in these markets. We need to refocus our efforts and utilize our ElderCare sales and marketing tools to reverse these trends and expand our leadership position.

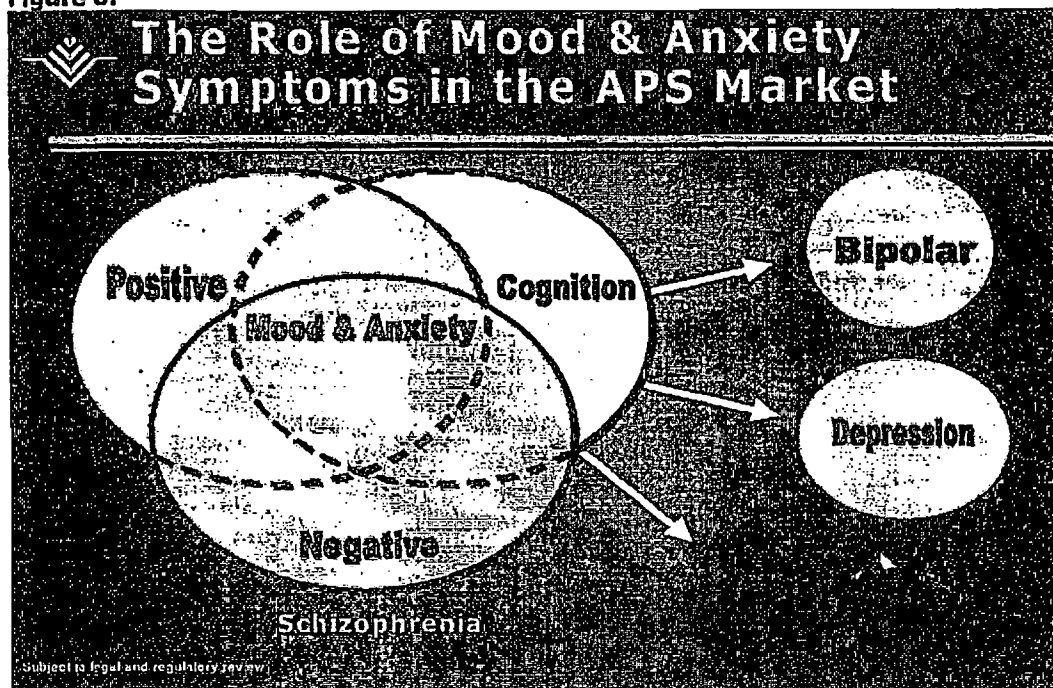
Our new rapidly dissolving tablet (see attached business plan in appendix) provides a line extension especially suited to the LTC marketplace. This coupled with a renewed focus and passion will help us to improve our share within this market.

Drive Short-Term Growth via Efficacy in Mood:

Simply maintaining market leadership is not the objective of the CNS Sales and Marketing Team. The team goal in 2003 is to increase the market share gap between RISPERDAL and its nearest competitor and achieve the upside forecast of \$1.62 billion in 2003. To realize these aggressive growth targets, the CNS team must capitalize on the evolving dynamics of the atypical marketplace and positively differentiate RISPERDAL from the competition along these dimensions by firmly establishing the superior efficacy of RISPERDAL in mood.

The mood and anxiety segment is defined as mood and anxiety symptoms associated with schizophrenia and mood and anxiety disorders (including bipolar, depression and the spectrum of anxiety disorders). This segment accounted for approximately 42% of total prescriptions in 2002 and contributed to 60% of the growth within the atypical marketplace – growing at an absolute rate eclipsing 30%.

Figure 6:



The shift in brand focus to establishing RISPERDAL efficacy in mood and anxiety symptoms is a natural, necessary response to the changing market dynamics that drive the prescribing decision. By making mood the heart of RISPERDAL's promotional, educational and publication platforms, specifically:

- Establishing mood efficacy in schizophrenia;
- Preparing market for bipolar launch; and
- Developing a depression efficacy platform,

The team will expand the growth phase of the RISPERDAL Oral life cycle through patent while conditioning the market for RISPERDAL CONSTA to expand beyond the boundaries of schizophrenia.

- **Establishing mood efficacy in schizophrenia:**

The distinction in the market definition relating to symptoms versus disorders is a critical distinction within the mood segment. This is important because it enables Janssen to leverage our strongest resource, the expanded CNS and Primary Care sales force, to strengthen the core position of RISPERDAL by shifting their promotional message. The message that is delivered to customers will shift from efficacy treating positive and

negative symptoms associated with schizophrenia to efficacy treating mood and anxiety symptoms associated with schizophrenia. By the end of 2003, we want to achieve a 75% awareness level among our target customer population regarding the RISPERDAL core position:

RISPERDAL delivers superior efficacy for the treatment of mood and anxiety symptoms uncompromised by long-term safety concerns such as diabetes.

- **Prepare market for bipolar launch:**
Complimenting the promotional shift to mood and anxiety symptoms of schizophrenia, there will be an aggressive bipolar pre-launch plan focused on increasing awareness of RISPERDAL for the treatment of mood disorders – more specifically bipolar disorder. The overall effectiveness of the RISPERDAL bipolar pre-launch campaign will determine RISPERDAL's ability to effectively challenge for market leadership in the bipolar segment. Success of the plan is defined as achieving:
 - 75% awareness levels of RISPERDAL bipolar data;
 - Redefining of the most influential attribute set within the bipolar market; and
 - Aligning key national and regional opinion leaders.

The strategies developed to ensure we accomplish the pre-launch objectives include:

- Build and broaden KOL relationships;
- Expand key drivers for treating bipolar disorder;
- Differentiate RISPERDAL from the competition in bipolar disorder; and
- Solidify communication platform with clinical data.

Upon receiving FDA approval for the treatment of bipolar disorder (1Q04), the RISPERDAL efficacy platform will be firmly established in mood and anxiety symptoms and the bipolar market will be properly conditioned. The presence of these two market dynamics will facilitate the introduction of RISPERDAL for bipolar disorder and maximize product penetration in this rapidly expanding segment.

Long-Term Growth:

The two prior strategic imperatives focused on how the CNS Franchise will secure our current market position as a foundation for growth, as well as what we will do to accelerate growth in the short-term. The Long-Term Growth strategic imperative demonstrates our focus on three key growth drivers over the coming years. These long-term growth drivers are:

- Child & Adolescent;
- Dementia; and
- RISPERDAL CONSTA™.

These three long-term growth drivers each represent individual opportunities to fuel the business. This section, however, specifically details the synergistic opportunities provided by these long-term growth drivers in concert with our base business. We will focus on how this long-term growth will integrate with our existing business, as well as with one another, to help us achieve our future business objectives.

These three growth drivers provide cumulative sales of approximately \$8.2 billion through 2013. This impressive number will not come to us magically, however. These three opportunities need to grow together, complement one another moving forward and build on the success of the RISPERDAL base business. Of the total estimated cumulative sales, approximately \$7 billion is

attributed to RISPERDAL CONSTA™ alone. This clearly demonstrates the critical role which RISPERDAL CONSTA™ plays as the lynch pin of our long-term growth.

- **The Child & Adolescent Opportunity:**

Child & Adolescent provides business opportunities on three key fronts. First, the extension of patent exclusivity provides incremental oral business, as well as an extended period of time to manage switches to RISPERDAL CONSTA™. Second, successful customer use of RISPERDAL within this patient population at lower doses (with low EPS) reinforces the "softer RISPERDAL" market image necessary to support our shift towards mood. Third, research within this population may provide for additional Indications, such as autism, for which we are seeking approval in 2004.

- **The Dementia Opportunity:**

Dementia grows in importance as we pursue our regulatory file for Psychosis in Dementia. This will provide obvious synergistic opportunities with ElderCare and Long-Term Care. These are areas of our business that require critical support. The Dementia filing aligns with our company-wide strategy to be #1 in ElderCare. We currently have a leadership position with a 50% share within this segment. This key launch will allow us to defend and grow this position.

- **The RISPERDAL CONSTA™ Opportunity:**

RISPERDAL CONSTA™ is our greatest platform for long-term growth. This is an opportunity which we will maximize by seeking synergy and a halo effect with the base business at launch and throughout its lifecycle. RISPERDAL CONSTA™ allows us to firm up our strength in schizophrenia, and then follow the path cut by the base business towards mood.

VII. KEY PROGRAMS AND TACTICS:**Solidify Market Leadership***(Neutralize EPS/TD, Positive Competitive Differentiation, Strengthen #1 Position LTC/EC)*▪ **Meeting It Head On Program**

Description:	Program to develop, train, and execute focused messaging to proactively discuss EPS and establish low-dose/low-EPS relationship: - Market Research - Sales Training - Regional Tracking - Sales Recognition
Objectives:	Educate prescribers on RISPERDAL's EPS/TD data, place into context of tolerability and focus on proper dosing
Metrics/Goal:	- Rep assessments (85% or >), Statistically significant decline in EPS/TD importance ratings on perceptual maps - Regional message recall (70% use of sales aid, 65% total message recall)
Audience:	Psychiatrists, PCPs, Neurologists, Representatives
Timing:	1Q03 – 2Q03

▪ **Zyprexa Rescue Trial**

Description:	Zyprexa to RISPERDAL switch study to investigate optimal switch strategy, metabolic effects, and efficacy improvement. ME will poster data at ACNP (12-02) and include in CME.
Objectives:	Assess efficacy, metabolic effects and optimal switch strategy in patients changed from olanzapine to risperidone
Metrics:	- Successful publication, CME responses and evaluation forms (content > 4.0) - Increasing net switches from Zyprexa to RISPERDAL by 5% as measured by NDC
Audience/Goal:	Psychiatrists, PCPs, Endocrinologists
Timing:	4Q03

▪ **RISPERDAL/Seroquel Head-to-Head Study**

Description:	RISPERDAL vs. Seroquel study in bipolar to investigate onset of action, efficacy, and impact on thyroid hormones and hypothyroidism
Objectives:	Assess onset of action, efficacy, cost-effectiveness and thyroid effects of risperidone and quetiapine
Metrics:	- Successful poster, abstract, and publication - CME responses and evaluation forms (Content > 4.0) - Incorporate into sales aid
Audience/Goal:	Psychiatrists, Neurologists and PCPs
Timing:	4Q03

▪ ***Abilify Blunting Program***

Description:	Campaign that capitalizes on pre-launch knowledge which includes sales training, launch flashcard and proactive task force
Objectives:	Thwart uptake of aripiprazole by educating prescribers or unknown mechanism of action and proactively selling RISPERDAL
Metrics/Goal:	- Message recall (50%) - Rep conference calls - Abilify early adopter study
Audience:	Psychiatrists and PCPs (depending on BMS strategy)
Timing:	1Q03

▪ ***"Increasing Your IQ on QI" Initiative***

Description:	Partner with key LTC customers to design & execute a comprehensive initiative on Quality Indicators. A QI Resource Kit will highlight new 2003 QI Index, education, and a focus on the "Falls and Fractures" QI
Objectives:	Maximize preferred status in LTC
Metrics/Goal:	Participation by All Tier 1 LTC Pharmacy Providers
Audience:	LTC Healthcare Providers
Timing:	2Q03

▪ ***Aggressive Conversion to RISPERDAL QuickSolv***

Description:	Fully integrated promotional campaign that is distinctive, persuasive and believable. Platform will support the overall product position and extend the value proposition by adding ease and convenience of administration. Campaign will consist of a journal ad, flashcard, direct mail, and placebo samples
Objectives:	Differentiate RISPERDAL QuickSolv from the competition to maximize penetration in LTC
Metrics/Goal:	75% total awareness levels among target audience, 5% of RISPERDAL total sales in LTC
Audience:	LTC and ElderCare customers
Timing:	2Q03 - 4Q03

Drive Short-Term Growth via Efficacy in Mood Symptoms*(Establish Mood Efficacy in Schizophrenia, Prepare Market for Bipolar Launch, Develop Depression Efficacy Platform)*▪ **Discover RISPERDAL For M&A Symptoms in Schizophrenia**

Description:	Closed round table, integration into core campaign, multi-media presentation
Objectives:	Challenge physicians to think differently regarding the profile of RISPERDAL on efficacy and safety in mood symptoms associated with schizophrenia
Metrics/Goal:	Eliminate significant difference in Perceptual Map on mood symptoms compared to Zyprexa and Seroquel
Audience:	Psychiatry and Primary Care
Timing:	1Q03 - 4Q03

▪ **Bipolar Care Options Program**

Description:	<u>Design</u> - Six National KOLs (Bipolar Institute) on steering committee - 120 Regional KOLs (working groups) <u>Rollout:</u> - Proceedings from working groups presented at Large Symposia / PR - Publication - CD ROM Speakers Kit - 3 Newsletters - Audio-conferences
Objectives:	Elevate importance of unmet physician and patient needs that compliment the expected communication platform of RISPERDAL in bipolar disorder
Metrics/Goal:	Perceptual Map identifies increase in importance of specific bipolar attributes > 10 citations in Literature referencing output of program
Audience:	Psychiatry
Timing:	3Q03 - 4Q03

Prepare Market for Long-Term Growth Opportunities
(Child & Adolescent, Dementia, RISPERDAL CONSTA)

▪ **C&A Mental Health Summit**

Description:	Workshops with KOL's and major C&A mental health advocacy organizations (NAMI, NMHA, CABF, CHADD, CAN, etc.), with oversight of 3rd party
Objectives:	Attain KOL/advocacy endorsement and consensus on the need for proper diagnosis and treatment
Metrics/Goal:	Publication of positive position paper
Audience:	Psychiatrists, Patient/family advocacy groups
Timing:	1Q03

▪ **RISPERDAL/REMINYL Co-Programming and Co-Messaging**

Description:	Co-Programming and Co-Messaging consist of: - Joint programming at industry-sponsored symposia - Leverage enduring materials across multiple audiences - Share exhibit space at specialty-specific conventions Cost savings realized through: - Optimization of Internal resources - Improved vendor efficiencies - Extended programming reach
Objectives:	Advance RIS/REM co-positioning and leverage synergies to penetrate PCP and Neurology (dementia, mood, schizophrenia)
Metrics/Goal:	Increased reach (PCP, neurology) at similar investment level
Audience:	Psychiatrists, neurologists, PCP's
Timing:	1Q03 - 4Q03

▪ **CONSTA: Partial Compliance Campaign**

Description:	Increase Partial Compliance awareness. Campaign will consist of: 2 Advertorials, Matching Reprint Mailers, Real World Compliance Video, ROSE Publication, Velligan Publication, Consensus Guidelines, Symposia and APA Booth
Objectives:	Broaden patient population for RISPERDAL CONSTA beyond current depot population
Metrics/Goal:	Awareness level: > 50% of Psychiatrists rate = 60% or > of their patient population as Partially Compliant
Audience:	Treatment Team, Pharmacists, Advocacy, Payers
Timing:	1Q-4Q 2003

VIII. SUCCESS PREDICTORS:

Throughout this year's tactical planning there has been a strong dedication across the franchise on focus, simplicity and integration. The entire franchise came together to remove the clutter, break down our internal barriers and simplify the communication of our strategic and tactical plans. All business segments have developed this plan in a coordinated manner with a single definition of success. We recognize that our business is complex, yet we have made it more complex than necessary in how we have planned, executed and communicated our plans in the past.

This newly aligned and coordinated franchise drove a clear and concise Business Plan for 2003. We believe this demonstrates a new era for RISPERDAL. This is not just how we developed and presented the plan. This is how we will function as a business.

Our move towards mood has provided us with strategic vision as a franchise. This has given us a firm direction that will focus all of our tactical efforts. The franchise is fully aligned, both strategically and tactically, behind our move towards mood.

Renewed focus on this shared strategic vision allows the franchise to better withstand challenges to the business. We are less inclined to become distracted by competitive threats because we have a strong sense of where we are headed. Rather than becoming caught up in a specific response to each new competitive challenge, we will sharpen our focus on our shared strategic direction. We alone can choose the direction for this brand. We will not allow the competition to choose it for us.

Our strategic alignment and focus will allow us to execute in the manner this franchise requires. Everything we do will be focused on our goals for growth. We will meet the competition head on with renewed strength. This resolve comes from acting as one brand with all growth assets focused on one strategic goal. We are the market leader and we will act like the market leader. We will harness the power we have in this brand and achieve the objectives laid out in this plan for 2003 and beyond. The following factors will be key in helping us be successful:

- Move to Mood;
- Neutralize EPS/TD;
- Alignment and Focus; and
- Execute, Execute, Execute.

Appendices

BRAND SUMMARY

1

	2000	2001	2002 YTD*	2003 Forecast
Market Size (\$000)	\$4,116 mil	\$5,439 mil	\$4,094 mil	\$7,500 mil
% Growth	26%	32%	20%	
Net Trade Sales (\$000)	\$1,083	\$1,240	\$1,052	\$1,527
% Growth	21.4%	14.5%	11.3%	8.3%
Unit Sales - tabs in millions	470.6	543.5	371.9	589.4
% Growth	24%	15%	8%	5.2%
Average Market Share (%)				
TRx	30.8%	31.4%	30.1%	28.1%
NRx	31.4%	31.4%	30.1%	28.1%
Dollars	32.3%	30.2%	28.4%	26.0%
Average Price/Dose	\$5.71	\$6.12	\$6.33**	

*YTD Aug 2002 - Dollar; YTD - Sept 2002 - Prescriptions; **AWP & NDTI MAT 6/02

Net Sales

	\$MM	% Chg	(000) Units	% Chg	Cost of Selling	% of Sales	PMEs of Sales	% Chg
2002 Oct Updt	\$1,410	13.8%	557.1	6.2%	\$162,170	11.5%	\$81,099	1.1%
2003 Bus Plan	\$1,527	8.3%	589.4	5.8%	\$218,909	13.8%	\$78,532	-4.3%

PME Breakdown

Area (%)	2003 PME (\$K)	2003 PME (%)	2002 PME (\$K)	2002 PME
RISPERDAL Oral	\$33,760	35.3%	\$37,022	43.6%
RISPERDAL CONSTA	\$14,500	15.6%	\$12,000	14.1%
Mood & Anxiety	\$5,025	5.4%	\$3,629	4.3%
Child & Adolescent	\$3,525	3.8%	\$3,744	4.4%
Medical Marketing	\$20,790	22.2%	\$15,480	18.2%
Public Sector & Inst.	\$3,000	3.2%	\$3,100	3.6%
Other	\$13,500	14.5%	\$10,018	11.8%
TOTAL Base PME's	\$94,100	100.0%	\$84,993	100.0%

PME Breakdown By Type

	Total		Med Ed		Samples		Journal Adv		PR		DTP/DTC		Agency	
	\$M	% Net Sales	\$M	% Net Sales	\$M	% Net Sales	\$M	% Net Sales	\$M	% Net Sales	\$M	% Net Sales	\$M	% Net Sales
2002 Oct Update	\$84.9	6.0%	\$15.5	11%	\$3.0	.2%	\$4.3	.3%	\$.78	.05%	\$.39	.03%	\$4.5	.32%
2003 Bus Plan	\$94.1	6.2%	\$20.8	13%	\$4.0	.3%	\$4.3	.3%	\$.90	.06%	\$.39	.03%	\$4.0	.26%

COMPETITIVE OVERVIEW

2

	2000	2001	2002 YTD*	2003 Forecast
Sales (\$M)	\$4,116	\$5,439	\$4,094	\$7500
RISPERDAL	\$1,325	\$1,629	\$1,162	\$2083 (gross)
Zyprexa	\$1,945	\$2,558	\$1,900	\$3,335
Seroquel	\$423	\$706	\$656	\$1289
Geodon	N/A	\$142	\$144	\$397
Clozaril	\$235	\$234	\$143	\$190
Abilify	N/A	N/A	N/A	\$250
Conventionals	\$188	\$169	\$88	\$101
Dollar Market Share (%)				
RISPERDAL	32.2%	30.0%	28.4%	25.83%
Zyprexa	47.3%	47.0%	46.4%	44.47%
Seroquel	10.3%	13.0%	16.0%	17.19%
Geodon	N/A	2.6%	3.5%	5.3%
Clozaril	5.7%	4.3%	3.5%	2.5%
Abilify	N/A	N/A	N/A	3.3%
Conventionals	4.6%	3.1%	2.2%	1.35%
TRx Market Share (%)				
RISPERDAL	30.8%	31.4%	30.1%	28.1%
Zyprexa	23.7%	26.2%	27.8%	27.0%
Seroquel	8.9%	12.5%	15.7%	17.3%
Geodon	N/A	1.5%	2.7%	4.0%
Clozaril	7.2%	6.6%	6.3%	4.6%
Conventionals	29.5%	21.8%	17.5%	6.3%
Avg. Price/Day**				12.7%
RISPERDAL	\$5.71	\$6.04	\$6.33	
Zyprexa	\$10.36	\$10.88	\$10.85	N/A
Seroquel	\$6.81	\$6.41	\$6.91	N/A
Geodon+	N/A	\$8.55	\$8.73	N/A
Clozaril	N/A	N/A	N/A	N/A
Conventionals	N/A	N/A	N/A	N/A

*YTD Aug 2002 - Dollar; YTD Sept 2002 - Prescriptions; / **AWP & NDTI MAT 6/02

*Caution: Limited Sample Size

Competitive Overview:

Brand	Launch Date	Indication	Efficacy or Safety Advantages	Formulations	Patent Expiration
Zyprexa	2000	• Zydys • Acute Bipolar • Maintenance	1. High product focused investments in promotional segments. 2. Perceived as "EPS-free". 3. Opinion Leader support 4. Zydys (rapidly dissolving formulation) 5. Focused corporate effort and positioning with aggressive marketing and share of voice	Tabs, Zydys (rapid dissolving)	2011
	2003	• Acute IM • Bipolar Maintenance	1. Fast onset of action	IM	2011
	2004	• Bipolar Depression (OFC)	1. Low EPS 2. Greater efficacy vs. SSRI monotherapy 3. Only APS with Bipolar maintenance and depression claims in combination		2011
	2005	• Bipolar Depression (monotherapy) • Dementia Depot 4wk	1. First agent to demonstrate utility in for both depression and mania in bipolar as monotherapy 2. TBD	Tabs Tabs Depot	2011
	2006	• TRD (Zyp-Zac)	1. Superior efficacy vs SSRI monotherapy		
Seroquel	2000	• Schizo Label Restriction	1. No EPS 2. Safety across the entire dose range, sedation, safe in PD/LBD	Tabs	
	2004	• Bipolar Mania • QD Tablet	1. Minimal EPS 2. Convenience	Tabs	
Geodon	2001	• Launch	1. No weight gain 2. No effect on Triglycerides	Tabs	
	2002	• IM Agitation	1. Faster onset of action	IM	
	2005	• Bipolar Mania	1. No weight gain	Tabs	
Abilify	2002	• Launch	1. 2nd Generation – Efficacy without safety concerns	Tabs	
	2005	• Acute Mania	1. Favorable side effect profile	Tabs	

COMPETITIVE SPENDING

3

	<u>Sales Force Contacts</u>		<u>Samples Extended Units (000)s</u>		<u>Journal (\$)</u>	
	2001	YTD Aug 2002	2001	YTD Aug 2002	2001	YTD Sep 2002
RISPERDAL	214,279	197,141	11,884	10,639	\$215	\$165
Zyprexa	358,473	386,887	17,452	17,259	\$400	\$195
Seroquel	156,550	132,804	13,746	13,554	\$217	\$209
Geodon	179,019	151,333	15,621	12,688	\$161	\$108

SALES FORCE COVERAGE

4

2003 Sales Force Promotion:

	Quarter 1	Quarter 2	Quarter 3	Quarter 4
Target Group (decile # physicians) 500 B/G	36,211 (10x/rep) (APS 02-90/PPI 20-90)	36,211	36,211	36,211
CNS	18,285 (20X/Rep APS 4-9 & 10X/Rep APS 2-3)	18,285	18,285	18,285
340	0	0	0	0
EC	37,183 (10x APS 10-90)	37,183	37,183	37,183
Hospital SF	N/A	N/A	N/A	N/A
Call Frequency (monthly, etc)				
Product Position (decile # physicians)* 500 B/G	REDACTED/Risp or RED Risp/RED Risp/REDACTED	REDACTED/Risp or RED Risp/RED Risp/REDACTED	REDACTED/Risp or RED Risp/RED Risp/REDACTED	REDACTED/Risp or RED Risp/RED Risp/REDACTED
CNS	N/A	N/A	N/A	N/A
340	Risp/REDACTED	Risp/REDACTED	Risp/REDACTED	Risp/REDACTED
EC	RED/Risp/REDACTED	RED/Risp/REDACTED	RED/Risp/REDACTED	RED/Risp/REDACTED
Hospital SF				
Total # Calls/PDEs (decile # physicians)* 500 B/G	128,865/27,765	146,410/59,290	181,492/73,712	181,492/73,712
CNS	235,530/235,530	235,530/235,530	235,530/235,530	235,530/235,530
340	0	0	0	0
EC	91,566/85,004	91,566/85,004	91,566/85,004	91,566/85,004
Hospital SF	31,196/16,638	31,196/16,638	31,196/16,638	31,196/16,638
Total Calls/PDES	487,157/364,937	504,702/396,462	539,784/410,884	539,784/410,884
Cost of Sales (\$M) (non-PME)		\$59,984,980 1 st qtr \$61,907,912 2 nd qtr	\$65,752,899	\$65,752,899

2003 Promotion Cycles:

EC RIS REDACTED	HSR REM REDACTED RED	Primary Care ACX REDACTED RED	CNS-M & L RIS/CON	CNS-I RIS/RED/CON
• 283 Reps • 366,265 Calls • 340,014 PDEs	• 106 Reps • 124,782 Calls • 66,551 PDEs	• 1,500 Reps • 483,977 Calls • 196,564 PDEs	• 494 Reps • 814,784 Calls • 814,784 PDEs	• 76 Reps • 127,336 Calls • 127,336 PDEs

Total Reps XX**Total Calls XX*****Total PDEs XX***

LILLY Zyprexa	ASTRA/ZENECA Seroquel	PFIZER Geodon	NOVARTIS Clozaril	BMS Abilify
• 1,400 Reps • 2,227,752 Calls • 1,934,524 PDEs • 34% SOV	• 820 Reps • 1,253,739 Calls • 689,593 PDEs • 12% SOV	• 1,251 Reps • 1,346,653 Calls • 876,826 PDEs • 15% SOV	• 45 Reps • 35,667 Calls • 35,677 PDEs • 1% SOV	• 650+ Reps • 967,920 Calls • 967,920 PDEs • 17% SOV

*95% Efficiency Factor Applied

STRATEGIC CUSTOMER SEGMENTS

5

	Still
MCO	
Segment Overview	PBM lives under management continue to grow, with PBMs currently managing prescriptions for about 170 million Americans¹. 93% of lives enrolled in third party plans receive benefits through a PBM. It is estimated that approximately 53% of the total PBM beneficiaries are subjected to a significant degree of formulary controls as PBM's move more toward three tier co-pays². This segment continues to consolidate with the top three PBMs accounting for 90% of the lives. PBM's are looking for ways to diversify their revenue sources through entrance into state Medicaid pharmacy management, offering services to pharmaceutical manufacturers, mail order opportunities and Internet/e-business solutions. Total managed Medicaid enrollment is approximately 21 million and remaining essentially flat. The leveling off of enrollment is due in part to changes in eligibility requirements enacted by state legislators. In the future, managed Medicaid enrollment is expected to grow, in part due to the requirement by many states that Medicaid participants enroll in managed care plans and the softening in the economy.
Key Issues	• Weakness in compliance and persistency among patients. • However, due to increasing costs and declining government reimbursement, many managed Medicaid programs are looking for ways to reduce their costs, such as restricting formulary access.
2003 Objectives	• Provide clinical information to physicians and improve patient compliance and persistency with RISPERDAL. • Obtain preferred formulary position and drive RISPERDAL market share at regional managed Medicaid accounts.
2003 Plans	• Compliance and persistency patient mailings through PBMs. • Leverage Medical Affairs' APS cost models, support mailings, and provider communication to assist plans with guideline implementation and/or formulary notifications.
Spending (\$M)	\$1.48 million (combined LTC/MCO RISPERDAL PME spend)

¹ Health Industries Research Center, National Accounts Fall/Winter 2002

² Health Industries Research Center, National Accounts Fall/Winter 2002

VHA/DoD	
Segment Overview	The Federal sector medical delivery system is one of the largest and most developed managed care systems in the United States. There are approximately 27 million veterans (15 million of whom are eligible for government medical care) and the Veterans Health Administration (VHA) will dispense in excess of 80 million prescriptions in 2003. The Department of Defense (DoD) has 8.2 million active duty, dependents and retirees eligible for health care. The DoD's Pharmacoeconomic Center develops and maintains the Basic Core Formulary, which is mandatory for all DoD centers. A separate mail order formulary is managed by Merck-Medco. Janssen secured the RISPERDAL market share leadership position within the VHA in July 2002, and September YTD figures show a 3.1% increase in net sales for a total of \$48.2 million. DoD sales also increased by \$4.7 million. Janssen has implemented a blanket purchase agreement for RISPERDAL incenting high market share. In addition, Janssen has designed and implemented a VHA specific Advisory Board in support of the CNS franchise.
Key Issues	• Maximizing RISPERDAL's co-first line choice (with Seroquel) on the VHA's atypical guidelines to ensure that RISPERDAL is the primary agent (pull through, etc.) • Ability to blunt competition from Seroquel • Utilization of RISPERDAL clinical, economic and outcomes data
2003 Objectives	• Sustain RISPERDAL market share leadership within the VHA • Facilitate rapid contract/formulary availability of CONSTA upon launch across all customer segments
2003 Plans	• Provide pull through and support activities for RISPERDAL per the VHA atypical guidelines • Support a VHA/Federal Advisory Board relative to RISPERDAL to solicit feedback on how best to support their atypical guidelines and identify customer positioning of CONSTA. • Identify key opinion leaders and formulary influencers that can be an effective support mechanism for rapid approval and update of CONSTA.
Spending (\$M)	

Medicaid	
Segment Overview	State Medicaid programs cover over 36 million low-income Americans and represent a major payment source for RISPERDAL prescriptions (\$673MM in annual sales). Public sector segments such as Medicaid have been under tremendous budgetary pressures over the past two years due to economic stagnation and growing pharmacy expenditures. As a result, these customers are moving towards new approaches in managing drug benefits to reduce pharmacy spend. These approaches include preferred drug lists, utilization controls and increased focus on reducing prices. A large majority of states have already passed legislation allowing the creation of preferred drug lists (typically based on acquisition cost, supplemental rebates, or reference based pricing). PhRMA and J&J/Janssen continue to fight against these restricted formulary approaches and price controls, while Janssen attempts to solidify product positioning against competition (particularly with RISPERDAL, among others). As opposed to products in commodity drug classes (i.e., Adphex), RISPERDAL may be well positioned to gain preferred status in some states. While typically a protected class with powerful advocacy groups, the growth of antipsychotics combined with budgetary constraints is driving state level restrictions. As evidence, Kentucky Medicaid recently placed Zyprexa under prior authorization. However, while RISPERDAL may be at an advantage, these controls may present a challenge for CONSTA (if priced at a premium).
Key Issues	• Evolution of state formulary management • Ability to maximize favorable first-line positions • Pull through capability • Medicaid reaction to CONSTA launch
2003 Objectives	• Protect and grow \$673MM in RISPERDAL sales • Implement a proactive strategy to review unique advantages of RISPERDAL with high-risk states • Leverage outcomes/clinical studies to demonstrate value in lieu of discounts • Partner with J&J Government Affairs to influence legislative and lobbying activities (consistent equal access/preference message)
2003 Plans	• Provide customized RISPERDAL presentations to high-risk states • Utilize RISPERDAL cost and clinical advantages, as well as contracting, to commit customers to RISPERDAL • Leverage new Medicaid/state teams to minimize access barriers and maximize pull through opportunities • Implement PE learnings to maximize pull through opportunities within "advantaged" states

LIFE CYCLE PLAN

6

Life Cycle Strategy:

To be incorporated

Life Cycle Plans:

Opportunities (Phase IV Studies, Line Extensions, Claims, Indications, Outcomes Research)	Rationale/Unmet Need	Submission Ready Publication Date	Est. Cost
BIPOLAR: Launch 2004			
RIS-IND-2: Bipolar: RIS Vs. Placebo monotherapy 3 week acute	Drive short-term growth via efficacy in mood	4Q02	
RIS_USA-239: Bipolar: RIS Vs. Placebo monotherapy 3 week acute	Drive short-term growth via efficacy in mood	4Q02	
RIS-INT-69: Bipolar: RIS Vs. HAL Vs. Placebo Monotherapy 3 week acute with 9 week maintenance	Drive short-term growth via efficacy in mood	2Q03	
RIS-INT-81: Bipolar: OL extension 9 weeks to USA-239 and IND-2	Drive short-term growth via efficacy in mood	2Q03	
RIS-USA-240: Bipolar: RIS Vs. Valproate Vs. Placebo monotherapy 3 week acute	Drive short-term growth via efficacy in mood	NA	
RIS-USA-241: Bipolar: 9 week open label follow up to USA-240	Drive short-term growth via efficacy in mood	NA	

Opportunities (Phase IV Studies, Line Extensions, Claims, Indications, Outcomes Research)	Rationale/Unmet Need	Submission Ready Publication Date	Est. Cost
BEHAVIORS & PSYCHOTIC SYMPTOMS IN DEMENTIA: Launch 2005			
RIS-INT-232: PAD: Psychoses in Alzheimer's Disease	Long-term Growth	3Q03	

Opportunities (Phase IV Studies, Line Extensions, Claims, Indications, Outcomes Research)	Rationale/Unmet Need	Submission Ready Publication Date	Est. Cost
REDACTED			

Opportunities (Phase IV Studies, Line Extensions, Claims, Indications, Outcomes Research)	Rationale/Unmet Need	Submission Ready Publication Date	Est. Cost
REDACTED			
RIS-USA-250: SCH: OLA to RIS Switch Study – Double blind switch via 3 protocols; extensive metabolic parameters measured as well	Solidify Market Leadership	4Q03	
REDACTED			
RIS-USA-T299: (EMRP) Dog Study: EMRP RIS Vs. OLA for diabetes	Solidify Market Leadership	2Q03	
RIS-SCP-402: HTH: A randomized, double blind comparison of the safety and efficacy of Risperidone Vs. Quetiapine in hospitalized patients with an acute exacerbation of schizophrenia	Solidify Market Leadership	2Q04	
RIS-Unassigned: HTH: A randomized, double blind placebo controlled comparison of the safety and efficacy of Risperidone and Aripiprazole and placebo in patients with schizophrenia or schizoaffective disorders and prominent anxio-depressive symptoms	Solidify Market Leadership	1Q05(acute) 3Q05 (chronic)	

Issues:

To be incorporated

RISPERDAL Oral MARKET RESEARCH PLAN

7

Key Research Areas:

- 1) Solidify market leadership
 - Customer segmentation
 - Regional message tracking
 - LTC Market assessment study
- 2) Positioning/Promotional Message Development
 - Positioning statement selection
 - Journal Ad/Sales aid development for mood and anxiety symptoms of schizophrenia
- 3) Competitive understanding
 - Track Abilify launch
 - Development of tactical messages targeted at diabetes/DKA, Seroquel, Abilify; and overcome EPS perceptions

Cross-Strategy Projects:

Program	Objective	Target	Timing (start)
Antipsychotic Annual Tracking Study	Evaluate attribute importance and APS product perceptions (brand image & positioning)		Q2 2003 (MT)
Customer Segmentation Study	Determine potential APS segments based on behavioral, attitudinal, demographic, and psychographic assessment of physicians		Q1 2003 (S)
CNS / PCP Message Tracking	Evaluate effectiveness of key sales messages delivered for RISPERDAL and competitive APS (National & Regional CNS)		Cycle I,II,III 2003 (CA)
APS Quarterly Tactical Assessment	Routinely track key perceptions and practice within APS market and address relevant tactical questions in timely and cost efficient manner		Qrtly 2003 (MT)
CNS Company Image Study	Assess Janssen/J&J Image in clinical research, development, and marketing within CNS category		Q3 2003 (CA)
PCP Antipsychotic Market Assessment	Wave II of market assessment research for broad PCP/APS market. Assess competitive strategies for PCP promotion.		Q2 2003 (MT)
Seroquel Heavy Users Exploratory Research	Assess physicians motivations for starting, switching, adding Seroquel therapy		Q1 2003 (CA)
Diabetes Advertorial Development	Develop impactful message to communicate relevant risks of diabetes with atypical APS for journal ad placement		Q1 2003 (PP)
Diabetes Promotional Material Testing	Develop appropriate promotional message to deliver importance of diabetes risk with APS		Q2 2003 (PP)
RISPERDAL Hi/Lo Share EPS Exploratory Res.	Assess physician strategies to avoid and/or manage development of EPS with RISPERDAL		Q1 2003 (S)
Atypical Safety Perceptions	Refine knowledge of physician segmentation of APS on safety dimension. Provide input for safety marketing strategies and tactics		Q2 2003 (MT)
Seroquel Message Development	Continuation of development work to provide field deliverable of Seroquel specific message		Q2 2003 (PP)

Solidify Market Leadership - Strengthen #1 Position LTC/EC:

Program	Objective	Target	Timing (start)
QuickSolv Post-Launch A&U	Track uptake and perceptions of RISPERDAL ODT by targeting segment		Q1 2003 (MT)
CVA Assessment / Response Testing	Track competitive efforts and physician reaction to Canadian CVA letter		Q1 2003 (MT)
LTC Market Assessment / Landscape Study	Qualitative/quantitative market assessment to determine key influencers, market drivers, and product perceptions in critical LTC marketplace		Q1 2003 (ME)

Drive Short-Term Growth via Efficacy in Mood – Establish Mood Efficacy in Schizophrenia:

Program	Objective	Target	Timing (start)
RISPERDAL Creative Concept Development	Qualitatively assess concepts for new RISPERDAL promotional campaign (started 4Q 2002)		1Q 2003 (PP)
RISPERDAL M&A Message Testing	Evaluate Mood and Anxiety in Schizophrenia promotional messages for CNS and PCP Audiences		1Q 2003 (PP)
RISPERDAL Sales Aid Development	Test content, layout and flow of 2nd Cycle sales aid (CNS & PCP)		1Q-2Q 2003 (PP)
RISPERDAL Journal Ad Development	Qualitatively assess journal ad for M&A promotional campaign		1Q 2003 (PP)
RISPERDAL Journal Ad Quant. Tip-In Testing	Quantitative tip-in test to evaluate effectiveness of journal ad		1Q 2003 (PP)
RISPERDAL Low Dose Strategy Assessment	Qualitatively evaluate low dose strategy in treating M&A symptoms of Schizophrenia		1Q 2003 (ME)

Drive Short-Term Growth via Efficacy in Mood: - Prepare Market for Bipolar Launch:

Program	Objective	Target	Timing (start)
Bipolar Message Development	Assess importance and impact of bipolar message elements with PCPs & Psychs		Q1 2003 (PP)
Bipolar Journal Ad Development	Develop RISPERDAL bipolar launch journal ad		Q3 2003 (PP)
Bipolar Journal Ad Tip In	Quantify stopping power, recall, and effectiveness of Journal Ad		Q3 2003 (PP)
Promotion Materials/Sales Aid Development	Develop RISPERDAL bipolar sales aid		Q4 2003 (PP)
Bipolar Continuous Online Panel	Bipolar market assessment and pre-launch awareness		Q4 2003 (MT)

Long-Term Growth – Child & Adolescent, Dementia:

Program	Objective	Target	Timing (start)
Non-Depot User Potential	Assess potential for RISPERDAL CONSTA use in non depot target physicians		Q3 2003 (ME)

LIFE CYCLE DEVELOPMENT PLANS

9

- **Bipolar Pre-Launch Plan**
- **QuickSolv Launch Plan**
- **Child & Adolescent Market Segment**

RISPERDAL®

Bipolar Pre-Launch Plan

2003 Business Plan Summary

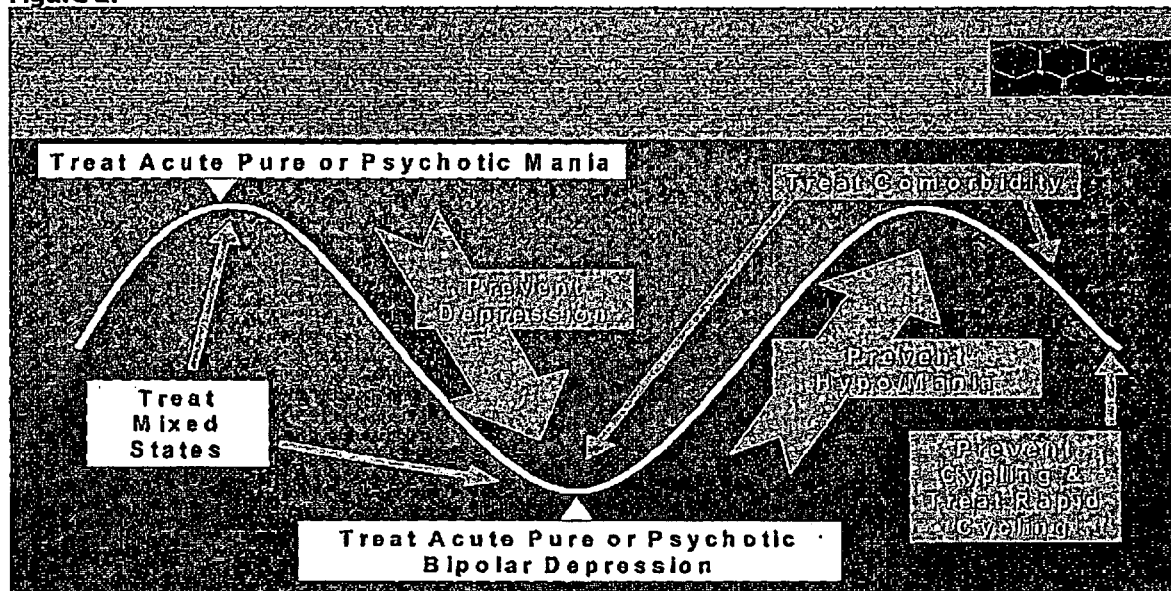
Table of Contents

RISPERDAL – Bipolar

- I. Situation Diagnostic/Analysis
- II. SWOT Analysis/Key Issues
- III. Pre-launch Objectives
- IV. Key Business Strategies
- V. Key Programs and Tactics
- VI. Budget Summary
- VII. Success Predictors

I. SITUATION DIAGNOSTIC/ANALYSIS:**Disease Overview:**

Up to 50% of patients with bipolar disorder attempt suicide (Jamison 2000) and it is estimated that 10% to 15% of these attempts are successful (Tondo 2000). This is the dire reality of bipolar disorder; a devastating brain disease characterized by drastic swings in mood, energy, and functional ability. Bipolar disorder is estimated to affect nearly 3.4% of the US population at some point in their lives (Hirschfeld 2002). The distinguishing feature of bipolar disorder compared to other psychiatric disorders, according to DSM-IV-TR, is that a patient must have had at least one episode of mania. The complexity of this disorder stems from the multiple phases of the disease (including mania, hypomania, mixed, depression and euthymia), the high incidence of comorbid conditions associated with bipolar disorder and the multi-faceted treatments objectives (see figure 1)

Figure 1:

Because bipolar disorder patients are most likely to present during their depressive phase, it is not surprising that almost 70% of bipolar patients are initially misdiagnosed and approximately 35% of bipolar patients wait 10 years prior to receiving the correct diagnosis. According to the 2000 DBSA Survey, the most frequent misdiagnoses are: depression (60%), anxiety (26%), schizophrenia (18%), borderline personality disorder (17%) and substance abuse (14%). The high prevalence of co-morbidity of anxiety disorders (60-90%) and substance abuse (60%) often masks the underlying disorder and leads to the high rates of misdiagnosis. When bipolar patients finally receive the correct diagnosis of bipolar disorder, the most common phase of presentation is a mixed state (28%) and bipolar NOS (26%), which is described as a less severe mixed state. Mania, depression, hypomania and euthymia represent 18%, 17%, 8% and 3% of bipolar diagnoses, respectively (Marketscan 1998-2000).

Bipolar patients come from diverse socioeconomic backgrounds. However, the majority of patients are higher functioning patients (compared to schizophrenics) as evidenced by the greater than 60% contribution of third party payor prescriptions to total bipolar prescriptions (Get source from Dennis M.) These higher functioning patients are also highly motivated and persistent in seeking education and treatment for their disorder because of the significant negative impact the disorder has on their lives.

Bipolar disorder was ranked as the sixth leading cause of disability worldwide by the World Health Organization's 1996 *Global Burden of Disease* report and imposes significant emotional and economic burdens on patients and loved ones. Patients suffering from bipolar disorder are likely to experience:

- Chronic illness: fewer periods of remission than other affective disorders;
- Major deterioration in quality of life (QOL) and level of functioning (job productivity and relationships);
- Manic symptoms are destructive, both financially and socially;
- Repeated depression may promote cognitive and social deficits;
- Increased divorce rates (three-fold higher than in general population) ; and
- Considerable demands placed on healthcare resources.

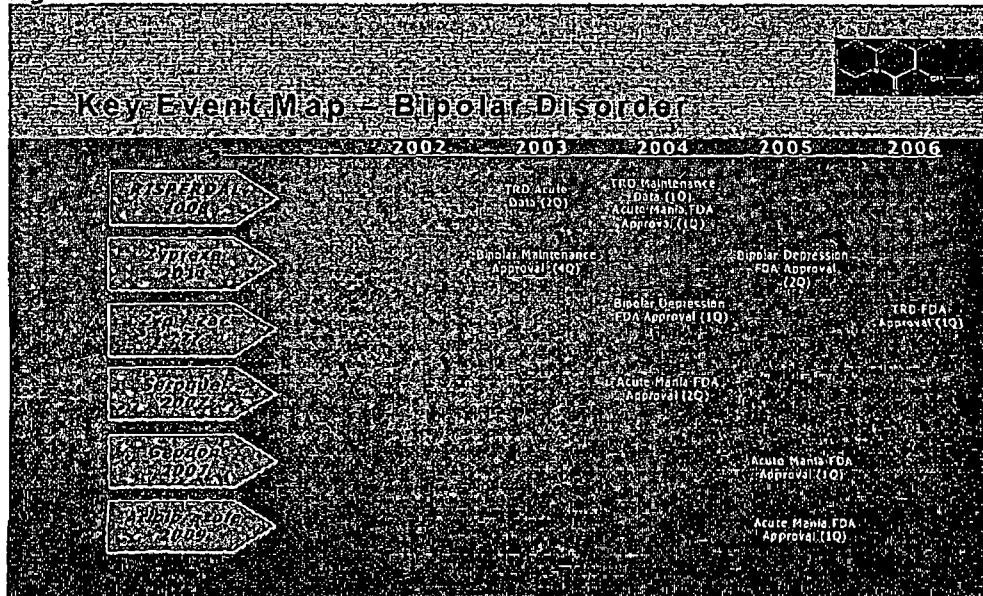
Market Overview:

In all phases of bipolar disorder, antipsychotics represent about 20% of treatment, AEDs represent about 31%, antidepressants 28%, and lithium comprises 14% of drug use (NDTI MAT 9/02). In general, the bipolar market is highly dissatisfied as evidenced by the fact that over three-quarters of treated patients are prescribed some form of combination pharmacotherapy and over 40% are taking three or more medications at any given point in time (Adelphi - 2002). However, using longitudinal databases that span one year or greater, nearly 100% of patients are on combination therapy during any given 12 month period.

Psychiatrists contribute approximately 84% of the total prescriptions in the bipolar market with the balance relegated to primary care physicians (NDTI, MAT 9/02). However, primary care physicians are becoming more comfortable treating bipolar disorder as illustrated by a more rapid growth rate compared to psychiatry (103% versus 67%). Physicians identify onset of action, demonstrated efficacy treating mania and depression and relapse prevention as the most important drivers (and areas of improvement) for treating bipolar disorder.

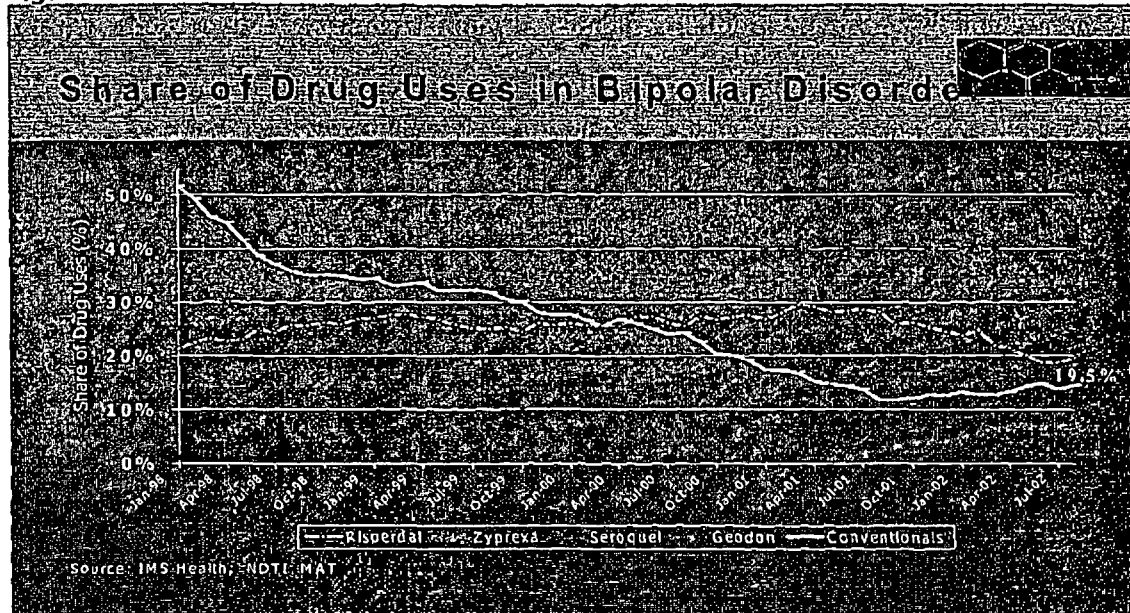
Overall, antipsychotics are utilized in over half of all bipolar patients (53% - Adelphi 2002). The greatest penetration rate for antipsychotics for bipolar disorder is in the **acute mania** phase where approximately 83% of patients receive an antipsychotic (up from 70% in 2001), predominantly as adjunctive therapy to a traditional mood stabilizer. Antipsychotics are also used in nearly two-thirds of **mixed** patients which are the majority of patients. The antipsychotic may be continued (with a mood stabilizer) in the **maintenance** phase of treatment in about 46% of patients.

Bipolar disorder prescriptions contributed to over 22% of the total atypical prescriptions and grew over 30% in absolute terms (NDTI, MAT 8/2002). Zyprexa remains the *only* atypical antipsychotic indicated for the short-term treatment of acute mania. However, RISPERDAL will be the next atypical to receive a bipolar indication with a targeted FDA approval of 1Q04. Seroquel, Geodon and aripiprazole have regulatory development plans in place to pursue an acute mania indication, as well and their respective approvals are projected within one year of each other (2Q04 - 1Q05). In addition to acute mania, Zyprexa, in combination with fluoxetine, is expected to receive approval for bipolar maintenance during 4Q03 and bipolar depression in 1Q04. Increased focus by all the atypicals in 2003 and the imminent indications to follow in 2004 will drive the growth of the atypicals by expanding atypical penetration across all phases of bipolar disorder; resulting in bipolar disorder becoming the largest segment within the atypical market.

Figure 2:

Competitive Overview:

Among antipsychotics, RISPERDAL's share of bipolar patients is 19.5% versus Zyprexa's share of 35.3%, Seroquel's share of 22.6% and Geodon's share of 7.2%. Zyprexa share of bipolar disorder peaked at 41.9% a year ago and has dropped 6.6% since, while both Seroquel and Geodon have grown their share by 5.4% and 4.0%, respectively. RISPERDAL's market share has declined 6.3% over the same time period.

Figure 3:

The competitive landscape of the bipolar market segment will shift dramatically from today's environment as existing competitors expand their indications and new competitors enter the marketplace. Zyprexa has an extensive clinical development program in place that is expected to generate an approval for bipolar maintenance in 2003 and bipolar depression in 2004. In mania, Lilly has aggressively targeted Depakote head-to-head in clinical trials and sales promotion, and is expected to continue to position Zyprexa as a more effective agent with a faster onset of action and a better tolerated 'mood stabilizer' that can be used in all phases of bipolar disorder. As the market leader, Lilly is investing in a "non-branded" direct to consumer campaign to expand the bipolar market while developing strong relationships among existing patients to build brand loyalty.

Seroquel and Geodon are expected to receive acute mania indications in 2004. AstraZeneca is nearing completion of Seroquel's bipolar development program which will likely lead to an indication for acute mania associated with bipolar I disorder as both monotherapy and adjunctive therapy. Additionally, Pfizer is expected to leverage their distinction as the only atypical to offer an IM formulation to more fully penetrate the bipolar market through the institutional setting. Moreover, the launch of aripiprazole as the next generation atypical with inherent mood properties and the introduction of lamotrigine for bipolar depression will increase the complexities of the marketplace and impose additional challenges that we must effectively and efficiently navigate to ensure a success launch for RISPERDAL in bipolar disorder.

2002 Key Lessons Learned:

- The competition has been able to negatively position RISPERDAL in bipolar disorder due to our lack of focus on the mood and anxiety segment
- The bipolar market is responsive to positive differentiation through publications of well controlled clinical trials
- A Consistent, focused core message in medical education and publications is required to increase awareness levels of RISPERDAL's utility for treating bipolar disorder
- Ability to reduce anxiety and demonstrated improvement of sleep are important characteristics for treating acute mania
- Combination therapy remains the mainstay treatment regimen for bipolar disorder
- Primary care is becoming an increasingly important customer segment in mood and anxiety representing 1/3 of the growth in this segment

Although the competitive environment will be fierce over the next two years, the imminent approval of RISPERDAL for the treatment of bipolar disorder represents a significant opportunity for RISPERDAL to extend the growth phase of the product life cycle curve and maximize product penetration into the rapidly expanding mood and anxiety segment. Establishing an efficacy platform in mood and anxiety symptoms associated with schizophrenia, coupled with a comprehensive bipolar pre-launch campaign in 2003, will strengthen the core positioning of RISPERDAL and facilitate uptake of RISPERDAL in bipolar disorder upon approval.

II. SWOT ANALYSIS, KEY ISSUES:

Strengths	Weaknesses
☐ First agent to be approved for the treatment of bipolar disorder as monotherapy and adjunctive therapy ☐ Favorable long-term safety profile (weight, somnolence, diabetes, QTc, TD) ☐ Efficacy in bipolar disorder in terms of onset of action and overall response rates ☐ Broadest dossier in anxiety disorders compared to other atypicals	☐ No bipolar indication – sales force unable to promote ☐ Indication / data gap vs. competitors in bipolar disorder (Zyprexa – bipolar maintenance, ZYP/ZAC – bipolar depression, Depakote – bipolar maintenance) ☐ Competitor profiles are seen as more appropriate for treating bipolar disorder (sedation as a desirable side effect – Zyprexa and Seroquel) ☐ High rates of EPS observed in clinical trials
Opportunities	Threats
☐ FDAMA data dissemination ☐ High prevalence of co-morbid anxiety and substance abuse associated with bipolar disorder ☐ Bipolar maintenance data with CONSTA ☐ Expanding use of atypicals by primary care physicians for bipolar disorder (maintenance) ☐ Leverage weight liability of Zyprexa in combination with mood stabilizers ☐ Strong data in mixed patients which represent the largest treatment segment	☐ Diabetes becomes a class effect and is an issue for use of all atypicals in bipolar disorder ☐ Growth of other drug classes outside of atypicals for treating bipolar disorder ☐ Launch of lamotrigine and Zyp/Zac for bipolar depression minimize importance of controlling/preventing mania relapse ☐ Geodon / Zyprexa IM use in ER (institutions) to control mania leads to increased use of Geodon/ Zyprexa orals in the community

Key Issues:

- Increasingly competitive and evolving marketplace
- Sub optimal product differentiation
 - Driven by the competition
 - Limited scientific data to support long-term safety in bipolar disorder
- Life cycle management: late stage of lifecycle limits investment opportunities

III. PRE-LAUNCH OBJECTIVES:

The overall effectiveness of the RISPERDAL bipolar pre-launch campaign will determine RISPERDAL's ability to effectively challenge for market leadership in the bipolar segment. Success will be measured along the following dimensions:

- 75% awareness levels of RISPERDAL bipolar data;
- Redefinition of most influential attribute set within the bipolar market; and
- Identification and alignment of Key National and Regional Opinion Leaders.

IV. KEY BUSINESS STRATEGIES:

CORE STRATEGIES	
☐	Build and Broaden KOL Relationships
☐	Expand Key Drivers for Treating Bipolar Disorder
☐	Differentiate RISPERDAL from the competition in bipolar disorder
☐	Solidify communication platform with clinical data

Core Strategies:**1. Build and broaden KOL relationships**

Alignment, support and involvement of national and regional opinion leaders in the bipolar segment of RISPERDAL will drive product uptake for bipolar disorder among high prescribers throughout the pre and post approval phases. National KOLs will assist the marketing team to identify segments of the market to develop and exploit; ensuring RISPERDAL is differentiable and marketable upon introduction for bipolar disorder.

Regional KOLs play a vital role throughout late stage development, launch and marketing phases of the development process. Regional KOLs have a two dimensional relationship (technical and personal) with the high users and influencers within our target customer population, resulting in a highest degree of impact and sustainability of their prescribing recommendations and guidelines within the community. Strong relationships between Janssen and regional KOLs will increase awareness of RISPERDAL bipolar data among our target audience and proactively shape their product perceptions of RISPERDAL for the treatment of bipolar.

2. Expand key drivers for treating bipolar disorder

Lilly has fully capitalized on being the first atypical approved for the treatment of bipolar disorder and has built a strong franchise for Zyprexa in the mood and anxiety segment. As the market leader, Lilly has established the key product attributes that currently drive prescribing decisions for bipolar patients. The data supporting Zyprexa along these key attributes is quite robust and continues to build with time. Future market entrants in bipolar will be measured along these attributes and the current critical contingencies are not optimally aligned with RISPERDAL's strengths.

Rather than launch with a "frontal attack" and compete on Lilly's terms, RISPERDAL will employ a "flanking attack" strategy and change the dimensions of the marketplace. Although the key attributes that Lilly established will remain important, a major focus of the RISPERDAL Bipolar Pre-Launch Plan is to expand the drivers for treating bipolar to include those that are aligned with RISPERDAL's strengths:

- Remission as a definition of response;
- Demonstrated efficacy as both monotherapy and adjunctive therapy;
- Onset of action; and
- Complete relief of the symptoms of bipolar disorder and the associated co-morbidities (anxiety).

3. Differentiate RISPERDAL from the competition in bipolar disorder**Communication Platform**

The communication platform for RISPERDAL in bipolar disorder will be distinct, differentiable and believable and strengthen the core positioning of RISPERDAL. The platform will leverage the RISPERDAL heritage, the inherent strengths of the RISPERDAL bipolar data and focus on exploiting large untapped market segments. The communication platforms that are currently being tested in market research are:

- RISPERDAL provides the quickest control of bipolar symptoms;
- RISPERDAL effectively treats the spectrum of symptoms associated with bipolar disorder and related co-morbidities;
- RISPERDAL, alone or as adjunctive therapy, is proven to control bipolar symptoms;
- RISPERDAL is the one to trust for the complete relief of bipolar disorder and its associated symptoms in mixed patients; and
- RISPERDAL enables bipolar patients to function better today, tomorrow, and in the days after.

4. Solidify communication platform with clinical data

The RISPERDAL bipolar communication platform is being developed primarily based upon the acute mania pivotal trial data. However, to treat the entire bipolar patient an agent must demonstrate the ability to control the acute symptoms as well as prevention of relapse into mania or depression. Controlled data in bipolar maintenance is a significant gap in the RISPERDAL bipolar dossier and must be addressed. In the short-term, leveraging retrospective database analyses and open label trials comparing RISPERDAL to other atypicals will fill the data need to demonstrate RISPERDAL's utility as maintenance treatment for bipolar disorder. Over the long-term, an investment in a regulatory quality bipolar maintenance trial with RISPERDAL CONSTA will firmly establish the RISPERDAL franchise as a dominant player in the bipolar segment.

V. KEY PROGRAMS AND TACTICS:

The tactical component of the pre-launch plan will integrate lessons learned across the brand in 2002 and build on the momentum generated by the publication of RIS-USA-102 establishing RISPERDAL's effectiveness in combination with a mood stabilizer. The execution and rollout of the tactical plan will be very systematic with each phase of the plan inextricably linked to the prior phase.

Strategy #1: Build and broaden KOL relationships

National KOLs establish the guidelines for treating psychiatric disorders and shape pharmacological development by identifying unmet needs within the current armamentarium. In essence, national KOLs establish the agenda for the future direction of psychiatry. Regional KOLs drive this agenda forward due to their technical and personal influence over the high volume prescribing community. Identification, alignment and involvement of KOLs at both the national and regional levels are essential to the foundation of the RISPERDAL launch in bipolar disorder.

Identification:

ILIAD (Influence Leader Identification and Advocacy Development): Using influence mapping techniques, the ILIAD initiative will survey a stratified sample of high prescribing APS physicians within the CNS sales force structure to identify opinion leaders at both the national and regional level. The output of this survey will yield a list of 12 to 15 national KOLs and 120 regional KOLs and will serve as the core audience for all targeted KOL/advisory board initiatives.

Alignment and Involvement:

MAP-KOLs (Medical Affairs Partnership with KOLs): MAP-KOLs is a program conceived by the RISPERDAL CONSTA team that produced outstanding results in 2002. Through this initiative, each month one national opinion leader will be invited to the Janssen campus for an intensive, interactive feedback and idea generation session focusing on commercial and clinical development strategy for RISPERDAL in bipolar disorder.

Advisory Boards: National and Regional Advisory Boards are invaluable opportunities for the brand team to interact with customers to better understand their evolving needs, key market dynamics at the local and national levels, competitive activity and clinical issues/opportunities related to efficacy, safety and dosing.

KOL Portal: The KOL Portal is a communication platform that engages national and regional KOLs in a consultative capacity by soliciting their insights and feedback throughout the year to help Janssen address business challenges and better develop RISPERDAL, both clinically and commercially. Between eight and twelve times annually, the brand team will have the ability to draw on the knowledge of KOLs to gain their insights on pressing business issues including issues management, key messages for publications and review of promotional campaigns and have the ability to integrate KOL feedback prior to widespread dissemination.

KOL Summary Tactics	
Program	Volume
ILIAD	Identify 12-15 National KOLs and 120 Regional KOLs
Regional Advisory Mtgs (6)	120 office/clinic-based psychiatry KOLs
Psych National Advisory Mtg (2)	15 Top Tier Academic KOLs
KOL Portal	Enroll national and regional KOLs identified in ILIAD to participate (8 to 12 surveys throughout the year)

Strategy #2: Expand key drivers for treating bipolar disorder

The lack of focus by RISPERDAL on the mood and anxiety segment over the past two years has enabled the competition to negatively position RISPERDAL for only the most severe bipolar patients and mold the key drivers of the bipolar market segment to compliment their product strengths. To break out of the niche and more ubiquitously penetrate the bipolar market segment upon approval, we must redefine the set of key attributes that drive the prescribing decision for treating bipolar disorder.

Bipolar Options (Optimal Therapeutic Interventions of New Strategies):

The Bipolar Options program will be the largest and most comprehensive Initiative relating to the treatment of bipolar disorder in 2003 – similar in scope to the 2002 APA Treatment Guidelines. The objective of this initiative is to fully explore the treatment considerations that are paramount to the diagnosis and treatment of bipolar disorder and publish a set of consensus guidelines that will change the way physicians approach diagnosing and treating their bipolar patients. The program will be led by eight of the top minds in the bipolar field, collectively known as the Bipolar Institute. Each member of the Bipolar Institute will lead a working group of 20 Regional KOLS and focus on one of the following areas:

- Diagnosis Issues;
- Treatment course and duration (including onset of action);
- The advantages and key considerations of combination therapy;
- Defining treatment outcomes;
- The impact of co-morbidities; and
- Adolescent Bipolar Disorder – an economic and emotional burden.

Each working group will be tasked with developing guidelines for their respective areas and will be presented at the Bipolar Summit. All participants will be invited to attend the Bipolar Summit and hear the output from each of the other working groups. The proceedings of the Bipolar Summit will be endured and rolled out to community psychiatrists through:

- Publication;
- Satellite Broadcasts;
- 3 CME Newsletters;
- Audio-conferences; and
- Speakers Kit – each participant will be encouraged to present the findings at a grand rounds within their affiliated institutions.

The key areas of the bipolar options program that will compliment the RISPERDAL communication platform are the advantages and key considerations of combination therapy, defining treatment outcome and the impact of co-morbidities.

Bipolar Options Program Overview	
Program Component	Description
Bipolar Institute Roundtable	Members of Bipolar Institute identify areas of focus and define scope for each working group
Working Group Sessions	One member of bipolar institute leads working group of 20 Regional KOLs to explore topic area and develop treatment considerations pertaining to topic
Bipolar Summit	Proceedings of working group presented at large symposia
Enduring Materials	Publication, Audio-conference, CME Newsletter, audio-conference, Satellite Broadcasts and Speakers Kit developed for rollout to community psychiatrists

Strategy #3: Differentiate RISPERDAL from the competition for the treatment of bipolar

The objective of the Bipolar Options program is to change the dimensions of the bipolar market. From a product perspective, it is important to anticipate the evolving treatment paradigm and firmly differentiate RISPERDAL from the competition along the key drivers that will be influential in the prescribing decision in the future.

The medical education plan is designed to raise awareness of the utility of RISPERDAL for treating bipolar patients along the key attributes that are anticipated to drive prescribing decisions. The medical education plan is highlighted by the publications of RISPERDAL pivotal and supportive monotherapy and adjunctive therapy clinical trials in first tier psychiatry journals. The Janssen Sales Force will distribute these articles under FDAMA guidelines. Completing the Med Ed plan is a series of education programs broadcasted through a variety of appropriate venues targeting both psychiatrists and primary care. Key tactics are listed below:

Medical Education Plan Overview	
Program	Volume
RIS-USA-102 Reprints (FDAMA)	150k reprints (150/rep)
RIS-USA-239 Reprints (FDAMA)	150k reprints (150/rep)
RIS-IND-002 Reprints (FDAMA)	150k reprints (150/rep)
RIS-INT-81 (FDAMA)	150k reprints (150/rep)
CME Audio-conference	3 Programs (16 dates each)
CME Tele-topics	3 Programs (12 dates each)
CME Posterbooks	1 Program (10,000 books/program)
CME Satellite Broadcast	3 Programs
CME Case-based Program	2 Programs (monograph, audiotape, newsletter)
CME Audio Grand Rounds	1 Program (6 grand rounds sessions)
Primary Data Set Slide Kits	10 kits

Building on the Medical Education Plan will be fully integrated in a promotional platform that is distinctive, persuasive and believable. Upon approval, the communication platform will support the overall product position of RISPERDAL and extend the value proposition of the franchise by establishing efficacy in mood disorders. The promotional campaign will consist of:

- Journal Ad;
- Core Sales Aid;
- Reprint Carriers;
- File Card; and
- MOA Three Dimensional Demonstration/Flashcard.

Strategy #4: Solidify communication platform with clinical data

Critical tactical components of the pre-launch plan include generation of key data sets to support the RISPERDAL Bipolar communication platform. Data from Outcomes Research and EMRP trials are projected to be available in 2003 in the areas of bipolar depression, bipolar maintenance, mixed episodes and patient functioning to fill the gaps in the communication platform in the short-term. And over the long-term, an investment in a comparative bipolar maintenance trial will firmly establish the RISPERDAL franchise as a dominant player in the bipolar segment.

Bipolar Maintenance Clinical Experience Trial: The hypothesis that this trial will attempt to support is critical for physicians who treat bipolar disorder – RISPERDAL delivers significant improvement in reducing mood and anxiety symptoms and preventing relapse (defined as hospitalizations) as bipolar maintenance therapy compared to olanzapine and quetiapine over a six-month period. To demonstrate significance along the primary endpoint, a large sample size will be required. This phase IV trial will enroll 3,000 physicians (5 patients per site) for a total sample size of 15,000 patients.

VI. BUDGET SUMMARY:

PME Category	2002 PME (000)	Proposed 2003 PME (000)	Proposed 2003 PME (allocation)
Journal Advertising / Development	\$0	\$100	1.1%
Misc. Agency Fees	\$30	\$100	1.1%
Sales Aids/ Promotional Development	\$100	\$500	5.5%
Advisory Boards	\$1,600	\$1,600	18%
Grants	\$250	\$500	5.5%
Medical Education	\$3,770	\$5,500	61%
Literature	\$150	\$300	3.3%
Internet / Intranet	\$100	\$400	4.4%
Total	\$6,000	\$9,000	100%

VII. SUCCESS PREDICTORS:

The ability of RISPERDAL to effectively penetrate the bipolar market and challenge for market leadership will be determined by our ability to:

- Fully explore and analyze every angle of data strengths and weaknesses to maximize the impact of the data rollout;
- Redefine key drivers for treating bipolar patients (completeness of response, co-morbidity, etc);
- Develop distinct, persuasive and believable communication platform for RISPERDAL in bipolar disorder;
- Create a stable of thought leaders for message pull through; and
- Educate and prepare sales representatives/medical affairs.

RISPERDAL®

**RISPERDAL® QuickSolv Launch Plan
2003 Business Plan Summary**

Table of Contents

RISPERDAL QuickSolv

- I. Situation Diagnostic/Analysis
- II. SWOT Analysis, Key Issues
- III. Launch Objectives
- VI. Key Business Strategies
- VII. Key Programs and Tactics
- VIII. Success Predictors

**RISPERDAL® QuickSolv Launch Plan
2003 Business Plan Summary**

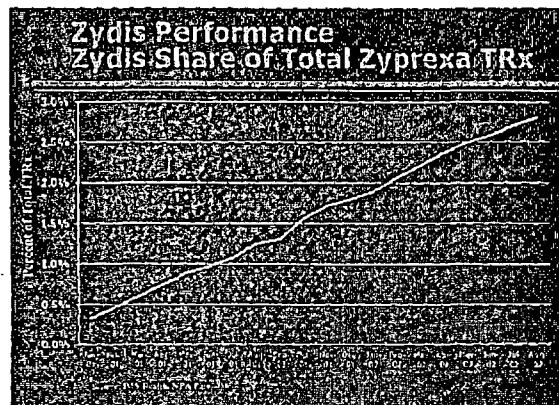
I. SITUATION DIAGNOSTIC/ANALYSIS:

Market Overview:

Zyprexa Zydys orally disintegrating tablet is the only fast dissolving formulation of an antipsychotic currently on the market. The formulation was launched by Lilly in September 2000, and has experienced a slow, limited adoption. Potential reasons for this modest uptake include a limited promotional effort, unclear marketing positioning, and pricing.

Despite the initial slow uptake, Zydys monthly TRx share has been steadily increasing and currently represents 3.1% of total Zyprexa prescriptions (Figure 1, IMS Health, September 2002). Projected sales for 2002 are estimated at \$100 million.

Figure 1:



RISPERDAL QuickSolv received an approvable letter on September 20, 2002. It is currently projected that it will be launched late 1Q03. The initial launch dosage strengths will consist of a 0.5 mg, 1 mg, and 2 mg tablet. A 3 mg and 4 mg tablet are in development and are estimated to launch 3Q04. From a financial perspective, there is incentive to maximize our conversion over to QuickSolv from RISPERDAL traditional tablets. QuickSolv has a 30% higher gross profit margin over traditional tablets due to the CPI penalty savings and price (assumed at 20%).

Customer Segment Overview:

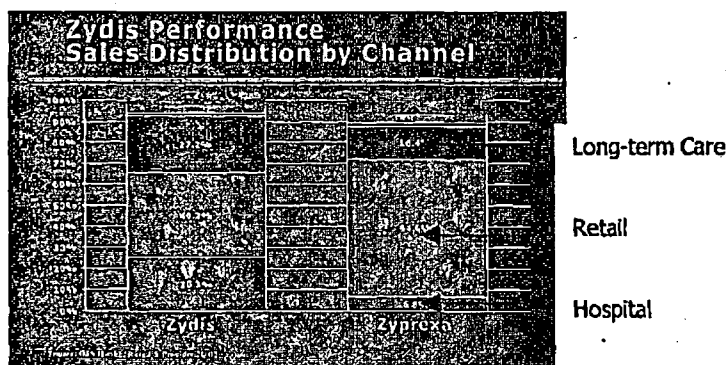
Qualitative and quantitative market research has determined that physicians generally view fast dissolving formulations as a niche product for patients who can't or won't swallow. Nevertheless, clinicians welcome new formulations because they offer greater flexibility and choice when treating their patients. Physicians claim that the availability of a fast dissolving formulation for RISPERDAL will not increase their prescribing of RISPERDAL (i.e., little or no incremental share) but rather provide increased convenience over the currently available RISPERDAL oral solution and tablets.

Market research and Zydys adoption trends have signaled that specific markets are more receptive to fast dissolving technology. In particular, the following patient-types were identified as those in which a fast dissolving tablet would be most beneficial:

- In general, any patient who can't or won't swallow;
- Patients with difficulty swallowing (elderly, pediatrics, neurological disorder patients);
- Patients presenting in the crisis setting; and
- Patients who cheek their medication (e.g., inpatients, corrections).

The three target treatment settings in which these patients reside include: institutions (crisis and inpatient), long-term care, and office-based psychiatry. Figure 2 represents Zydys performance in these three segments.

Figure 2:



The greatest areas of Zydys penetration (defined as Zydys dollar share as a percent of total Zyprexa sales) include the long-term care and hospital channels. In these channels, Zydys share of total Zyprexa sales are 12.7% and 5.8%, respectively (IMS Health, August 2002).

An analysis of Zydys TRx distribution by specialty indicates that approximately 75% of Zydys prescriptions are sourced from psychiatry, while 15% is sourced from primary care. The 15% contribution by primary care is lower than the 25% contribution of primary care to overall Zyprexa TRx. This discrepancy is likely due to different patient populations seen by primary care physicians as compared to psychiatrists.

Lessons Learned:

- Zydys demonstrated modest sales performance with slow uptake:
 - Limited promotional efforts and resources;
 - Unclear marketing positioning: apparent transition from compliance to elderly message; and
 - Price premium over Zyprexa traditional tablets has blunted willingness of some physicians to prescribe and has limited formulary access (e.g., not on National VA Formulary, prior authorized on some state Medicaid formularies).
- Specific market segments are more receptive to fast dissolving technology;
- Fast dissolving formulations (such as Zydys) are used in same populations where RISPERDAL oral solution is used; and
- Perception exists of faster onset of action with fast dissolving tablets.

II. SWOT ANALYSIS, KEY ISSUES:

Strengths	Weaknesses
☐ RISPERDAL #1 in product class ☐ Perceived faster onset of action ☐ Convenience (difficulty swallowing, no water) ☐ Available as unit dose ☐ Adherence/No cheeking	☐ No 0.25 mg tablet for target segments ☐ Perceived tolerability challenges w/ RISPERDAL ☐ No clinical data to support use ☐ Taste at higher doses: 3, 4 mg

Opportunities	Threats
☐ Long-term care contracting and pull-through ☐ LTC packaging ☐ Continuum of care from acute care to CONSTA to promote compliance ☐ Pressure to decrease acute IM use in hospitals ☐ Potential for low dose, mood hook ☐ Untapped market due to little Lilly promotion ☐ Pediatric market (upon pediatric indication)	☐ Lack of reimbursement for premium priced line extension ☐ Relatively satisfied market ☐ Generic competition in 2008 with new technology ☐ VA label and impact on elderly use

Key Issues:

- There is limited perceived benefits of fast-dissolving technology in the CNS marketplace
- Pricing

III. LAUNCH OBJECTIVES:

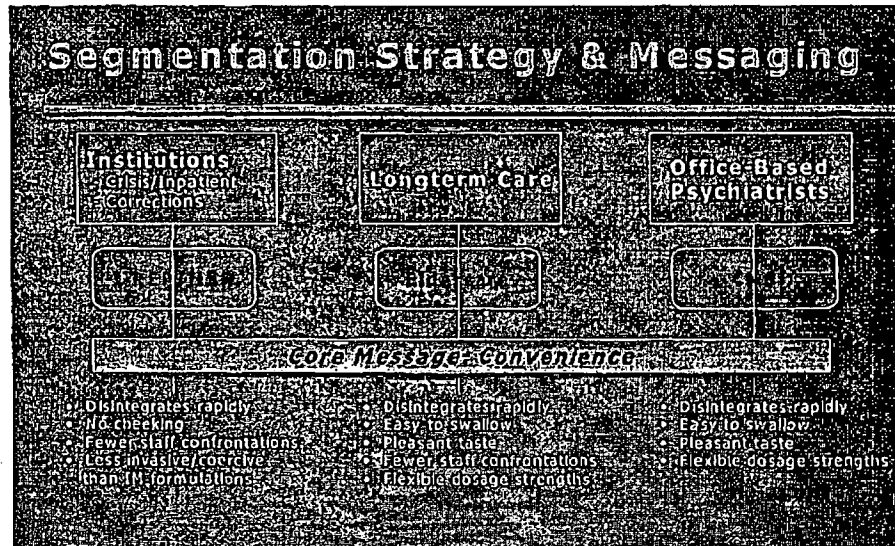
- Create immediate awareness and rapid uptake of RISPERDAL QuickSolv through multi-faceted communication venues: personal/non-personal promotion and medical marketing
- Ensure production and distribution of product is comprehensive and timely
- Educate and train the Sales Force and Medical Affairs about RISPERDAL QuickSolv
- Generate clinical data to confirm value proposition of RISPERDAL QuickSolv

IV. KEY BUSINESS STRATEGIES:

Communication Platform:

Figure 3 illustrates market segment targets and messages by sales force. Despite the different patient-types in each segment, the overriding core message that resonates best in all segments is "convenience". Specific sub-messages by segment have been developed based on market research and will be used to tailor each sales call based on treatment setting.

Figure 3:



1. Target market segments which benefit most from rapidly disintegrating technology

The two target markets in which fast dissolving technology is most beneficial are Institutions (crisis setting and inpatient) and Long-term Care.

Institutions:

In the crisis setting, QuickSolv represents a potential growth opportunity and an effective pre-launch blunting strategy for Zyprexa IM. To date, use of RISPERDAL in this treatment setting has been limited by the lack of availability of a unit dose oral solution formulation. QuickSolv will address this unmet need and provide a solid foundation for our acute care strategy currently under development. QuickSolv represents an opportunity for a continuum of care from acute care to long-term management with RISPERDAL CONSTA to promote compliance.

Long-term Care:

Approximately 33% of RISPERDAL Brand TRx's are written in the long-term care segment. Zyprexa and Seroquel are challenging RISPERDAL's dominance in this segment. QuickSolv can serve as a growth platform by targeting this segment with specialized Bingo Card packaging and performance-based contracting to drive share in this critical market.

2. Explore potential of RISPERDAL QuickSolv to serve as a mood platform

Physicians currently do not view RISPERDAL as a first choice for mood symptoms in schizophrenia. We will be conducting marketing research to determine if QuickSolv, which is available in lower doses, will facilitate clinicians to consider low dose RISPERDAL – its profile and efficacy for mood symptoms in schizophrenia.

3. *Profit maximization*

Development of various forecast model scenarios to ensure profit maximization based on CPI penalty savings, price premium, rebates, and conversion rates.

V. KEY PROGRAMS AND TACTICS:

	1 st Quarter	2 nd Quarter	3 rd Quarter	4 th Quarter
Personal Promotion	Flashcard Placebo Card Shelf Talker Physician Premiums	Flashcard Placebo Card		
Non-Personal Promotion		Journal Ad Direct Mail PharmAlert PDR Addendum Convention Panel	Journal Ad Direct Mail	Journal Ad
Publications				RIS-NED-25 RIS-USA-125 QuickSolv Review
Educational (CME)			CME Self-study on Dysphasia in Elderly	
Public Relations	Press Release			
Other	GNP Programs Bingo Card	GNP Programs	GNP Programs	GNP Programs

VI. SUCCESS PREDICTORS:

- Bend and peel or pouch primary packaging: avoidance of scissor cut
- Widespread formulary access
- Specialized packaging in LTC
- Performance-based LTC contracting with QuickSolv incentive
- Generation of clinical data to support marketing platform: crisis setting, long-term care setting, corrections, etc.

RISPERDAL®

Child and Adolescent Market Segment

2003 Business Plan Summary

Table of Contents

RISPERDAL – Child and Adolescent

- I. Introduction
- II. Situation Diagnostic/Analysis
- III. 2002 Product Performance Summary
- IV. SWOT Analysis, Key Issues
- V. 2003 Strategic Objectives
- VI. Key Business Strategies
- VII. Key Programs and Tactics
- IX. Success Predictors

Appendices

- 1. RISPERDAL C&A Summary
- 2. Competitive Overview
- 3. Market Research Plan

RISPERDAL®
2002 Business Plan Summary
Child & Adolescent

I. INTRODUCTION:

The child and adolescent market continues to represent an area of great scientific interest and opportunity for RISPERDAL (risperidone). The mental health needs of children and their families in the United States are well documented. The U.S. Surgeon General estimates that 1 in 10 children in this country suffer from a serious mental health problem. However, less than a third of these children receive any care -- and even less receives appropriate care. Despite this, the use of pharmacological therapies in the treatment of children and adolescents with mental illness has grown dramatically over the last decade. This is particularly true for atypical antipsychotics, as total prescriptions for this class have grown at an annual rate of 20% over the past 5 years. RISPERDAL is the most prescribed of the atypical antipsychotics; however, as is the case with the other atypicals, RISPERDAL is not currently indicated for use in children or adolescents. This business plan will focus on continued market understanding, medical education efforts, the drug commercialization efforts necessary to capitalize on the market opportunities for the brand in the child and adolescent segment.

The clinical development program for RISPERDAL has yielded important new efficacy and safety data in the child and adolescent area. These efforts have previously been focused in the area of Disruptive Behavior Disorders and Subaverage IQ. Several trials, RIS-USA-93 and RIS-CAN-19 (as well as the open label, 48 week follow up trials, USA-97 and CAN-20), initially designed to support filing for an FDA indication, have been completed and have yielded an impressive volume of new efficacy and safety data. Unfortunately, the FDA determined that Disruptive Behavior Disorder lacks the diagnostic specificity necessary to receive an approved indication. Nevertheless, these studies have contributed significantly to the clinical knowledge of RISPERDAL in the child and adolescent population, and provide a basis for ongoing medical education activities. Going forward, regulatory and clinical development efforts will include the evaluation of the NIMH RUPP Risperidone in Autism database to support filing for potential autism indication, adolescent schizophrenia indication, and the fulfillment of the FDA Written Request requirement for additional 6 month patent exclusivity. It is expected that the request will include the following requirements:

- Pediatric PK trial;
- Adolescent schizophrenia trial; and
- Pediatric bipolar trial.

The child and adolescent market offers several unique challenges not found in other areas where RISPERDAL is used. First and foremost, the sensitivity towards medications and their use in children shapes this segment. This issue is prominent in medical as well as lay press and public discussions regarding pediatric psychopharmacology. This results in many stereotypes and stigmas that prevent some children from receiving appropriate treatment. Additionally, the child and adolescent market is not driven by diagnosis, but rather by treatment of symptoms such as aggression, agitation, self-injurious behavior, and explosive rage. This lack of consistent diagnosis stems from a reluctance to "label" children at an early age, as well as a fundamental lack of consensus regarding the actual underlying disease states causing this symptomatic behavior. As a result, multiple diagnoses and comorbidities are the rule, rather than the exception in this area. These issues have influenced the clinical development process and limited the ability to achieve an FDA approved indication for RISPERDAL in children.

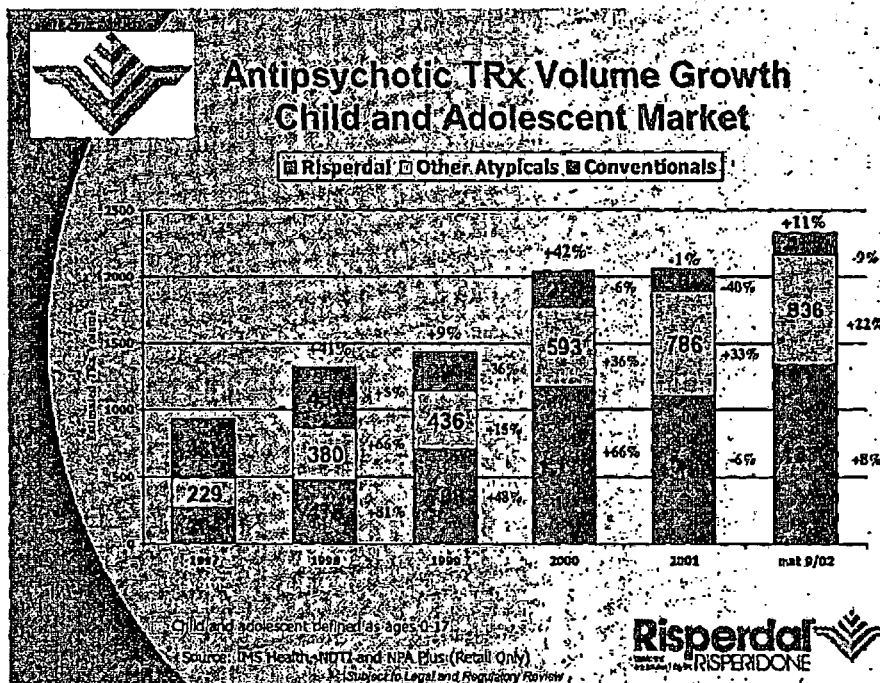
Johnson & Johnson has a unique opportunity in the child and adolescent psychopharmacology marketplace due to its product offerings across multiple operating companies. In addition to RISPERDAL, TOPAMAX (topiramate) and CONCERTA (methylphenidate HCl) are all used with this patient population. In addition to this product offering, Johnson & Johnson can also draw upon the expertise of the Johnson & Johnson Pediatric Institute to assess this complex marketplace.

II. SITUATION DIAGNOSTIC/ANALYSIS

Market Overview:

The U.S. Child and Adolescent antipsychotic market (defined as patients ≤ 17 years of age; in previous years, this has been defined as ≤ 19 years of age) is valued at over \$400 million (IMS Health & NDTI). In terms of total prescriptions, this market has been growing steadily over the past several years, with the exception of 2001, where the market actually declined by 1%. Possible explanations for this decline include: 1) negative publicity directed at pediatric psychopharmacology, leading to reluctance on the part of some physicians to prescribe antipsychotics for children, and 2) education regarding appropriate use of these drugs that resulted in a decrease in the average dose of antipsychotic used (see Figure 1). In 2002 YTD, growth in the child and adolescent antipsychotic market has returned at a robust rate of 11%. This market represents approximately 18% of all RISPERDAL drug uses in the U.S., twice that of the 9% of uses reported for antipsychotics as a class.

Figure 1:



The bulk of RISPERDAL use in the child and adolescent market is for mood and anxiety related diagnoses (keeping in mind the limitation previously mentioned regarding diagnosis vs. symptomatic treatment). Bipolar Disorder with 18% of uses leads the way in this area followed by Depression with 10% and Anxiety with 3% (see Figure 2). This represents an overall mood and anxiety use of 31% of the total atypical drug use for children. ADHD/Conduct Disorder makes up the next largest market segment with 20% of total drug uses, followed by schizophrenia/psychosis at 15%, and autism at 14%. These usage patterns are consistent with those for all atypical antipsychotics in aggregate. However, it is challenging to interpret these data diagnostically, as children may have comorbid conditions that are not fully reflected in the NDTI audit.

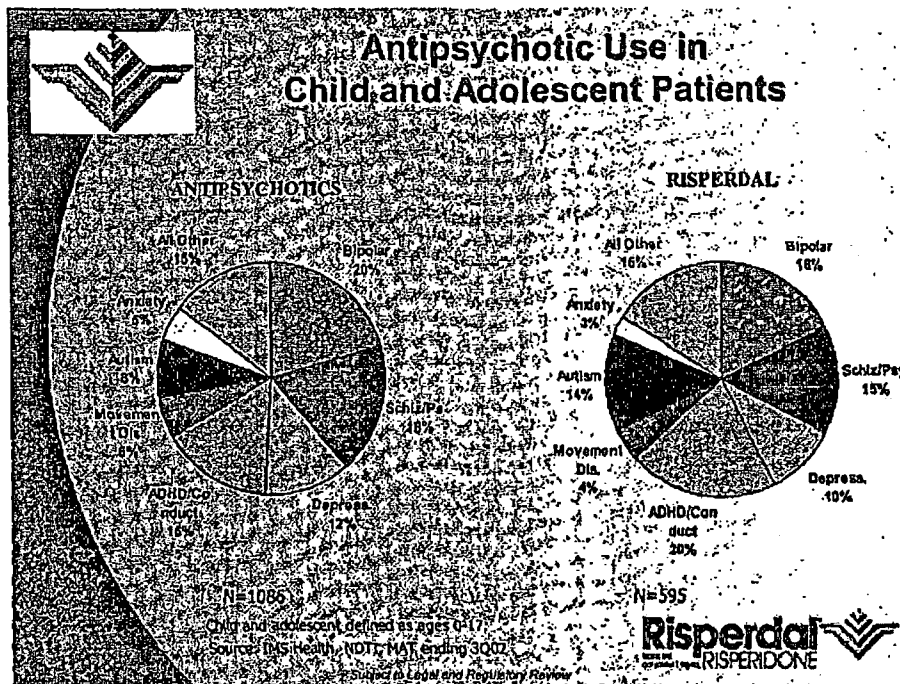


Figure 2:

Within the child and adolescent market, it is useful to look at the breakdown of drug use by age group. RISPERDAL drug use occurs 36% of the time in the 13-17 age group (adolescent), 45% of the time in the 7-12 age group (child), and approximately 19% of the time in the ≤ 6 age group. The use in younger children is primarily limited to autism spectrum and disruptive behavior disorders, or to the treatment of focused symptoms of aggression, which are more easily diagnosed at an earlier age than other major psychiatric illnesses such as schizophrenia or bipolar disorder.

Competitive Overview:

RISPERDAL remains the most widely prescribed antipsychotic in the child and adolescent market segment (55% market share – see Figure 3). However, there is growing competition from the other atypical antipsychotics. Following is an overview of major competitors:

Product/ Company	% Share* 2002 YTD	Strengths (+) Weaknesses (-)
Zyprexa (olanzapine) Eli Lilly	15%	+ Experience in adult market in schizophrenia and acute mania - Limited clinical data in children and adolescents - High weight gain relative to other compounds in the class; metabolic dysregulation
Seroquel (quetiapine) AstraZeneca	16%	+ Relatively benign side effect profile + Sedative properties perceived as advantageous - Limited of clinical data in children and adolescents - Inconsistent efficacy and dosing variability
Geodon (ziprasidone) Pfizer	9%	+ Relatively benign side effect profile, including perceived low weight gain - Limited of clinical data in children and adolescents - Spillover of QTc prolongation concerns

* Share of total antipsychotic market, including conventionals

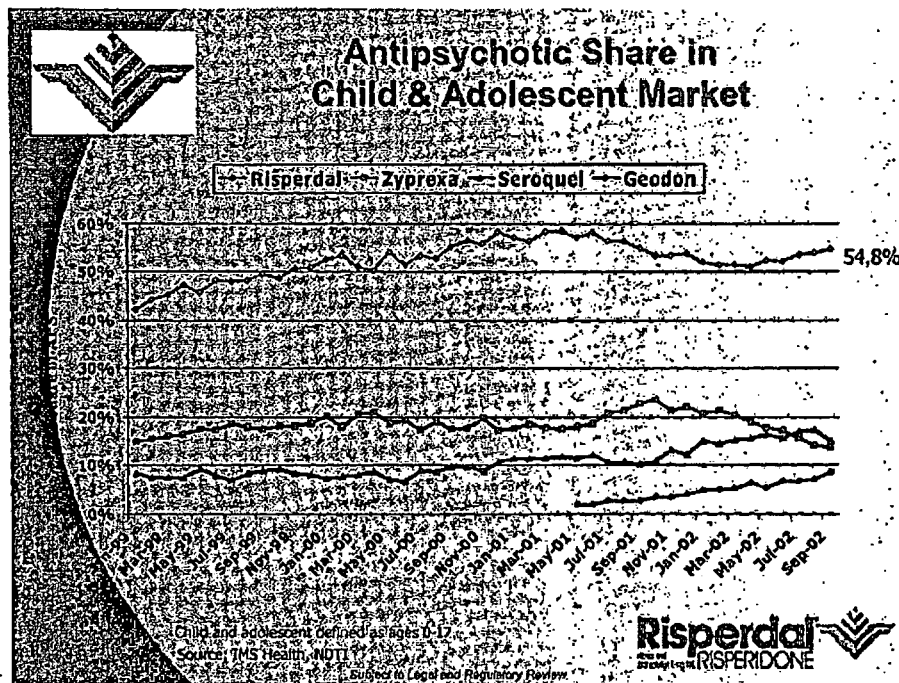


Figure 3:

All competitive products in this market have clinical development programs underway. Competitive intelligence in this segment indicates that Bipolar Disorder (specifically Pediatric Mania) is a major area of focus of all competitors. However, no competitor is likely to gain FDA approval in this market segment prior to late 2004. Barring an unforeseen setback, Seroquel will most likely be the first competitor to gain this indication. It is also important to note that Abilify (aripiprazole) will be launched very shortly. Given the expected positioning of this new product (comparable efficacy, better safety profile, unique mechanism of action), it is anticipated that Abilify will make early inroads into the child and adolescent market.

Customer Segment Overview:

Psychiatrists account for almost 70% of all RISPERDAL prescriptions, followed by pediatricians at 18%, neurologists at 10%, and primary care physicians at 3%. It is notable that pediatricians and neurologists are accounting for an increasing share of prescriptions for RISPERDAL. Psychiatrists are responsible for managing the majority of patients as well as the more difficult to treat illnesses such as psychosis and mood disorders. In general, pediatricians and primary care physicians are more likely to follow patients already diagnosed and treated. The exception to this is in geographic areas where these primary care physicians have become the de facto child psychiatrist for the area. This is fairly common due to the overall shortage of child psychiatrists in the United States. There are an estimated 6500 child psychiatrists practicing in the U.S. The American Academy of Child and Adolescent Psychiatry (AACAP) estimates that at least 20,000 child psychiatrists are needed to provide adequate care to all children in need of mental health treatment.

Parents and teachers also play a very important role in this market. Parents of children with illnesses such as autism and bipolar disorder are often strong advocates of clinical trials and drug therapy, and are active members of advocacy groups such as National Association of Mental Illness (NAMI), National Mental Health Association (NMHA), Child and Adolescent Bipolar Foundation (CABF), and Cure Autism Now (CAN). Teachers are often the first to see symptoms that necessitate treatment in these children. This information is typically shared with the parents when it becomes a "problem" for the teacher in the classroom environment. Social workers will occasionally play a similar role, especially with children in the criminal justice system.

III. 2002 PRODUCT PERFORMANCE SUMMARY

RISPERDAL did not have a 2002 forecast for the child and adolescent segment due to the lack of an FDA approved indication. However, qualitative goals were established for 2002, and are summarized below:

2002 Qualitative Objective	Results
☐ Remain the gold standard in the child and adolescent market by being recognized as the antipsychotic with the strongest clinical efficacy and safety data.	☐ 4 significant publications in 2002 (3 conduct disorder studies, and NIMH RUPP Autism Study in NEJM) ☐ New data postered at APA, AACAP ☐ Positive feedback from HOVS, Regional and National Advisory Board Meetings
☐ Ensure that clinicians recognize the appropriateness of antipsychotic therapy as part of the overall therapeutic approach to patient care	☐ Positive feedback from HOVS, Regional and National Advisory Board Meetings
☐ Work synergistically with J&J Pediatric Institute	☐ Ensured participation of members of J&J Pediatric Institute in C&A Core Team Meetings

Lessons Learned:

- Child and Adolescent market is large and growing
- Increasingly competitive market, and increased comfort with newer agents
- Prolactin, EPS, TD, and weight gain continue to be important issues (particularly long-term implications); safety is the driving factor in determining atypical drug use
- Competitors are driving negative safety and tolerability perceptions of RISPERDAL
- Advocacy seeking to define a public position regarding C&A use of antipsychotics
- A proactive approach to education and public relations are necessary to break down barriers and eliminate stigmas that exist in this area
- FDA approval is necessary in order to maximize educational efforts and initiate promotional opportunities
- Pediatricians and Neurologists are playing an increasingly important role in this market
- Pediatric bipolar is area of major focus of clinical study for scientific community and competitors

IV. SWOT ANALYSIS, KEY ISSUES

Strengths	Weaknesses
☐ APS market leader in this area ☐ Low dose availability; positive experiences ☐ Trust/experience with RISPERDAL ☐ Proven/strong efficacy; strong clinical data available ☐ Perceived side effect advantages relative to other APS ☐ Early onset of action ☐ Thought leader support	☐ Safety perceptions – Prolactin, EPS, TD, weight gain ☐ Lack of Indication ☐ No ability to promote ☐ Limited clinical development program ongoing ☐ Lack of sedation relative to other APS ☐ Lack of awareness of appropriate dosing

Opportunities	Threats
☐ Poor perception/experience with other APS (Zyprexa – metabolic issues) ☐ External data sources (NIMH – RUPP) ☐ Clinical partnerships (Mass General) ☐ Potential J&J Pediatric synergies (MCC, OMP, Alza) ☐ Under-serviced/unsatisfied market ☐ Advocacy partnering for educational initiatives ☐ Better diagnosis (DSM-V, consensus guidelines – TRAAY) ☐ RISPERDAL ODT	☐ Negative public relations/media reporting – effect on patients, providers, and company ☐ Lack of consensus – no diagnostic specificity ☐ Migration to other classes of drugs ☐ Further delay of labeling/exclusivity ☐ Perceived legal liability by prescribers ☐ Emerging clinical data for Geodon, Seroquel, Zyprexa ☐ Increased focus of competition on C&A market (aripiprazole launch) ☐ Sensitivity regarding use of APS in C&A

KEY ISSUES:

- Use of psychotropic medications in children and adolescents remains controversial
- Limited education and awareness of appropriate use of APS
- Physician misperception of RISPERDAL safety profile, driven primarily by increasingly competitive market
- Lack of Indication

V. 2003 STRATEGIC OBJECTIVES:

Quantitative:

There are no quantitative objectives for this segment due to the lack of indication for child and adolescent use.

Qualitative:

- Raise awareness regarding prevalence, economic and emotional burden of untreated C&A mental illness
- Develop educational platform to establish the role of APS in the treatment of C&A mental illness
- Establish RISPERDAL as having a favorable risk-benefit ratio relative to other compounds
- Partner with JJPRD and Pediatric Drug Development to facilitate development plans

VI. KEY BUSINESS STRATEGIES:

KEY BUSINESS STRATEGIES	
☐	Partner with scientific community and patient/family advocacy organizations to raise awareness regarding prevalence, economic and emotional burden of untreated C&A mental illness.
☐	Educate health care providers on therapeutic options for treating mental illness in children.
☐	Educate health care providers on the safety profile of RISPERDAL.
☐	Clarify FDA requirements for pediatric exclusivity and support efforts to obtain child and adolescent labeling.

VII. KEY PROGRAMS AND TACTICS:

The overall tactical budget for the child and adolescent programs is \$6.4 million. The breakdown of tactics by strategy and budget are listed below.

Strategy 1: Partner with scientific community and patient/family advocacy organizations to raise awareness regarding prevalence, economic and emotional burden of untreated C&A mental illness

	1 st Quarter	2 nd Quarter	3 rd Quarter	4 th Quarter
Public Relations	C&A Mental Health Media Briefing Ongoing Public Affairs activity	Ongoing Public Affairs activity	Ongoing Public Affairs activity	Ongoing Public Affairs activity
Other	Ongoing support for advocacy	Ongoing support for advocacy	Ongoing support for advocacy	Ongoing support for advocacy

Strategy 2: Educate health care providers on therapeutic options for treating mental illness in children

	1 st Quarter	2 nd Quarter	3 rd Quarter	4 th Quarter
Poster/Discussion		CDMR data reanalysis	CDMR data reanalysis	
Publications	RIS-USA-97		RIS-INT-41	
Educational (CME)	"Branded" Pediatric Educational Institute	Psychlink/Teletopics "Branded" Pediatric Educational Institute AAP Symposium C&A CME Conference	Psychlink/Teletopics "Branded" Pediatric Educational Institute AACAP Symposium	Psychlink/Teletopics "Branded" Pediatric Educational Institute
Advisory Meetings	CNS Summit	National Ad Board HOV (2) Regional Ad Board (2)	HOV (2) Regional Ad Board	HOV (2)

Strategy 3: Educate health care providers on the safety profile of RISPERDAL

	1 st Quarter	2 nd Quarter	3 rd Quarter	4 th Quarter
Poster/Discussion		CDMR data reanalysis	CDMR data reanalysis	
Publications	RIS-USA-97		RIS-INT-41	
Educational (CME)	"Branded" Pediatric Educational Institute	Psychlink/Teletopics "Branded" Pediatric Educational Institute AAP Symposium C&A CME Conference	Psychlink/Teletopics "Branded" Pediatric Educational Institute AACAP Symposium	Psychlink/Teletopics "Branded" Pediatric Educational Institute
Advisory Meetings	CNS Summit	National Ad Board HOV (2) Regional Ad Board (2)	HOV (2) Regional Ad Board	HOV (2)

Strategy 4: Clarify FDA requirements for pediatric exclusivity and support efforts to obtain child and adolescent labeling

- Explore potential indication for autism by utilizing NIMH RUPP Autism database
- Support fulfillment of FDA Written Request for pediatric exclusivity (schizophrenia, bipolar disorder, and PK studies)
- Support adolescent bipolar study as required by FDA Pediatric Rule

Tactical Highlights:**1. Children's Mental Health and Media Summit**

Description: One day meeting of key scientific opinion leaders, advocacy organizations, and medical/mass media. Case study of negative media reporting will be presented, followed by presentations from scientific opinion leaders and advocacy on impact of these reports on research, diagnosis, and treatment of children with mental illness.

Cost: \$0.4 million

Measurement: Success of program will be assessed by routine monitoring of media, with specific focus on frequency of fair balanced media reports regarding childhood mental illness. Additionally, the decrease in the number of factually incorrect stories that are reported will also be an indication of program success.

2. "Branded" Pediatric Educational Institute

Description: Multi-medium, comprehensive, branded educational campaign on the role of APS in the treatment of C&A mental health. To include Centers of Excellence, regional CME symposia, monographs, and newsletters. Opportunities to incorporate other products from other J&J operating companies will be identified (Concerta).

Cost: \$1.8 million

Measurement: Success of program will be assessed via standardized CME metrics (program redemption, educational impact, satisfaction, etc.).

3. National and Regional Advisory Boards, HOVs

Description: C&A Advisory Boards are designed to enhance understanding of key market dynamics, clinical issues related to efficacy, safety, and dosing, competitive activity, and data needs. In addition to the actual advisory boards a web-based communications platform will be developed to rapidly communicate with all advisors on an ongoing basis. There will be one National Advisory Board for Key Academic Thought Leaders, three Regional Advisory Boards for Regional Thought Leaders and six Home Office Advisory Boards for – separated by region due to differing regional issues.

Cost: \$2.1 million

Measurement: Program success will be measured by the refinement of the clinical development plan, new extramural research ideas, and other educational and advocacy related initiatives.

Budget Summary:

Description	2002 PME (\$K)	Proposed 2003 PME (\$K)	2003 PME %
Medical Marketing/Education	\$3,890	\$3,300	52%
CME Branded Initiative		1,800	
PsychLink/Teletopics		450	
Symposia (2)		350	
Publications		500	
National Ad Board		200	
Advisory Boards (RAB/HOV)	\$1,800	\$1,900	30%
Public Relations	\$325	\$500	8%
C&A Summit		\$400	
Other		\$100	
Grants	\$160	\$300	5%
Other	\$225	\$400	6%
TOTAL C&A	\$6,400	\$6,400	100%

VIII. SUCCESS PREDICTORS:

The success of the child and adolescent program will depend on several factors:

- The extent to which new or reanalyzed data is generated and disseminated via educational and advisory venues;
- The ability to satisfy requirements for pediatric exclusivity, FDA pediatric rule; full assessment of NIMH RUPP database for potential autism indication; and
- The change in public dialogue and perception of psychopharmacology as an appropriate means of addressing severe childhood mental health problems.

Appendices

RISPERDAL Child & Adolescent SUMMARY

1

	1999	2000	2001	YTD 2002
Market Size (\$MM)	\$178	\$277	\$344	\$280*
% Growth		55.4%	24.2%	
Net Trade Sales (\$MM)	\$102	\$160	\$157	\$151*
% Growth		57.9%	-2.1%	
Drug Uses Market Share (%)	50.9%	58.7%	53%	54.8%*
Average Price/Day (AWP)	\$5.87	\$5.78	\$6.20	\$6.52*
Average Dose/Day (mg/day)	1.8	1.7	1.8	1.9*

* Based on NDTI Mat Sep02 data & YTD Aug02 dollars

COMPETITIVE OVERVIEW**2**

	1999	2000	2001	2002 YTD
Product Uses Market Share (%)				
RISPERDAL	50.9%	58.7%	53%	54.8%*
Zyprexa	18.8%	16.9%	23%	13.7%*
Seroquel	8.1%	10.5%	12.4%	15.1%*
Geodon	-	-	3.9%	8.7%*
Avg. Price/Day (AWP)				
RISPERDAL	\$5.87	\$5.78	\$6.20	\$6.52*
Zyprexa	\$8.41	\$8.64	\$10.49	\$11.70*
Seroquel	\$10.73	\$6.89	\$7.70	\$6.37*
Avg. Dose/Day (mg/day)				
RISPERDAL	2.1	1.7	1.8	1.9*
Zyprexa	7.5	6.9	8.0	8.6*
Seroquel	321.0	212.0	263.1	198.2*

* Based on NDTI Mat Sep02 data & YTD Aug02 dollars

MARKET RESEARCH PLAN**3**

Program	Objective	Target	Timing (start/finish)
RISPERDAL Annual Tracking Study	Evaluate attribute importance and APS product perceptions across disease states and customer segments	Psychs, PCP	2Q03
Child and Adolescent Landscape Study	Assess treatment patterns, decision making processes, attitudes and usage of APS in child and adolescent segment	Psychs, Peds, PCP	Q103
TBD - based on identified needs and evolution of clinical development plans	TBD	Psychs, Peds, PCPs	Q403

Goff, Brian [JANUS]

From: Shaw, Christi [JANUS]
Sent: Wednesday, September 17, 2003 3:17 AM
To: Goff, Brian [JANUS]
Subject: FW: Risperdal Bipolar mania and diabetes labeling US

Sensitivity: Confidential

Just keeping you in the loop.

-----Original Message-----

From: Pruden, Gary [JANUS]
Sent: Tuesday, September 16, 2003 3:01 PM
To: Norton, David [JANUS]; Miller, Peter [JANUS]
Cc: Fabbri, David [JANUS]; Shaw, Christi [JANUS]; Huston, Thad [JANUS]; Mehrotra, Louise [JANUS]; Sipos, Ellen [JANUS]
Subject: FW: Risperdal Bipolar mania and diabetes labelling US

David / Peter,

Update from today's activities and teleconference with FDA. It was clear, FDA had not put a lot of thought process into the class label issue. (they mentioned it was from the recent VA study, however they have not seen the final analysis - we may be better!)

From our perspective we looked at some rough financial scenarios to put into perspective:

- Scenario - Accept current label & launch Bipolar ~55-100 mm downside (based on final assumptions)
 - Scenario - Submit further data to agency strive for revised wording but agency fails to accept post review. Cost of delaying Bipolar approval till January ~5-7 mm downside
 - Scenario - Submit further data to agency, meeting in Dec for review...FDA accepts revisions. (i.e.- Low risk for Risp, we get precaution vs warning for others) Other competitors get class label
- Upside ~100 mm+** in incremental sales (We are doing a Ben Zander here- think of the possibility)

The team strategy here is that we are headed down the road of submitting data to "prove" differences here. The agency clearly indicated they were receptive and had not looked at our data. In the end if this causes too much delay for Bi-polar or Consta, we can accept their label and gain an approval.

The team felt that this was worth an FDA meeting in December to culminate all of our data and create an opportunity for real differentiation on this issue.

I will give you both a call later, David...I understand Garry Neil will give an update to GOC tomorrow.

Gary

-----Original Message-----

From: Caers, Ivo [PRDBE]
Sent: Tuesday, September 16, 2003 2:30 PM
To: Neil, Garry [PRDUS]
Cc: Pruden, Gary [JANUS]; Vergis, Janet [PGSMUS]; Grebb, Jack [PRDUS]; Miller, Peter [JANUS]; Grossman, Fred [PRDUS]; Mahmoud, Ramy [JANUS]; Singer, Jack M [PRDUS]
Subject: Risperdal Bipolar mania and diabetes labelling US

Dear Garry

See a status report on Risperdal bipolar approval and diabetes class label in US label.

A proposed label for Risperdal in Bipolar mania was obtained from the FDA on Friday Sept 12. This proposed label included a class label warning on atypical antipsychotics and diabetes. It describes the observations of hyperglycemias up to ketoacidosis or hyper osmolar coma. It states that it is based on epidemiological evidence and that there is insufficient data to make estimates on risk differences among different atypical antipsychotics:

"Epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics studied. The available data are insufficient to provide reliable estimates of differences in hyperglycemia-related adverse event risk among the marketed atypical antipsychotics"

A separate letter was obtained Sept 16 with a formal request to add this label text to our Risperdal label.

Today, Sept 16, Ramy Mahmoud and Fred Grossman had a telephone discussion with Tom Laughren, Psychopharmacology team leader, on our request to have a scientific discussion on this issue.

Summary of discussion:

Tom Laughren was not prepared to discuss the data - the review is being lead by the safety division (Judy Racoosin). He thought that the decision for this class label was based on a recently presented VA study indicating a higher risk for diabetes with several atypical antipsychotics incl. Risperdal.

On our point that there is additional data available that do not support the "all atypicals are comparable statement", he replied that the FDA is open to review such additional data and that the FDA needs to make sure the labelling is accurate.

He also said that "atypical antipsychotics" was broadly defined. We interpret this to mean that all new antipsychotics from clozapine up to Abilify will have been requested to include this class label.

Tom Laughren was not prepared to de-link this discussion from the Bipolar approval and said we should send in our comments to the proposed bipolar label. He commented that without an agreement regarding this class label, there would be an approvable letter rather than an approval letter.

He agreed that this class label change should be implemented simultaneously for all atypical antipsychotics but said that the FDA cannot guarantee this and implied that they often make use of approvals to drive rapid implementation.

We are free to send in our arguments regarding Risperdal and hyperglycemias any moment independent from the approval process of the bipolar mania indication.

Our objectives:

Accepting this class label would take away a competitive advantage (low propensity to induce hyperglycemias/ diabetes) we have vs. some atypical antipsychotics such as olanzapine and clozapine. Moreover, the class label is not in line with the weight of evidence known to us from our own epidemiological studies and other sponsors studies.

We strive towards anything better than a class label for Risperdal or at least have the class label adapted so that the "all atypicals comparable" phrases would be removed or replaced by "they are not all alike".

Our actions:

We will prepare for a full package covering the following:

- Epidemiological review and literature review incl. relevant case reports of relevance. (Amy Grogg)
- Review of relevant pathophysiology incl. new animal data we have. (Andrew Greenspan with support by J&JPRD expert Francis Bruce(?))

- Updated Pharmacovigilance overview (Pat Kaufman)

- updated clin trial review (Sally Berry)

Packed in a briefing document to send in Mid October 2003 in preparation of a meeting with the FDA to be requested for 3 weeks later.

We are aware this may also affect the timeline for an approval for Risperdal Consta in the assumption the FDA would issue an approval on Oct 28.

The consecutive timelines after this meeting are unpredictable but we will know after early November what our chances are. We always can accept either the present text or at that point achieved compromise to allow approvals of Bipolar mania and Risperdal Consta.

A core team of Ivo Caers, Marielle Eerdeken, Sally Berry, Sagar, Adusumalli, Fred Grossman, Jack Grebb, Pat Kaufman and Ned Brann (J&JPRD) Ramy Mahmoud, Amy Grogg, Andrew Greenspan (JPI MEd Aff), David Fabbri (JPI marketing) and Katie Rielly-Gauvin (PGSM) will coordinate and drive these activities further and report on the status at least twice weekly to Sr Management.

Ivo Caers

DESCRIPTION

RISPERDAL® (risperidone) is an antipsychotic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-(2-[4-(4-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinylethyl]-6,7,8-trimethyl-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{28}H_{34}FNO_4$, and its molecular weight is 416.49.

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 lactic 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 (K_i 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 H₁ histaminergic receptors. RISPERDAL® antagonizes other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (K_i of 47 to 253 nM) for the serotonin $5HT_1$, $5HT_1$, and $5HT_1$ receptors, weak affinity (K_i of 620 to 600 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-6}$ M) for cholinergic muscarinic or D_1 and D_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 P₄₅₀2D6, 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=23%).

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The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is cytochrome P₄₅₀2D6, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, sedatives, and other drugs. Cytochrome P₄₅₀2D6 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 quindine. 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 56 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.

DEFENDANT'S
EXHIBIT

20

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of cytochrome P₄₅₀2D₆ could interfere with conversion of risperidone to 8-hydroxyrisperidone. This in turn 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 P₄₅₀2D₆. 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 8-hydroxyrisperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfamethoxazole (100 ng/mL), warfarin (10 ng/mL) and cefazolin (10 ng/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL, and 8-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 concentrations 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 8-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 manic phases 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, hallucinations, delusions, suspiciousness, and unusual thoughts/ideas) is considered a particularly useful subset for assessing schizotypic psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, very familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but well validated 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 4-week, placebo-controlled trial (n=180) involving titration of RISPERDAL[®] in doses up to 16 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=151) involving 4 fixed doses of RISPERDAL[®] (2, 4, 8, 16, and 32 mg/day, on a BID schedule), the 8 mg/day group was generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score. The 32 mg/day RISPERDAL[®] dose group were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 8 mg/day dose group.
 - (3) In an 8-week, dose comparison trial (n=135) 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 placebo on the PANSS negative subscale. The most consistently positive responses were seen for the 8 mg/day dose group.
 - (4) In a 4-week, placebo-controlled dose comparison trial (n=248) involving 2 fixed doses of RISPERDAL[®] (4 and 8 mg/day on a BID schedule), both RISPERDAL[®] dose groups were generally superior to placebo on several PANSS measures, including a response measure (a 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/day than for the 4 mg/day 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 (4 to 8-week) controlled trials of schizophrenia inpatients (See CLINICAL PHARMACOLOGY).

The effectiveness of RISPERDAL[®] in long-term use, that is, more than 8 to 16 weeks, has not been systematically evaluated. In controlled trials, the clinical response to RISPERDAL[®] was maintained for up to 16 weeks. Periodic re-evaluation of 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 hyperreflexia, muscle rigidity, and increased or abnormal body temperature. Other features include leukocytosis, tachycardia, diaphoresis and cardiac dysrhythmias. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In setting at a diagnosis, it is important to identify causes which are the clinical picture include both serious medical conditions (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 hyperthermia.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to supportive 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 reoccurrence of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrence of NMS has 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 rule out completely the possibility of its development in younger patients. 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; (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate; or (3) in whom 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.

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 8-hydroxyrisperidone appears to prolong the QT interval in some patients, although there is no average increase in QT interval, even at 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, which can be fatal. In patients receiving 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-increase period, probably reflecting its α_1 -adrenoceptor antagonist properties. Syncope was reported in 0.2% (2/507) of RISPERDAL[®] treated patients in phase 3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (once 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.

Serotonin Receptor Interactions: During premarketing testing, seizures occurred in 0.3% (2/507) of RISPERDAL[®] treated patients, two in association with hypotension. 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.

Hypersensitivity: 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 cancer cells 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 administered by direct questioning of patients. This adverse event is dose related, and in a study involving a check-in 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 6% 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 driving a motor vehicle, until they are reasonably certain that RISPERDAL[®] therapy does not affect them adversely.

Pruritus: Rare cases of pruritus have been reported. While the relationship of the events to RISPERDAL[®] use has not been established, other drugs with α_1 -adrenoceptor blocking effects have been reported to induce it. It is possible that RISPERDAL[®] may share this capacity. Severe pruritus may require surgical intervention.

Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 29-year-old female patient receiving RISPERDAL[®] in a large, open, premarketing experience (approximately 1300 patients). She experienced fever, liver, 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 viral meningitis.

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 Disease: Critical experience with RISPERDAL[®] in patients with certain concomitant systemic illnesses is limited. Caution is advised 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 angina. In patients with these diagnoses, the risks of critical studies were evaluated during the product's premarketing testing. The electrocardiograms of approximately 300 patients who received RISPERDAL[®] and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the results are summarized in Table 1. In patients receiving 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 RISPERDAL[®] group and 1 in the placebo group. In these patients, the QTc interval was prolonged by 20 msec or more, and caution should be observed in cardiac patients (See WARNINGS AND PRECAUTIONS).

Increased plasma concentrations of risperidone and 8-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 drug 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 use of RISPERDAL[®] and other drugs should be advised to inform them that they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interaction.

Alcohol: Patients should be advised to avoid alcohol while taking RISPERDAL[®].

Laboratory Tests
No specific laboratory tests are recommended.

Drug Interactions
Risperidone and 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.

Serotonin Receptor Interactions: Risperidone, RISPERDAL[®] may enhance the hypotensive effects of other serotonergic 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.

Risperidone may increase the plasma concentration of the anti-psychotic drug (risperidone plus 8-hydroxyrisperidone) by raising the concentration of risperidone. Although not the active metabolite, 8-hydroxyrisperidone, drugs that inhibit cytochrome P₄₅₀2D₆ and other P₄₅₀ isoenzymes: Risperidone is metabolized to 8-hydroxyrisperidone by cytochrome P₄₅₀2D₆, 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 8-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 8-hydroxyrisperidone. Analysis of clinical studies involving a variety of doses of risperidone and 8-hydroxyrisperidone does not suggest that these two metabolites 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 P₄₅₀ isoenzymes, including 1A1, 1A2, 1C2, 1C3, and 2C9, are only weak inhibitors of risperidone metabolism.

Drug Interactions: Cysteamine and N-acetylcysteine both inhibit the metabolism of risperidone in a dose-dependent manner. 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 0.5, 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 (mg/kg) on a mg/m² basis. The maximum human dose (16 mg/day) 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 pancreatic adenomas and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² 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 (2.4)	0.2 (2.4)
Endocrine pancreatic 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	0.6 (37.5)	1.5 (9.4)
Mammary gland hyperplasia	rat	male	1.5 (9.4)	0.4 (2.4)

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RISPERDAL 2000 BUSINESS PLAN

I. RISPERDAL® (risperidone)

A. Strategic Vision

The vision of the RISPERDAL franchise is to reinforce the position of RISPERDAL as the antipsychotic of choice and to further establish Janssen as a leader in the CNS marketplace. Our focus in 2000 will be to enhance the leadership of RISPERDAL as the most effective atypical antipsychotic for first-line treatment of both psychotic and non-psychotic disorders. These disorders include schizophrenia, schizoaffective disorder, bipolar disorder, dementia and conduct disorders. RISPERDAL will also be building a foundation to launch future CNS products such as VESTRA, REMINYL, TOPAMAX-Bipolar and other future CNS compounds.

B. Market Overview/Situation Analysis

The antipsychotic market is valued at approximately \$2.9 billion (\$3.4 billion in RISPERDAL dollars), representing a dollar increase of over 23% from last year. It is projected that this increase in dollar volume will continue as the market rapidly converts from conventional antipsychotics (declining at about 10 share points per year) to more expensive atypical antipsychotics.

RISPERDAL has remained the #1 most prescribed antipsychotic in the United States for over 3 years. The current NRx share of 28.8% (Oct 99) represents an all time high.

In 2000, schizophrenia will remain a critical area of focus for RISPERDAL. Schizophrenia is the foundation for antipsychotic use and represents the greatest dollar potential (~\$1.3 billion in RISPERDAL dollars). RISPERDAL currently has 18.0% share (MAT Sept 99) of the schizophrenia market, compared to 25.1% for Zyprexa. In 2000, our objective will be to accelerate RISPERDAL share growth, and ultimately retake the lead in this critical market.

The geriatric market represents RISPERDAL's second wave of growth. The incidence of dementia in the U.S. is about 3 MM people and demographic trends suggest the aging population will continue to drive market growth well into the next century. With one-half of all nursing home residents suffering from dementia (650 K), the long-term care (LTC) segment is a significant opportunity for RISPERDAL. In addition, many patients still live at home so prescriptions are being generated in the retail market as well. RISPERDAL LTC NRx is growing at a rate of 26% versus last year. In addition, YTD LTC segment sales exceed \$120 MM, an increase of 11.5% over 1997. This solid sales growth has been facilitated by the introduction of 0.25mg and 0.5mg tablets, which are parity-priced with 1mg tablets. The parity pricing has helped to maintain sales despite a declining average daily dose. In fact, RISPERDAL continues to be the number one prescribed antipsychotic in LTC in terms of both market share and dollars. Increasing competition from Zyprexa and Seroquel is making this a much more competitive segment than in the past.

Bipolar disorder represents about one-fifth of the prescriptions for RISPERDAL, with a market potential estimated at nearly \$600 MM. RISPERDAL has experienced significant growth in this market with a 25.2% share (MAT Sept 99), down from 26.8% in December 1998. Zyprexa has a current market share of 34.7%. Lilly's recent FDA "approvable letter" for Zyprexa bipolar labeling appears to have overcome an earlier setback in September 1998. A critical success factor for RISPERDAL will be effective positioning of the efficacy of RISPERDAL as adjunctive therapy without the significant weight gain liability of Zyprexa.

The continued publication of data supporting the efficacy and safety of RISPERDAL will drive the use of this product in a variety of psychotic conditions. Specifically, future developing markets for RISPERDAL include stuttering, conduct disorders in children and adolescents, post traumatic stress disorder and dual diagnosis.

In 2000, three major market forces will affect the overall antipsychotic marketplace:

- Increasing competitive intensity among existing atypical antipsychotics.
- Continued demand for new data and additional formulations of atypical antipsychotics.
- Changing reimbursement environment.

Competitive Intensity in Differentiating Atypical Compounds

The competitive environment of the atypical antipsychotic marketplace has intensified with a corresponding increase in the total dollar value of the market (an increase of 23% over last year). All pharmaceutical companies invested in the atypical antipsychotic marketplace have increased promotional intensity substantially. Most noteworthy have been Eli Lilly's expansion of LTC and bipolar-focused sales forces, AstraZeneca's increase by 100 LTC representatives, and significant spend by Pfizer in medical education programs and opinion leader focus in preparation for Pfizer's Zeldox. RISPERDAL must position itself as the antipsychotic with superior efficacy in order to differentiate from the other atypicals in 2000.

Continued Demand for New Data and Additional Formulations of Atypical Antipsychotics

Because of the importance of Zyprexa to the growth of Eli Lilly, a significant amount of resources—both human and financial—are devoted to their clinical development program. In addition to an extensive schizophrenia clinical program, Lilly has an advanced program for bipolar disorder which has resulted in an 'approvable letter' from the FDA. Lilly is also pursuing indications for dementia and Parkinson's dementia. In addition, new formulations including Zydis (a QuickSolv-like formulation), a patch, and a long-acting (depot) injection are also being aggressively developed. It is anticipated that Pfizer will re-file an NDA for ziprasidone in 1Q'00 with oral tablets, an IM formulation, and a claim for relapse prevention. Other schizophrenia products in development include aripiprazole (an Otsuka compound co-licensed with Bristol Myers Squibb - NDA late 2001) and Zomaril (Novartis - NDA mid-2001). RISPERDAL is significantly behind Zyprexa in terms of published clinical data as well as clinical research programs. Clearly, a major challenge for the CNS Franchise will be in providing resources to adequately support the development of new clinical data and formulations for RISPERDAL.

Changing Reimbursement Environment

The superior efficacy and safety profile of the atypicals has increased the NRx volume growth, and has dramatically increased the total dollar volume within the antipsychotic class. Atypical antipsychotics represent nearly two-thirds of NRx volume and over 90% of the existing dollars.

With the rapid shift towards the more expensive agents, it is anticipated that payors will continue to focus more attention on the use of atypical antipsychotics. Such changes will offer challenges and provide opportunities for RISPERDAL. In addition, there is a potential for change in the Medicaid reimbursement system. In 1998, the Prospective Payment System (PPS) was introduced in the Medicare nursing home population. PPS transfers the financial risk from Medicare to nursing home providers. Depending on the success of Medicare PPS, Medicaid may implement its own version of capitated payment. With over 80% of RISPERDAL sales distributed via the public sector, this could have a significant impact on our business. Thus, the need to quickly expand and solidify RISPERDAL use becomes even more important.

C. Life Cycle Analysis – Schizophrenia/Geriatrics/Bipolar/Conduct Disorder

The atypical antipsychotic market is becoming increasingly competitive. The need to differentiate RISPERDAL from the competition with clinical data, new indications and additional formulations is critical. The primary focus will be to leverage our competitive advantage in schizophrenia, followed by expanding use in geriatric psychosis, bipolar disease, and conduct disorders. The potential of these markets is noted below:

<u>Disease</u>	<u>Yearly Patient Population</u>	<u>\$ Potential</u>
Schizophrenia	2,500,000	\$1.3 B
Bipolar Disorder	3,500,000	\$640 MM
Dementia	2,900,000	\$500 MM
Conduct Disorders	6,800,000	\$300 MM

Schizophrenia:

The reanalysis of the RIS-112 data (RISPERDAL vs. Zyprexa) provides us with a strong opportunity to differentiate RISPERDAL from Zyprexa in the Schizophrenia market. In order to maximize these data, Medical Affairs will be analyzing the data to support several poster presentations and at least two manuscripts. RIS-79 (relapse prevention), is another important data set with regard to the schizophrenia market. Long term data is essential in this market. While the initial results of RIS-79 were released in 1999, several additional analyses are planned for 2000, as it is a robust data set. In addition, RIS-79 will be the key study to go for a long-term maintenance sNDA and potentially a superiority claim over Haldol for positive symptoms.

Dementia:

In order to maximize our competitive position and support our growth in dementia, a label change is critical. It is essential to co-operate with the FDA and opinion leaders in preparation for the Advisory Committee meeting scheduled for spring 2000.

With the increasing number of atypical antipsychotics on the market, the need to differentiate RISPERDAL from the competition on both efficacy and safety will be critical. The focus will be on expanding the data and supply of published literature on RISPERDAL in dementia patients with Alzheimer's Disease suffering from psychotic symptoms and behavioral problems. We have a large database with RIS-USA-63/RIS-USA-70 and RIS-INT-24/26, which could provide a wealth of data for years to come if analyzed effectively. It will also be important for us to

conduct head-to-head studies vs Zyprexa to combat the results of the Lilly sponsored RISPERDAL vs Zyprexa trial in dementia.

As we develop new formulations for RISPERDAL with depot we will need to ensure that appropriate low dose formulations for dementia patients are developed at the same time as doses for schizophrenic patients.

In order to maximize our CNS portfolio in geriatrics it will be critical to conduct studies with RISPERDAL and REMINYL regarding safety interactions and enhanced efficacy for both memory enhancement and behavioral control.

Bipolar:

The bipolar program includes RIS-102 and INT-46, both of which are critical for 2000 in order for us to remain competitive within the bipolar market. Both studies are acute mania, add-on studies and will form the basis for a bipolar sNDA to be submitted in June 2000. Acute mania monotherapy studies are expected to start 2Q'00.

Conduct Disorders:

RIS-USA-93 and the long-term extension RIS-USA-97 will provide us with data on the safety and efficacy of RISPERDAL in children with conduct disorders. These data will help us extend RISPERDAL use within the pediatric market and will potentially extend our patent with an additional 6 months.

The consistent practice of performing additional analysis on existing data sets is critical to maximizing the data, and therefore our publication exposure in the marketplace. However, with increasing competition, the need for new clinical data supporting the use of RISPERDAL in each strategic areas is also essential.

The long-term development plan for RISPERDAL is prioritized according to market potential. Our number one priority is the development of a RISPERDAL depot formulation. Several other new formulations, indications and line extensions are planned for launch within the next 1-5 years. A summary timeline of the new developments for RISPERDAL are summarized below:

	2000	2001	2002	2003	2004
Brand Introductions		QuickSolv Approval POC Approval	Depot (2-wk formulation)	Bipolar Monotherapy	Depot (4-wk formulation)
Label Changes New Indications New Data	Dementia Labeling Stuttering Data Dual Diagnosis Data Glucose Metabolism Data Long-term Conduct Disorder	Acute Mania Bipolar (adjunctive therapy Labeling) Maintenance Label	Conduct Disorders		Palmitate

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	Data				
Key Publications	Comparative Data (RIS-112) Relapse Prevention (RIS-079) Bipolar – Acute (RIS-102/46) Conduct Disorder (RIS-93/RIS-97)	First-Break Data			

D. RISPERDAL- Schizophrenia 1999 Accomplishments and Lessons Learned**Accomplishments**

- Overall NRx market share reached an all-time high seven out of eight months in 1999
- RISPERDAL sustained double-digit sales growth for the fifth consecutive year
- Zyprexa posted its first NRx share decline since launch
- The Janssen booth at the 1999 APA was rated Number One by attendees
- The CNS Summit has become a highly regarded meeting among opinion leaders

Lessons Learned**We need to focus on a specific promotional schizophrenia message**

Since the launch of RISPERDAL in 1994, the base promotional message has focused on efficacy in "psychosis." This broadly defined message has been effective in diversifying the range of diagnoses for which RISPERDAL has been prescribed, but has also diluted the core message for schizophrenia. Zyprexa surpassed RISPERDAL in schizophrenia market share in May of 1998, and while RISPERDAL has remained flat at an NRx share of 18.2%, Zyprexa has grown its NRx share in schizophrenia to a new all-time high of 25.1%. In 2000, our promotional and medical education activities will need to focus on driving a strong evidence-based message for the efficacy of RISPERDAL in the treatment of schizophrenia.

Seroquel (quetiapine) cannot be ignored

In spite of the fact that the psychiatric community continues to question the efficacy of Seroquel, it currently has a NRx share of 7.1%. In addition, Seroquel has shown consistent growth that has actually outpaced growth rates for both RISPERDAL and Zyprexa in the last year. Zyprexa is and will remain the main competitor for RISPERDAL, but it will be important to make sure that we maximize every opportunity to blunt the continued growth of Seroquel.

Weight gain is a defensive issue for Zyprexa, and an offensive issue for ziprasidone

Lilly is now defensively addressing the issue of weight gain in their sales materials, but Pfizer is quickly trying to pre-position ziprasidone as weight neutral. There is also further evidence that Zyprexa may be associated with causing Type II diabetes in some patients. We will need to explore this further, as this would have significant impact on the medical community. Until we know further, we need to continue to firmly position RISPERDAL as the most effective first-line atypical, while differentiating on weight gain as a secondary message.

The antipsychotic marketplace is still price inelastic

Despite the fact that Zyprexa is typically priced 40% higher per prescription than RISPERDAL, the market still remains slow to react to this difference in terms of formulary positioning.

Publication opportunities have not been fully leveraged

Janssen is significantly behind Eli Lilly in terms of studies and related publication volume. There have been few new studies since launch in 1994, and the data sets we do have are not fully leveraged to produce multiple publications.

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E. SWOT Analysis - Schizophrenia

The SWOT analysis is the basis for RISPERDAL-Base promotional activity in 1999:

<u>Strengths</u> Superiority in positive and negative symptoms over Haldol Relapse prevention data (RIS-79) New data Vs Zyprexa (RIS-112) Rapid onset of action Low weight gain QD dosing Low TD Low anticholinergic effects Low sedation	<u>Weaknesses</u> Publication Volume Dose-Dependent EPS Perceived TD liability (EPS) Prolactin elevation Perception of more complex dosing Breadth/number of speakers
<u>Opportunities</u> Acute care setting Psychiatric Residents Low cost/changing reimbursement environment Opinion leaders	<u>Threats</u> WLF ruling Zeldox (ziprasidone launch) tablets and IM formulations Zyprexa "Zydis" (quick-solv) and IM formulations Growth trend of Seroquel Zyprexa bipolar approval

F. Key Issues - Schizophrenia

Increasing Competitive Intensity

1) *Decreasing share of voice*

In the year 2000, there will be four atypicals on the market which are actively promoted, with a fifth due to be approved by year-end (ziprasidone). While this increases the "noise level" for the atypicals overall, it also creates more fierce competition. There will be more representatives promoting each drug, either from corporate mergers (Astra-Zeneca), sales force expansions (Janssen and Lilly), or a new drug launch (Pfizer). From a promotional standpoint, representatives then face more competition for physician time. At a different level, there will be increased competition for opinion leader relationships. Medical education will also be more challenging, with five companies actively pursuing the antipsychotic market, and therefore competing for physician time at major meeting symposia, and representative delivered programs. To be successful in 2000, we will need to ensure that promotional messages are solid in content, and that they are consistent from rep-to-rep and program-to-program. We will also need to continue to strengthen our existing relationships with key opinion leaders, and strive to further widen our circle of key contacts.

2) *Existing perception gap*

To regain market share in the treatment of schizophrenia, we must address current perceptual gaps relating to the product profile of RISPERDAL. Market research has shown that prescribers feel that Zyprexa is superior to RISPERDAL in the treatment of negative symptoms, and that it has a superior EPS profile. In contrast, however, the large evidence

of clinical data demonstrates both drugs to be equal. In addition, weight gain and diabetes were not listed as part of the top 10 attributes of importance to physicians, although both were rated strongly in favor of RISPERDAL. Our current promotional message focuses on efficacy, low weight gain and appropriate dosing. We will need to continue to drive this core message, and work to close the existing perceptual gaps versus Zyprexa. We also need to raise the overall importance of weight gain and diabetes with key prescribers.

3) *Sub-optimal physician targeting*

In the interest of pursuing high volume prescribers, Janssen has not devoted a great deal of selling time to psychiatric residency programs, acute setting psychiatrists, or psychiatric nurses. We now have a dedicated sales force in institutional settings that will allow us more time with these important customers. Promoting RISPERDAL to all of these key customers (in addition to high volume physicians) will allow our representatives cover the continuum of patient care.

Poor Compliance

Similar to other atypicals, market research has shown that for every 100 patients, who begin RISPERDAL treatment, only 15 will remain on RISPERDAL one year later. The reason for this alarmingly high rate is complex, stemming partly from the diagnosis itself and compounded by a very fragmented mental healthcare system. Countless programs have been put in place from various organizations, all aiming to correct the problem. While this is a key issue for RISPERDAL, any tactics aimed at addressing poor compliance must be carefully considered as to their projected impact.

Low Cost and Challenging Reimbursement Environment

In spite of the fact that RISPERDAL is 40% less expensive per patient than Zyprexa, and approximately 30% less expensive than Seroquel, we have not yet seen payors move toward preferring one atypical over another on formularies to any significant degree. We must first differentiate the efficacy and safety product profile of RISPERDAL with payors. This message can then be combined with a strong cost-effective message to move toward gaining preferred formulary status.

Secondarily, the JanssenCares patient assistance program has experienced some blatant misuse in certain states. Some counties have decided to implement this patient assistance program as a chief source of funding for RISPERDAL medication, instead of paying for the drug based upon county budgets. We will need to evaluate whether this "misuse" is part of the cost of doing business, or if we should redesign the program at the risk of alienating key customers.

Timing and Scale of Clinical Development Plan

The role of our clinical data development is crucial for maximizing RISPERDAL's potential in Bipolar Disorder. Clinical data is essential to support our strategy of differentiation. Positive data to show RISPERDAL's superior properties of rapid onset of action and low weight gain in relation to Zyprexa, Depakote, and Lithium will be important for success in 2000.

Aggressive Competition

Zyprexa is RISPERDAL's main competitor in Bipolar Disorder. Lilly has recently received a FDA approvable letter for bipolar mania for Zyprexa. This letter was issued in October 1999 and formal approval should occur during the last quarter of 1999. Lilly will be able to promote Zyprexa for Bipolar Disorder in 2000, which makes the timing of our clinical development plan even more crucial, as it will determine our capacity to promote RISPERDAL in Bipolar Disorder.

G. 2000 Business Objectives - Schizophrenia

Quantitative:

Base business sales: \$583 MM

December Schizophrenia share: 20.0%

Qualitative:

To accelerate share growth in schizophrenia, with the ultimate goal of recapturing the lead position in the treatment of schizophrenia. With the introduction of the RISPERDAL relapse prevention study in schizophrenia, as well as the competitive trial versus Zyprexa, we will have the evidence we need to reclaim the number one position.

H. Key Strategies with New Tactics for 2000 - Schizophrenia

Strategy #1: Differentiate RISPERDAL from the competition

- RISPERDAL.com
- Influence Network Marketing dinner meetings
- Field-Based Psychiatry Advisory Forums
- Ziprasidone Blocking Kit
- Sales Training Motivational Tapes

Strategy #2: Expand Reach on Key Customer Base

- Janssen Resident of the Year Award
- Residency to Practice Management Seminars
- Virtual Hallucinations Education Endeavor
- ER education pack
- Psychiatric Nurse Home Office Advisory Forum
- APNA Newsletter

Strategy #3: Solidify and Expand Opinion Leader Support

- Speaker Intranet/Slide Updates

Strategy #4: Explore Compliance Opportunities

- Compeer Program
- Discharge Planning Kit
- DTP Pharmacy Intervention

Strategy #5: Maximize Cost and Reimbursement Opportunities

- Leveraging Economic/Clinical Competitive Advantages
- Public Sector Forums

I. Sales Force Requirements - Schizophrenia

Call activity and capacity are as follows:

Sales Force	Annual Call Capacity	RIS 1st	RIS 2nd	VESTRA 1st	VESTRA 2nd
S (165)	254,100	254,100			192,693
I (52)	114,400	114,400			71,500
T (121)	199,650	33,275	124,780	166,375	
Total	568,150	401,775	124,780	166,375	264,193

Scios (94) 50,000 50,000

Message:

The sales force message for 2000 will be:

- **Differentiate on efficacy in schizophrenia**
 - significantly superior: positive and negative symptoms
 - improvement as soon as week one
 - sustained improvement
- **Discuss low weight gain**
 - 5.7 lbs. after one year
 - consider the short term/long term effect of weight gain
- **Stress appropriate dosing**
 - starting dose 2 mg QD
 - target 4-6 mg in schizophrenia

Specialty "S" and Target "T" reps will co-promote RISPERDAL in community office-based settings. Institutional reps will be asked to spend time with their key customers in the ER, to promote the use of RISPERDAL in the acutely agitated patients. They will also be asked to spend more selling time with psychiatric residents so that these important customers of the future can begin to build positive experience with the use of RISPERDAL. It will also be important for institutional reps to interact with and promote the benefits of RISPERDAL to psychiatric nurses, because these customers are highly influential in generating medication switches.

Programs:

All medical education program topics will be designed to discuss the same three key communication points.

- Teletopics
- Distance Learning Network Satellite Programs
- Peer to Peer Meetings
- Speaker Programs
- Symposia
- Audiotapes

See attachment 5a for complete listing

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J. Business Imperatives - Schizophrenia

Publication of Relapse Prevention and RISPERDAL vs Zyprexa Studies

These two studies provide solid evidence of the superior efficacy of RISPERDAL in the treatment of schizophrenia. The data strongly reinforce our sales message in schizophrenia and publication will significantly aid us in regaining lost market share in schizophrenia. Once published, we will submit these studies to internal review, with the ultimate goal of having the sales force distribute them under Washington Legal Foundation guidelines.

Lessen the Perceptual Gap Between RISPERDAL and Zyprexa in Negative Symptoms and EPS; Elevate Importance of Weight Gain and Diabetes

We will conduct another perceptual map survey with 300 key customers in 1Q'00. We will minimize the gap between RISPERDAL and Zyprexa on these two attributes, utilizing the 1999 survey for baseline results. We will also shift the overall importance of weight gain into the top ten categories, and raise awareness of diabetes risk with competitors.

Implement Ziprasidone Blocking Strategy with Sales Force Prior to Launch

We will provide the sales force with a thorough review of Pfizer as a company, their strategies for ziprasidone, and an overview of the clinical data with thorough commentary and interpretation. We will also provide the sales force with specific lists of physicians who are likely to prescribe ziprasidone at launch. It will be imperative that 100% of the sales force is fully trained and understands how to position RISPERDAL versus ziprasidone by August of 2000.

Establish Productive Working Relationships within Public Sector Markets

Timely identification and management of RISPERDAL business opportunities, threats and vulnerabilities will be essential. Reimbursement managers will establish productive working relationships with payers in Medicaid, State Mental Health, CMHCs, Counties, VAs, Department of Corrections and Behavioral Health Organizations leveraging clinical and pharmacoeconomic advantages.

Manage Public Sector Market Trends such as Budget Limitations (Diminishing Elasticity, Zyprexa Expenditures), Medicaid Managed Care and State DUR Threats

We will design and implement CME public sector forums, maximize our Performance Guarantee Program, and DUE forms with targeted top level decision makers and institutions. Each reimbursement manager will be responsible for multiple programs and selected participation in advisory boards (Corrections, VA, Medicaid and State Mental Health) with the overall goal of maximizing RISPERDAL's formulary position and business growth.

D. RISPERDAL- Geriatrics 1999 Accomplishments and Lessons Learned**Accomplishments**

- Increased RISPERDAL market share in dementia from 43.0% in Sept. 1998 to 51.1% in Sept. 1999 for a total increase of over 8 share points.
- Launch of the .25 mg and .5 mg tablets.
- Doubled use of teletopics to over 500.
- Increased attendance at nurse programs by 30%.
- Enhanced relationships with key associations including AMDA, ASCP, and AAGP.
- Better understanding of dosing by physicians. All called on physicians are primarily using low doses in the elderly in the .25 - 2 mg range.

Lessons Learned

- In the geriatric market it is vitally important to balance our safety and efficacy messages. Market research has indicated efficacy is the most important attribute a physician looks for in gaining control of agitated and/or aggressive behaviors. Our physicians believe this is a clear Risperdal strength. While no single safety parameter is more important than efficacy, it is also clear safety is extremely important, i.e., EPS, TD, sedation, anticholinergic profile, etc. We have the most robust data available and we intend to continue to leverage this data stressing, in parallel, our unsurpassed efficacy and safety messages.
- Without proper education PPS and OBRA regulations could negatively impact antipsychotic prescriptions in the nursing home. PPS has more fully impacted nursing homes, as the 3 year staged national rollout is nearly complete. This has caused some nursing homes to increase pressure on physicians to prescribe less expensive drugs such as conventionals. Proper education on overall health care cost reductions and improved patient care with RISPERDAL is important in this environment.
- Nurses are key influencers over switching and diagnoses. Physicians are very open to taking advice from director's of nursing and other nurses since they are with the patients, observing symptoms and side effects for such a great amount of time.
- Important to stress proper dosing or physicians will switch because of EPS. EPS with RISPERDAL is dose dependent and when used at 2 mg or greater in geriatric patients there is far greater risk of EPS. Currently, the dosing in our package insert does not indicate the truly appropriate range for patients.
- Target audiences are still interested in treating behavioral symptoms more than "psychotic" symptoms. Physicians will treat psychotic symptoms such as paranoia, delusions, and hallucinations when they involve aggression or agitation that becomes problematic for the patient and staff.
- The LTC market is very responsive to promotion, however it is becoming increasingly more competitive as Eli Lilly and AstraZeneca both have launched sales forces in the LTC market.

E. SWOT Analysis - Geriatrics

<u>Strengths</u> Efficacy/safety data (RIS-63 & RIS-70) Market leadership Performance based contracts J&J LTCM/ElderCare team Availability of dosing options	<u>Weaknesses</u> EPS at $\geq 2\text{mg/day}$ Physician/customer targeting due to data Delay in label change for RISPERDAL No switching or 'head-to-head' data Dosing confusion OBRA Orthostatic hypotension
<u>Opportunities</u> RIS-OLZ Dementia Trial Additional 'pull-through' programs REMINYL synergy OL/association relationships WLF AUS-5 Study	<u>Threats</u> Dementia label for Zyprexa Dementia label denied for RISPERDAL Competitive sales force expansions Zeldox/Aricept/Zoloft synergy Seroquel geriatric focus AChE, AC & ADP use PPS Lilly comparative trial

F. Key Issues - Geriatrics

Increasing Competitive Intensity

As the competition grows among the atypical antipsychotics and our competitors add 'ElderCare-like' sales forces it becomes more important for us to maintain our share of voice. Our competitors are also publishing off-label data prolifically and these may dilute the impact of our few small Phase IV studies in geriatric patients. In addition, both Lilly and Zeneca have increased their share of voice at national conventions and with national and regional CME education.

Increased Focus on Opinion Leaders

Competitive intensity is increasing for share of voice with the opinion leaders as well. In geriatrics there is a small number of really top tier opinion leaders. These individuals are all being strongly pursued by both Eli Lilly and AstraZeneca. We will need to ensure coverage of these opinion leaders in order to build and maintain the relationships we have already established. We should also leverage our REMINYL position when maximizing our relationships with the opinion leaders.

Perceptual Gap

A perceptual gap exists between RISPERDAL's clinical data in geriatrics and the perception physicians hold who treat geriatric patients. RISPERDAL is perceived as having a worse safety profile than the drug actually has, often because physicians are using inappropriately high doses. In addition, most physicians do not recognize that RISPERDAL is the only drug with proven data on efficacy in geriatric patients.

Sub-optimal Customer Targeting

Sub-optimal customer targeting exists as a result of lack of decile data on physicians who treat geriatric patients in nursing homes and hospitals. A broad number of health care professionals, with a varied understanding of antipsychotics, influence patient treatment and switching. It takes a great deal of time and education to ensure that all of the members of the treatment team understand the impact of using RISPERDAL in their geriatric patients or any one "weak link" in the treatment team can negatively impact the business. The primary care audience needs additional education and coverage. This will be substantially increased in 2000, with over half of the antipsychotic decile 4-9 primary care physicians called on. Our coverage will increase to almost 75% after the sales force expansion.

Reimbursement "Window of Opportunity"

We have a reimbursement window of opportunity that is beginning to close as the Prospective Payment System (PPS) more fully impacts nursing homes. By the end of 2000 PPS should be fully implemented nationwide. PPS encourages nursing homes to manage total drug costs downward and thus encourages the use of conventionals vs. atypicals. It will be important for RISPERDAL to capture as much share as possible in order to prevent possible erosion of market share and to insure there is a better understanding of the overall treatment cost savings with RISPERDAL. In addition, the cost gap between RISPERDAL and other atypicals is narrowing in patients diagnosed with dementia. Zyprexa's dosing size continues to decline which makes it only slightly more expensive than RISPERDAL and the newest atypical, Seroquel appears to be priced at a slight discount to RISPERDAL although the data is fairly thin to determine the average dose and cost in dementia patients.

FDA Changing Position

The FDA has recently developed some hesitation on granting specific indications on the use of antipsychotics in Alzheimer's patients with psychotic symptoms. Previously, the FDA had indicated it was very likely RISPERDAL would be granted this label change. The FDA has declined approval for Zyprexa and has announced it will hold an advisory committee meeting in the spring of 2000 to discuss all the issues before granting any approvals.

G. 2000 Business Goals & Objectives - Geriatrics

Quantitative:

Geriatric Sales: \$302 MM

December Share: 57%

Qualitative:

Maximize and grow RISPERDAL's market leadership in geriatrics and LTC

H. Key Strategies and Tactics - Geriatrics

Strategy #1: Optimize safety and efficacy positioning

- CNS Advisory Forums
- Dementia labeling change preparation (FDA advisory committee meeting) and Dementia launch promotion and PR preparation
- Dementia IPT CD-ROM
- CME speaker's bureau

Strategy #2: Rapidly drive market penetration

- Nursing home team education
- PPS video and symposia
- TeleTopics

Strategy #3: Expand reach to key customers

- PCP CME teleconferences
- Nurse collegia
- Patient/caregiver educational brochures

Strategy #4: Develop advocacy and opinion leader support

- PCP Advisory boards co-sponsored by RISPERDAL and REMINYL brand teams
- Advisory boards with geriatric psych residency training directors
- Advisory boards with Directors of Assisted Living Facilities
- Advisory boards with key Nurse Practitioners
- Educational program development with AAGP, AMDA, AGS, NADONA, ASCP

Strategy #5: Strengthen data generation and dissemination

- Analyze RIS-63 and RIS-70 data
- Increase number of small, investigator initiated studies in geriatric patients
- Increase body of peer reviewed published data for use under WLF

I. Sales Force Requirements - Geriatrics

Calls – ElderCare, with the expansion to 136 representatives by March, should provide a total of 65,500 calls for RISPERDAL - geriatrics for 2000.

Message – ◦ RISPERDAL has proven efficacy in treating geriatric patients

- RISPERDAL has an excellent safety and tolerability profile in geriatric patients
- RISPERDAL is easy to dose with our flexibility of formulations and easy titration

Programs -

ElderCare

- Speaker's bureau
- TeleTopics
- PCP teleconferences
- Videos
- Case workbooks
- Nurse Collegia
- Advisory Forums
- SLU Preceptorship
- Giveaways
- Backgrounder
- Patient/caregiver brochure
- Patient pill box
- New campaign materials
- Safety fact sheets
- Dementia launch
- Advisory Forums
- SLU Preceptorship
- IPT CD-ROM

LTC Business Management Team

It is increasingly important to work closely with this team and we will continue to support their efforts with their primary customers the pharmacy providers (Omnicare, PharMerica, NCS and NeighborCare). We have set aside specific programs and budgets for this team.

- Speaker's bureau
- TeleTopics
- Videos
- GNC education program
- Advisory Forums
- Giveaways
- Backgrounder
- Safety fact sheets
- Dementia launch
- Advisory Forums
- SLU Preceptorship

J. Business Imperatives - Geriatrics

Expand Reach with PCPs

The ElderCare initial expansion will increase the size of the sales force from 86 to 136 representatives. This will enable the sales force to increase reach and frequency of antipsychotic decile 4-9 primary care physicians from 2,600 in January to 4,500 by March. It is imperative that we reach all 8,000 decile 4-9 physicians with Risperdal promotional items at least twice in 2000. This will be done through direct mail and teleconferences where we do not have coverage of physicians. In addition, we will achieve 2 calls per quarter on at least 90% of the 4,500 primary care physicians we are calling on with ElderCare.

Implement a Successful Plan for the FDA Advisory Committee

A white paper will be developed which will effectively summarize RISPERDAL's efficacy and safety data in geriatrics. Data will be compiled from key Janssen studies such as RIS-USA-63, RIS-USA-70, RIS-INT-24 and RIS-INT-26. This will be disseminated prior to the FDA Advisory Committee meeting on the use of antipsychotics in the elderly. We will also leverage the behavioral data contained in our REMINYL Phase III trials.

In addition, a complete backgrounder on the FDA advisory committee members will be disseminated to internal Janssen personnel. The backgrounder will include publication histories, and other appropriate information and this will assist our regulatory group in negotiating a favorable outcome for RISPERDAL regarding label changes in geriatrics.

Generate/Disseminate Clinical Data

It will be critical to generate publications in 2000 through additional analysis of the large RIS-USA-63 and RIS-USA-70 databases. Preliminary analysis should be complete by Q3'00 and pursuit of publications, where applicable, should be sought by end of year.

We will also begin comparative studies with RISPERDAL vs. Zyprexa by end of Q2'00 to assess primarily anticholinergic side effects with other secondary measures in place. A

RISPERDAL/REMINYL combination use study should be assessed by end of Q2'00 and if it is determined that it is in the best interest of both products the study should begin, at the latest, by the beginning of Q4'00. The RISP/REM study will likely primarily focus on PK and safety issues with efficacy a secondary measure.

Increase Focus on Opinion Leaders

Opinion leader development is an important strategy for us in 2000 and as such it will be very important for us to ensure both MSL and representative coverage of at least the top 30 opinion leaders in geriatrics. MSL capacity will be assessed to determine if they will be able to call on additional opinion leaders. The representatives will call on the top 100 opinion leaders in geriatrics at least 10 times.

D. 1999 Bipolar Accomplishments and Lessons Learned**Accomplishments**

- Focused marketing effort to maximize synergies between RISPERDAL and TOPAMAX
- Organized brand team and developed strategic and tactical plans for 2000
- Initiated Bipolar opinion leader development in conjunction with TOPAMAX

Lessons Learned**RISPERDAL used as add on agent for antipsychotic effects in bipolar disorder**

The norm in the treatment of bipolar disorder is to combine therapies. Market research shows that 73% of patients are treated by a combination of therapies. In this context RISPERDAL is not an exception and has been prescribed as an add-on therapy for its antipsychotic effects.

Need data in bipolar disorder to further differentiate RISPERDAL from Zyprexa

In order to differentiate RISPERDAL from Zyprexa, we need to generate clinical data in bipolar disorder and communicate positive results effectively to the psychiatric community. Market research indicates that physicians perceive RISPERDAL as stronger on "improving quality of life" and "reduced risk of weight gain". We must generate clinical data to show that. Positive data from clinical studies will be the foundation for growth in the bipolar segment.

Patients change therapy due to weight gain

The importance of the weight gain side effect is evident. Weight gain affects compliance. Market research shows that one third of the patient population changes therapy due to weight gain. In this way, weight gain is a major obstacle for compliance in the treatment of bipolar disorder. Market research indicates that at least 50% of prescribers associate the use of Zyprexa, Depakote, or Lithium with weight gain. While low weight gain is an important property for patients and prescribers, Zyprexa, Depakote, and Lithium are not associated with this attribute according to the physicians' perception.

Effectiveness and weight gain are 'differentiating' factors

Effectiveness, including rapid onset of action and low weight gain are key properties that may become important differentiating factors for RISPERDAL in bipolar disorder. The psychiatric community considers these attributes important as they improve compliance and patients' quality of life. As we generate and disseminate positive clinical data to support those attributes for RISPERDAL, we will have a strong competitive advantage in relation to Zyprexa, Depakote, and Lithium.

E. SWOT Analysis - Bipolar

The SWOT analysis is the basis for RISPERDAL Bipolar promotional activity in 2000:

<u>Strengths</u> Familiar APS profile Low weight gain Cost advantage vs. Zyprexa Faster onset of action vs. mood stabilizers "Improves quality of life" RIS-USA-112 Data (Anxiety/Depression)	<u>Weaknesses</u> Dose-dependent EPS risk Conventional agents perceived as faster acting in mania Perceived mania induction
<u>Opportunities</u> RIS-USA-102 Unsatisfied Market & RIS-INT-46 Data Leverage Topiramate interest into RISPERDAL support BD depression & maintenance Improve compliance	<u>Threats</u> Zyprexa BD mono-therapy label change: Acute indication (4Q'99), Depression (4Q'01), Maintenance (4Q'02), Zyprexa vs Depakote data Zeldox launch Seroquel fast growing market share

F. Key Issues - Bipolar

Large Dissatisfied Market

The diagnosis, and treatment and management of bipolar disorder is very complex. Market research indicates that the psychiatric community is not satisfied with the available choices for treatment of bipolar disorder. 98% of specialists want to make adjustment in treatment. This dissatisfied population of physicians and patients represents a major opportunity for RISPERDAL given its superior attributes of rapid onset of action and low weight gain.

Timing and Scale of Clinical Development Plan

The role of our clinical data development is crucial for maximizing RISPERDAL's potential in Bipolar Disorder. Positive data to show RISPERDAL's superior properties of effectiveness, rapid onset of action and low weight gain in relation to Zyprexa, Depakote, and Lithium will be important for successful differentiation.

Aggressive Competition

Lilly has recently received a FDA approvable letter for acute bipolar mania for Zyprexa. This letter was issued in October 1999 and formal approval is expected in December. Lilly will be able to promote Zyprexa for Bipolar Disorder in 2000, which makes the timing of our clinical development plan critical.

Weak Opinion Leader Support Base

A key factor for RISPERDAL's success in bipolar is opinion leader support. Few programs were developed to enhance RISPERDAL's opinion leader support in the past. Consequently, few opinion leaders supported the use of RISPERDAL bipolar disorder. Opinion leader support is essential for obtaining expert endorsement for use in bipolar disorder. These same expert

endorsement for use in bipolar disorder. These same experts also conduct seminars and dinner meetings, etc., at which they endorse RISPERDAL.

Poor Patient Compliance and Management

The poor patient compliance and management in bipolar represents a major opportunity for RISPERDAL. Many bipolar patients are non-compliant with their medications for a variety of reasons. Side effects from mood stabilizers, such as weight gain, tremor, hair loss causes 50% of patients to discontinue therapy at some time during treatment. In fact they average length of therapy is only 70 days, in a disease which daily therapy is recommended. Non-compliance increases the chance of an acute bipolar episode and also reduces the sales of drugs used to treat bipolar disorder. Improvement in patient compliance and management will enhance RISPERDAL usage and strength its position as the treatment of choice in bipolar disorder.

G. 2000 Business Goals & Objectives - Bipolar

Quantitative:

Bipolar business sales: \$175 MM

December TRx: 32.0%

Qualitative:

Differentiate RISPERDAL from other agents in Bipolar Disorder capitalizing on RISPERDAL's effectiveness as add-on therapy, fast onset of action, and low weight gain.

H. Key Strategies and Major Tactics - Bipolar

Strategy #1: Differentiate RISPERDAL & Disseminate Benefits for Appropriate Patients

- RIS-102/46/112 Dissemination Program
- Regional CME Programs: 3 Tracks
- RISPERDAL Evolution
- Publication Program
- Bipolar Sales Training and Targeting Program

Strategy #2: Strengthen Opinion Leader and Advocacy Support

- Millennium Leaders
- RISPERDAL BD Symposia
- CME Casexchange BD Meetings
- MSL Program
- Janssen Resident of the Year Award

Strategy #3: Improve Compliance and Optimize Patient Management

- NDMDA Ultra-Care & Patient Max Programs: Diagnostic Kit and Patient Treatment Guide
- NIMH Educational Program: "New Developments in the Diagnosis and Management of BD for Community Psychiatry"

I. Sales Force Requirements - Bipolar

Programs:

The sales force will be involved in three medical educational programs and one training program, as follows:

RIS-102/46/112 Dissemination Program

The sales force will disseminate a sealed reprint pack to physicians with the results of the RIS-102, 46, and 112 studies. We expect to have the sealed reprint packs by the end of the first cycle for RIS-112 and third and fourth quarters for RIS-102 and RIS-46.

CME Casexchange Programs

All sales representatives will be involved in this program. Each sales representative will invite 10 to 12 psychiatrists to each dinner. A logistics agency will be utilized to assist in the organization of this program. Janssen will sponsor a series of 320 CME accredited dinner meetings in 2000.

Regional CME Programs: 3 Tracks

These 60 one-day CME programs will be held in the top 25 markets across the country. Each meeting will have at least 50 community psychiatrists attending. Our sales force will be able to deliver invitations during the recruitment process. We recommend the attendance of sales representatives and district managers to each meeting.

Bipolar Sales Training Program

The sales representatives will be trained on bipolar disorder. We are planning presentations at the district meetings and sales training classes. Didactic materials will also be provided to sales representatives. Training videotape on bipolar disorder is expected to be completed by the end of the first quarter.

Targeting

Treatment of bipolar disorder, and consequently the use of drugs to treat the disease, is concentrated among minority of psychiatrist. Approximately 3500 physicians are responsible for half of the prescriptions for mood stabilizers. Similarly, 7000 psychiatrist are responsible for 80% of the total volume and 10,000 for 90% of volume. Cross-mating decile 8,9, 10 mood stabilizers and antipsychotics identify 3600 high volume target psychiatrists. Approximately 67% are currently called on by the Janssen sales organization. Targeted lists by territory will be available for use in 2000.

J. Business Imperatives - Bipolar

In order to achieve the presented business goals and objectives, the following deliverables are critical:

Use appropriate data to blunt Zyprexa launch

It is mandatory to utilize onset of action, effectiveness, and weight gain data currently available to blunt the Zyprexa launch. All data about RISPERDAL's superior attributes must be well disseminated to the psychiatric community.

- Regional CME programs completed – 20 per quarter 2Q'00 through 4Q'00
- 300 CME case exchange (dinner meeting) programs completed
- 4 posters, 2 journal articles, and 1 supplement in each quarter of 2000

Quality and timing of studies

The quality and timing of RIS-USA-102 and RIS-INT-46 studies are crucial in order to achieve the 2000 qualitative and quantitative objectives. Positive and timely data will help to differentiate RISPERDAL from Zyprexa.

- RIS-USA-102 Manuscript completed and submitted 1Q'00
- Accepted for publication and published 2Q'00
- Field force sealed reprint distributed 2Q'00
- RIS-INT-46 sealed reprint distributed 4Q'00

Strengthen Opinion Leader Support

It will mandatory to strengthen bipolar opinion leader support. Existing relationships should be reinforced and new relationships established. Support from Bipolar opinion leaders will be crucial to success in 2000.

Opinion Leader Support

- Develop individual relationship plans for top 100 opinion leaders and MSL call plan
- Conduct 1 regional advisory board per quarter and 2 national advisory boards in 2000
- Sponsor 1 national preceptor program per quarter in 2000
- Sponsor 5 visiting professors programs per quarter in 2000

**RISPERDAL SUMMARY
ATTACHMENT 1**

	1997	1998	1999 YTD 10/99	2000 Forecast
Market Size (\$)	\$1.7 B	\$2.4 B	\$2.9 B	\$3.4 B
% Growth	47%	41%	21%	17%
Net Sales (\$MM)	\$589 MM	\$695 MM	\$734 MM	\$1059 MM
% Growth	17.1%	18.0%	25.5%	15.0%
Unit Sales	264.9	303.2 MM	316.7 MM	452.5 MM
% Growth		14%	29%	16%
Market Share (%)				
TRx	20.7%	23.7%	26.1%	27.6%
NRx	22.0%	25.0%	27.5%	30.0%
Dollars	36.3%	31.9%	32.1%	31.1%
Share of Business by Indication/Specialty (NRx %)				
Schizophrenia	33%	18%	18%	20%
Bipolar Disorder	14%	27%	25%	32%
Dementia	12%	45%	50%	52%
Share of Business by Indication/Specialty (Dollar %)				
Schizophrenia	37.1%	23.2%	21.3%	19.8%
Bipolar Disorder	45.1%	33.1%	32.2%	34.3%
Dementia	48.1%	55.3%	57.6%	59.3%
Average Price/Dose	\$4.27/Day	\$4.15/Day	\$4.82/Day	\$4.80/Day

**RISPERDAL
COMPETITIVE OVERVIEW
ATTACHMENT 2**

	1997	1998	1999 YTD	2000 Forecast
Sales (\$MM)				
RISPERDAL	\$618 MM	\$753 MM	\$620 MM	\$1059 MM
Zyprexa	\$575 MM	\$1054 MM	\$780 MM	\$1420 MM
Seroquel	\$19 MM	\$88 MM	\$104 MM	\$277 MM
Conventionals	\$250 MM	\$214 MM	\$117 MM	\$150 MM
Dollar Market Share (%)				
RISPERDAL	36%	32%	32%	31%
Zyprexa	34%	45%	46%	42%
Seroquel	1%	4%	6%	8%
Conventionals	15%	8%	6%	4%
NRx Market Share (%)				
RISPERDAL	22.0%	25.0%	27.3%	30.0%
Zyprexa	12.3%	20.0%	23.2%	25.4%
Seroquel	0.2%	3.1%	5.7%	9.4%
Conventionals	57.6%	46.2%	37.9%	26.8%
TRx Market Share (%)				
RISPERDAL	20.7%	23.7%	26.0%	27.6%
Zyprexa	9.9%	17.6%	21.0%	23.4%
Seroquel	0.1%	2.4%	4.9%	7.8%
Conventionals	58.2%	47.9%	39.9%	29.8%
Avg Price/Dose				
RISPERDAL	\$4.27	\$4.15	\$4.82	\$4.80
Zyprexa	\$7.41	\$7.42	\$7.51	\$7.73
Seroquel	N/A	\$4.57	\$4.62	\$4.66

Competitive Brand Overview (current or future):

Brand	Launch Date	Indication	Efficacy or Safety Advantages	Formulations	Patent Expiration
Zyprexa / Lilly	10/96	Mgt of psychotic sx	Low prolactin/EPS	Tablet	2010
Seroquel / AstraZeneca	10/97	Mgt of psychotic sx	Low prolactin/EPS	Tablet	2007
Zeldox / Pfizer	3Q'00	Mgt of psychotic sx	Low weight gain Relapse prevention	Tablet, IM	2007

**BRAND
COMPETITIVE SPEND
ATTACHMENT 3**

	<u>Sales Force</u>		<u>Samples</u>	<u>Med Ed (\$MM)</u>	<u>Journal (\$MM)</u>	<u>DTC (\$)</u>
	<u># Reps</u>	<u># Calls/Yr</u>	<u># YTD SEP/99</u> <u>EUSMP</u> <u>(000's)</u>			
RISPERDAL	317	245,000	8633	11.0 MM	\$1.5 MM	N/A
Zyprexa	559	241,000	8897	9.3 MM	\$1.7 MM	N/A
Seroquel	330	96,000	10535	3.7 MM	\$1.0 MM	N/A

*Units are a more accurate comparison of sample share of voice than dollars which are based on retail value.

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**RISPERDAL - Schizophrenia
SALES FORCE COVERAGE
ATTACHMENT 4**

2000 Promotion Cycles:

Assumption March 1, 2000 VESTRA Launch

	Cycle 1		Cycle 2		Cycle 3	
Target Group (# physicians)						
S-Rep - APS 7-9	9,600		9,600		9,600	
T-Rep - ADP 5-9	18,050		18,050		18,050	
I-Rep - 450 Instit.	6,120		6,120		6,120	
Eldercare SF	12,700 Targeted MDs		12,700 Targeted MDs		12,700 Targeted MDs	
Scios - APS 5-7	6,601		6,601		6,601	
Call Frequency						
Eldercare SF	1x per month (80%)		1x per month (80%)		1x per month (80%)	
S-Rep	2x per month Dec 8&9		2x per month Dec 8&9		2x per month Dec 8&9	
T-Rep	1x per month ADP 5-9		1x per month ADP 5-9		1x per month ADP 5-9	
I-Rep	2x per month top 75		2x per month top 75		2x per month top 75	
(Monthly, etc)						
Product Position						
S-Rep	RIS-1/VES-2		RIS-1/VES-2		RIS-1/VES-2	
T-Rep	VES-1/RIS-2		VES-1/RIS-2		VES-1/RIS-2	
I-Rep	RIS-1/VES-2		RIS-1/VES-2		RIS-1/VES-2	
Eldercare SF	1) RISPERDAL 2) DURAGESIC 3) ACIPHEX		1) RISPERDAL 2) DURAGESIC 3) ACIPHEX		1) RISPERDAL 2) DURAGESIC 3) ACIPHEX	
Total # Calls, Support	# Calls	PDEs	# Calls	PDEs	# Calls	PDEs
S-Rep	84,700	84,700	84,700	84,700	84,700	84,700
T-Rep	58,231	45,753	49,912	24,956	49,912	24,956
I-Rep	38,133	38,133	38,133	38,133	38,133	38,133
Eldercare SF*	47,500	47,500	65,600	65,600	85,000	85,000
Scios	16,666	16,666	16,666	16,666	16,666	16,666
Total	245,230	232,752	255,011	230,055	274,411	249,455
Cost of Sales (\$MM)						
Eldercare	\$ 5.9 MM (130Kx136)		5.9 MM		5.9 MM	
CNS	\$14.6 MM (130Kx338)		14.6 MM		14.6 MM	
(non-PME)						

- Includes expansion of Eldercare 50 reps in March and 40 Reps in July

**RISPERDAL - Schizophrenia
PROGRAMS/KEY TACTICS BY CYCLE
ATTACHMENT 5a**

	Cycle 1	Cycle 2	Cycle 3	Total Spending (\$M)
Sales Force (support*)	Base Sales Aid/Slim Jim Acute Flash Card/Slim Jim Promotional Patient Video Schizophrenia Wall Chart Ziprasidone Backgrounder Hospital Display Panels Motivational Audiotape RISPERDAL University Discharge Planning Kit	Motivational Audiotape Discharge Planning Kit	Base Sales Aid/Slim Jim Promotional Patient Video Motivational Audiotape Discharge Planning Kit	6.3M
Medical Education	Teletopics (CME) Distance Learning Network CME) Peer-to-Peer Dinner Programs Speaker Intranet Speaker Training Direct Fax Program RISPERDAL.com APNA Newsletter Public Sector Forums (CME) Progress in Psychoses(CME)	Teletopics DLN Peer-to-Peer Dinner Programs Speaker Intranet Speaker Training Direct Fax Program RISPERDAL.com APNA Newsletter Public Sector Forums(CME) Progress in Psychoses(CME)	Teletopics DLN Peer-to-Peer Dinner Programs Speaker Intranet Speaker Training Direct Fax Program RISPERDAL.com APNA Newsletter Public Sector Forums(CME) Progress in Psychoses (CME)	18.1M
Journal				2.2M
Public Relations	Virtual Hallucinations on the Road	Virtual Hallucinations on the Road		500K

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DTP (DTC)	RISPERDAL.com DTP Pharmacy Intervention	RISPERDAL.com DTP Pharmacy Intervention	RISPERDAL.com DTP Pharmacy Intervention	650K
Other	Pilot: Residency to Practice Management Home Office Psychiatry Advisory Forum CNS Summit Compeer Program	Field-Based Psychiatry Advisory Forum Resident of the Year Award Home Office Psychiatry Advisory Forum	Field-Based Psychiatry Advisory Forum Home Office Psychiatry Advisory Forum	3.2M

- Access tools, etc.

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**RISPERDAL - Schizophrenia
MEDICAL EDUCATION
ATTACHMENT 6a**

Medical Education Goals:

- To grow RISPERDAL NRx schizophrenia market share, grow the lead for RISPERDAL as the number one prescribed antipsychotic, blunt continued growth of Zyprexa and Seroquel, and pre-position the launch of Zeldox.
- To reinforce key promotional message: RISPERDAL offers superior efficacy in the treatment of positive and negative symptoms, with low weight gain, at appropriate doses of 4-6 mg/day in the treatment of schizophrenia.

Target Audiences:

- High Prescribing Psychiatrists
- Key Opinion Leaders
- Psychiatric Residents
- Psychiatric Nurses
- Pharmacists

Key Messages:

RISPERDAL offers superior efficacy in the treatment of positive and negative symptoms, with low weight gain, at appropriate doses of 4-6 mg/day in the treatment of schizophrenia.

Rationale:

Primarily three-customer segment drive RISPERDAL market share. Therefore, the majority of medical education PME's will be directed to high volume prescribers, speakers, and key opinion leaders. Medical education is a critical medium for informing these segments on the benefits of RISPERDAL.

Key 2000 Tactics (not an all-inclusive list):

Program Name	Timing	# Participants	Cost	Measurement
Natl. & Regl. Speaker Training	Q1-4	500	\$ 420,000	Phys. evals
Speaker Intranet Site	Q1-4	All speakers	50,000	# of hits
Prog. in Psychoses Symposia	Q1	4,000	1,021,250	Phys.evals
Distance Learning Network	Q1-4	12,000	475,000	Phys. evals
Teletopics	Q1-4	15,000	1,279,297	Phys.evals
Rep Visiting Faculty Programs	Q1-4	30,000	7,252,500	Rep feedbck
Psychiatry Advisory Forum	Q1-4	400	1,300,000	Phys.evals
Promo Dinner Meetings	Q1-4	325	160,000	Early View

Total Med Ed Budget:
21.5M

**RISPERDAL - Schizophrenia
JOURNAL ADVERTISING
ATTACHMENT 7a**

Advertising Goals:

1. Heighten awareness of RISPERDAL as the antipsychotic with unsurpassed efficacy and tolerability.
2. Reinforce brand recognition and brand image
3. Reinforce the leadership position of RISPERDAL

Target Audience/Segments:

Psychiatrists (primary) – institutional and office-based
Psychiatric Nurses
Case Managers

Brand Positioning by Segment:

RISPERDAL is the only atypical that offers superior efficacy for a broad range of psychotic symptoms combined with an excellent tolerability profile for long-term patient well-being.

Unique Selling Proposition:

RISPERDAL offers superior efficacy uncompromised by excessive weight gain.

Media Vehicles:

Journal Advertising

**RISPERDAL - Schizophrenia
PUBLIC RELATIONS
ATTACHMENT 8a**

Public Relations Goals:

Leverage trade, media, and investor media to grow RISPERDAL leadership position in schizophrenia and strengthen Janssen's position as a leader in CNS.

Target Audience(s):

- Providers (Psychiatrists, nurses, pharmacists)
- Patients, caregivers, and patient advocates
- Analysts
- Internal Janssen customers

Key Messages:

RISPERDAL is the number one prescribed antipsychotic. The key communication points will reflect our current sales message of superior efficacy with low weight gain. This message is supported by the relapse prevention trial and the RISPERDAL vs Zyprexa trial.

Rationale:

- Support of field selling efforts
- Expand reach into customer/caregiver market

2000 Tactics:

- Virtual Hallucinations Educational Endeavor
- Ongoing media intervention
 - competitive issues management
 - patient success stories
- Targeted medical meetings support

<u>Program Name</u>	<u>Timing</u>	<u>Estimated No. of Exposures</u>	<u>Total Cost</u>	<u>Measurement</u>
Virtual Hallucinations		10 cities/250 per city	500K	N/A

**RISPERDAL - Schizophrenia
DIRECT TO PATIENT/CONSUMER
ATTACHMENT 9a**

DTP (DTC) Goals:

Heighten awareness of RISPERDAL with patients, caregivers and families

Target Audience(s):

Patients

Families

Caregivers

Key Messages:

RISPERDAL is an effective and safe medication that can offer patients differential and substantial benefits in the treatment of mental illness

Rationale:

Noncompliance is one of the biggest obstacles in treating the mentally ill. These programs will be designed to remind patients/reinforce the benefits of staying compliant with medication.

2000 Tactics:

RISPERDAL.com

Pharmacy Intervention Plan

RISPERDAL Promotional Video

<u>Program Name</u>	<u>Timing</u>	<u>Estimated No. of Exposures</u>	<u>Total Cost</u>	<u>Measurement</u>
RISPERDAL.com	Q1-4	120K per year	150K(Phase1)	#hits/month
Pharmacy Interven.	Q1-4	10% retail Rxes	500K	Rx refills
RIS Promo Video	Q1,Q4	Unlimited	250K	Rep feedback

**RISPERDAL - Schizophrenia
BRAND CONVENTIONS/MED MEETINGS
ATTACHMENT 10a**

Meeting Name	No. of Attendees	No. of Symposia	Major Messages	New Data	Entertainment	Total Budget
Biological Psychiatry	300	-	Poster data that supports main messages	RIS 79 sub-analyses	Dinner	150K
APA	15,000	3 base	Schizophrenia, Weight gain Acute	RIS 79 sub-analyses	2 social events	4MM
Institute on Psychiatric Services	3,000	2	Schizophrenia		-	650K
US Psych Congress	4,000	2	Schizophrenia		Social Event for Clinical Scholars	750K
ACNP	1500	-	Poster data that supports main messages	Dependent	1 dinner	200K
ACEP	5,000	1	Psychoses in the Acute Setting	Currier	-	200K
APNA	500 nurses	1			-	150K
NCDEU	250	-	Poster data that supports main messages	Dependent	-	35K
ACCP	1200	1	Schizophrenia	Dependent	-	200K
ASHP	1500	1		Cost/Relapse prevention	-	200K

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**RISPERDAL
STRATEGIC CUSTOMER SEGMENTS
ATTACHMENT 11**

2000 Brand Marketing Objective:

Customer Segments:

	Managed Care	Long Term Care
Segment Overview	Atypicals are a low interest and low intervention category for Janssen Top 14 Accounts. (Exceptions: PCS and VA). RISPERDAL market share exceeds national average (50% in three product market) likely due to lesser restrictions to use versus Medicaid and LTC markets	• J&J Growing Leadership position in post-acute care market • Evolution of hybrid customers • Strong growth in Alternate Mkts (ALF (dementia), HHC, Hospice) • Information Opportunities (physician lists, outcomes research)
Key Issues	• RISPERDAL treated therapeutic areas are low interest to MCOs limiting partnering opportunities • To deliver value offerings for managed care plans must address other needs (NCQA/Hedis compliance) • Few MCO Psychiatric Thought Leaders exist	• PPS/Medicare R Benefit • Consolidation & emergence of hybrid customers • Growing focus from competitive pharmaceutical manufacturers
2000 Objective	• Develop new compliance program that is designed to meet MCO needs for NCQA/HEDIS eligibility • Impact MCO Thought Leaders in identified areas	• Deliver \$302 MM in LTC sales • Exceed 43% DACON Share • Widen lead with Zyprexa by an additional 5 points w/Tier 1 customers
2000 Plans	• Medi-Cal regional symposia (D. Smith) • New England MCO Thought Leader Panel (D. Nelson) • Interest customers in ACQUIRE program and linked RISPERDAL compliance program • Expand Thought Leader base and track through PsychScape	• Active Intervention Programs @ all Tier 1 Customers • Consultant Pharmacists training (Tier 1 Accounts) • Targeted experts-conference calls • EC/LTC joint physician targeting by regional sites • Focus on IMD facilities in CA • LTCM Speaker / Meeting
Spending (\$MM)	\$400,000	\$140,000

	Reimbursement / Payors
Segment Overview	• 85% of RISPERDAL sales paid by public sector (Medicaid, State Mental Health, Counties, VA's and Department of Corrections).
Key Issues	• Funding stream, cost of atypicals, and step therapy algorithms. • Shift from Medicaid to managed care resulting in reimbursement barriers/system fragmentation (i.e. inpatient to outpatient, continuum of care). • Jancare usage as payor of first resort
2000 Objective	• Maximize public sector RISPERDAL market share, protect existing markets and expand sales in underachieving markets.
2000 Plans	• Public Sector Forums (CME) • Advocacy Relations (NAMI & NMHA) • Algorithm Implementation and Support • Corrections Advisory Board • State Mental Health Advisory Board • Performance Guarantee Program • Creative Contracting Initiatives • VA Advisory Board • Consumer Media Training • Reduce GPO rebates
Spending (\$MM)	

	Reimbursement / Payors
Segment Overview	85% of RISPERDAL sales paid by public sector (Medicaid, State Mental Health, Counties, VA's and Department of Corrections).
Key Issues	- Funding stream, cost of atypicals, and step therapy algorithms. - Shift from Medicaid to managed care resulting in reimbursement barriers/system fragmentation (i.e. inpatient to outpatient, continuum of care). - Jancares usage as payor of first resort
2000 Objective	Maximize public sector RISPERDAL market share, protect existing markets and expand sales in underachieving markets.
2000 Plans	- Public Sector Forums (CME) - Advocacy Relations (NAMI & NMHA) - Algorithm Implementation and Support - Corrections Advisory Board - State Mental Health Advisory Board - Performance Guarantee Program - Creative Contracting Initiatives - VA Advisory Board - Consumer Media Training - Reduce GPO rebates
Spending (\$MM)	

**RISPERDAL - Schizophrenia
MARKET RESEARCH
ATTACHMENT 13a**

2000 RISPERDAL Schizophrenia Marketing Objective:

- Differentiate RISPERDAL from the competition
- Expand reach on key customer base
- Explore compliance opportunities

2000 Market Research Plan:

Objective	Rationale	Target	Timing (start/finish)
Understand current market perceptions	Track changes in competitive landscape; exploit opportunities	Psychs/PCPs/Opinion Leaders	1Q/2Q
Develop and test promotional materials	Maximize RISPERDAL communication effectiveness	Psychs/ER Psychs/PCP	1Q/3Q
Competitively pre-position vs. Zeldox	Maintain/grow share of market	All	4Q'99/1Q
Track Zeldox trial lists	Explore reasons for use; develop defensive promotional materials	Lead users	Immediate post-launch
Grow share in ER user base	New volume opportunity	ER Psychs	1Q
Optimize rep/doc communication	Marketing efficiency	All detailed audiences	2Q/4Q
Differentiate RISPERDAL in compliance	Increase sales volume	Psychs	1Q

RISPERDAL - Geriatrics
PROGRAMS/KEY TACTICS BY CYCLE
ATTACHMENT 5b

	Cycle 1	Cycle 2	Cycle 3	Total Spending (\$MM)
Sales Force (support*)	ElderCare • SLU preceptorship • IPT CD-ROM • Backgrounder CNS I-reps • Backgrounder • SLU preceptorship	ElderCare • SLU preceptorship • IPT CD-ROM • New promo materials • Safety fact sheets CNS I-reps • Institutional brochure • New promo materials • Safety fact sheets • SLU preceptorship	ElderCare • IPT CD-ROM • New promo materials • Safety fact sheets • Dementia launch CNS I-reps • Institutional brochure • New promo materials • Safety fact sheets • SLU preceptorship • Dementia launch	\$1.7MM
Medical Education	• Speaker's bureau • TeleTopics • PCP teleconferences • Videos • Nurse collegia	• Speaker's bureau • TeleTopics • PCP teleconferences • Videos • Case workbooks • Nurse collegia	• Speaker's bureau • TeleTopics • PCP teleconferences • Videos • Case workbooks • Nurse collegia	\$6.2MM
Journal	• See Journal advertising attachment			\$1.2MM
Public Relations	• Advisory Committee Prep		• Coaching the Caregiver	\$.88MM
DTP (DTC)	• Patient/family educ.	• Patient/family educ.	• Patient/family educ. • Coaching the caregiver literature/video • Dementia launch promotion	\$.88MM
Other	• CNS Advisory forums	• CNS Advisory forums	• CNS Advisory forums	

* Access tools, etc.

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**RISPERDAL - Geriatrics
MEDICAL EDUCATION
ATTACHMENT 6b**

Medical Education Goals:

Educate key prescribers and influencers on the use of antipsychotics in geriatric patients in order to increase diagnoses and appropriate treatment of psychotic symptoms. Through education we will be able to encourage switching from conventional drugs with a poorer efficacy and side effect profile in geriatrics to atypicals and present data comparing the atypicals.

Target Audiences:

- Geriatric psychiatrists
- Psychiatrists treating large numbers of geriatric patients
- Antipsychotic decile 4-9 PCPs
- Medical directors in nursing homes
- Directors of nursing in nursing homes
- Nurse practitioners
- Psychiatric nurses

Key Messages:

RISPERDAL has a proven history of efficacy, safety, and tolerability in geriatric patients with psychosis. Continuing education will allow opinion leader presenters and experts to share key data in dementia patients on efficacy, safety and dosing that is currently not in our labeling, but widely sought after information in educational programs.

Rationale:

Medical education is a critical medium to educate decision makers and influencers on the appropriate use of RISPERDAL in the treatment of psychotic symptoms.

2000 Tactics: (Not all inclusive)

<u>Program Name</u>	<u>Timing</u>	<u>Approximate No. of Participants</u>	<u>Total Cost</u>	<u>Measurement</u>
Speaker's bureau	Q1-Q4	20,032	\$2.88MM	Rep/Physician evaluations
TeleTopics	Q1-Q4	23,000	\$.60MM	10% ElderCare participation per program date
PCP teleconferences	Q1-Q3	15,000	\$.25MM	Physician evaluations
PCP symposia	Q2-Q4	1,000	\$.55MM	Minimum 800 attendees
Videos	Q1-Q4	60,000	\$.95MM	40% return for CE credit
Nurse collegia	Q1-Q4	3,000	\$.50MM	Nurse evaluations
Case workbooks	Q2-Q4	50,000	\$.26MM	30% return for CE credit
<u>Total Med Ed Budget: \$6.2 MM</u>				

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**RISPERDAL - Geriatrics
JOURNAL ADVERTISING
ATTACHMENT 7b**

Advertising Goals:

To utilize a proven media that is effective and efficient to deliver a detailed message in a broad based and frequent manner to a select target audience. This message will be that RISPERDAL should be their first choice for treating psychosis in the elderly effectively and with minimal side effects.

Target Audience/Segments:

Primary: Geriatric Psychiatrists, NH/AMDA Medical Directors, Geriatricians

Secondary: HVP (including antipsychotic deciles 4-9) and Attending PCPs,

Consulting Pharmacists, Psychiatrists, Neurologists, Psychiatric Nurses, Nurse Practitioners

Tertiary: VA/Federal and NH Directors of Nursing

Brand Positioning by Segment:

Across all target audience segments: RISPERDAL is a safe choice for effectively managing psychotic symptoms in geriatric patients.

Unique Selling Proposition:

RISPERDAL is the number one prescribed antipsychotic with efficacy safety and dosing data

Media Vehicles:

American Journal of Geriatric Psychiatry (AAGP)

American Journal of Psychiatry (APA)

Annals of Long-term Care (AGS)

Caring for the Ages (AMDA)

Clinical Geriatrics (AGS Affiliation)

CNS Spectrums

Diversion (Janssen sponsored Psychiatry Edition- 15,000 targeted RISPERDAL psychs)

Federal Practitioner

Geriatrics

Journal of the American Geriatrics Society (AGS)

Journal of the American Medical Directors Association (AMDA)

Journal of the American Psychiatric Nurses Association (APNA)

Journal of Clinical Psychiatry

Medical Economics Janssen sponsored Psychiatry Edition- 15,000 targeted RISPERDAL psychs)

Neuropsychiatry Reviews

Primary Psychiatry

Psychiatry Times

**RISPERDAL - Geriatrics
PUBLIC RELATIONS
ATTACHMENT 8b**

Public Relations Goals:

Increase the awareness of RISPERDAL as an option in treating the psychotic symptoms and behavioral problems observed in a large number of geriatric patients. Our public relations plans are developed upon the assumption that RISPERDAL will receive FDA approval for treating dementia patients with psychotic symptoms.

Target Audience(s):

- Adults who are caring for or involved in the medical treatment of they're elderly parents or spouse.
- Providers (psychiatrists, nurses, PCPs, pharmacists, other nursing home staff)
- Janssen and J&J employees

Key Messages:

Psychotic symptoms related to dementia are devastating to families and are the #1 cause of nursing home placement. It is important to recognize and treat psychotic symptoms to ensure improved quality of life for the dementia patient and their caregiver.

Rationale:

Antipsychotics are misunderstood in dementia patients. Patients and family members often regard antipsychotics as being for only "crazy" people and need to understand how common the symptoms are and that they can be treated effectively. In addition, our education can be combined with REMINYL's education on dementia and the overall need to treat patients for both the cognitive and behavioral aspects of the disease.

2000 Tactics:

<u>Program Name</u>	<u>Timing</u>	<u>Estimated No. of Exposures</u>	<u>Total Cost</u>	<u>Measurement</u>
Advisory committee prep	Q1	NA	\$.03MM	Prepare regulatory for FDA meeting
Coaching the caregiver	Q4	3M	\$.85MM	Reach minimum 100,000 health care professionals Reach minimum 2.5M patients/family caregiver

**RISPERDAL - Geriatrics
DIRECT TO PATIENT/CONSUMER
ATTACHMENT 9b**

DTP (DTC) Goals:

Increase the awareness of RISPERDAL as an option in treating the psychotic symptoms in geriatric patients. Prior to our indication we are limited to non-branded education, however immediately upon launch we will release direct to patient and caregiver information. Pure direct to patient promotion is not realistic with our patients as many of them have progressed to middle and late stage dementia and are no longer caring for themselves.

Target Audience(s):

- Adults who are caring for or involved in the medical treatment of they're elderly parents or spouse.
- Nurses and other caregiver staff in nursing homes and assisted living facilities.

Key Messages:

Psychotic symptoms in geriatric patients are devastating to patients and problematic for families and caregivers. It is important to recognize and treat psychotic symptoms to ensure improved patient treatment.

Rationale:

Improving the understanding of how to recognize and treat psychotic symptoms in geriatric patients will increase treatment and ensure better patient outcomes with RISPERDAL.

2000 Tactics:

<u>Program Name</u>	<u>Timing</u>	<u>Estimated No. of Exposures</u>	<u>Total Cost</u>	<u>Measurement</u>
Caregiver brochure	Q1-Q4	90,000	\$.22MM	Reach min. 30,000 providers Reach min. 60,000 consumers
Caregiver brochure In Spanish	Q1-Q4	30,000	\$.08MM	Reach min. 10,000 providers Reach min. 20,000 consumers

**RISPERDAL-Geriatrics
BRAND CONVENTIONS/MED MEETINGS
ATTACHMENT 10b**

Meeting Name	No. of Attendees	No. of Symposia	Major Messages	New Clinical Data	Entertainment	Total Budget (\$K)
PRI-MED SOUTH 1/14-16	4,500 (300-400)	W/REMINYL	- Internal medicine - Family practitioners - Apply recognized guideline approaches for treating dementia and psychosis	TBD	- Dinners with Opinion Leaders - Poster sessions	\$60K
AAGP (Geriatric Psych) 3/12-15	800 (200-300)	1	Pharmacotherapy In Dementia: Expanding the Boundaries	TBD	Wine and Cheese Party	\$310K
AMDA 3/16-19	1,200 (100)	1	- Initial therapy of RISPERDAL in long-term care for treatment of psychosis and dementia related behavior - Outcome results: costs and quality of life	TBD	TBD	\$210K
PRI-MED WEST 4/6-8	4,500-7,500 (300-400)	W/REMINYL	- Internal medicine - Family practitioners - Apply recognized guideline approaches for treating dementia and psychosis	TBD	TBD	\$120K
APA 5/13-18	11,000 (500-700)	1	- RISPERDAL is initial therapy for patient with dementia and agitation - EPS is dose related	TBD	AAGP Board Dinner	\$80K

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AGS 5/16-22	1,500 (200)	1	- Recognized guidelines for managing agitation - Dementia: psychotic and behavioral aspects managing agitation, psychosis	TBD	TBD	\$130K
NADONA/LTC 6/3-7	400 (100-150)	1	- RISPERDAL is safe, well tolerated and efficacious - Dosing critical to side effect management and efficacy	TBD	TBD	\$110K
LTC Congress 6/12-14	850	1	- Nursing Home Directors - Multi Disciplinary - Outcomes results: costs and quality of life	TBD	Bags	\$150K
WORLD ALZHEIMER CONGRESS 2000 7/15-18	TBD	W/REMINYL	Outcomes results: costs and quality of life	TBD	ElderCare Evening	\$300K
PrIMed East (9/15/17)	4,500	W/REMINYL	- Internal medicine - Family practitioners - Apply recognized guideline approaches for treating dementia and psychosis	TBD	TBD	\$60K
AAFP	9,000	W/REMINYL	- Internal medicine - Family practitioners - Apply recognized guideline approaches for treating dementia and psychosis	TBD	TBD	\$75K

APNA (Psych Nurses) 10/24-29	(400-500)	TBC	- Established link between psychosis, agitation, and benefit of optional treatment by one agent - Accurate dosing is critical to minimize intervention, and offer care	TBD	- APNA Board Dinner - CME (1/2 day) - Nurse Scholars	\$200K
AOA (Orlando, FL) 10/29-11/2	4,000	W/REMINYL	Osteopathic physicians apply recognized guideline approaches for treating dementia and psychosis	TBD		\$160K
ASCP 11/1-4	4,300 (200-300)	1	- First line used in LTC market - Safety and tolerability as well as efficacy of dosage is accurate - Guidelines and government issues	TBD	TBD	\$210K

- (x) Is the potential attendees to the actual symposium

**RISPERDAL - Geriatrics
MARKET RESEARCH
ATTACHMENT 13b**

2000 Brand Marketing Objective:

- Optimize efficacy and safety positioning for RISPERDAL
- Rapidly drive RISPERDAL market penetration
- Expand reach to key customers

2000 Market Research Plan:

Objective	Rationale	Target	Timing (start/finish)
Understand current market perceptions	Track changes in competitive landscape; exploit opportunities; maintain share leadership	Psychs/PCPs/ Opinion Leaders	1Q/2Q
Develop primary care opportunities	High under-targeted PCPs dementia volume	PCPs	2Q
Understand physician influencers in LTC	Increase share of long-term care Rx's	Psychs/ Medical Directors/ Rn/Pharm Directors	2Q
Optimize rep/doc communication	Marketing efficiency	All detailed audiences	2Q
Develop and test promotional materials	Maximize RISPERDAL communication effectiveness	Psychs/PCPs	1Q
Determine impact of geriatric nurse consultants	Assess continuation of contract	LTC Psychs/ Nurses	3Q

**RISPERDAL – Bipolar
PROGRAMS/KEY TACTICS BY CYCLE
ATTACHMENT 5c**

	Cycle 1	Cycle 2	Cycle 3	Total Spending (\$MM)
Sales Force (support*)	Bipolar Training Program	Bipolar Training Program	Bipolar Training Program	\$0.3 MM
Medical Education	RIS-102/46/112 Dissemination Program Regional CME Programs RISPERDAL Evolution Millennium Leaders: Regional and National Advisory Boards, Medical Education Meetings, New Leaders Preceptor Programs, RISPERDAL BD Symposia CME Casexchange Meetings Janssen Resident of the year award	RIS-102/46/112 Dissemination Program Regional CME Programs RISPERDAL Evolution Millennium Leaders: Regional and National Advisory Boards, Medical Education Meetings, New Leaders Preceptor Programs, RISPERDAL BD Symposia CME Casexchange Meetings Janssen Resident of the year award	RIS-102/46/112 Dissemination Program Regional CME Programs RISPERDAL Evolution Millennium Leaders: Regional and National Advisory Boards, Medical Education Meetings, New Leaders Preceptor Programs, RISPERDAL BD Symposia CME Casexchange Meetings Janssen Resident of the year award	\$6.6 MM
Journal	Publication Program: Posters, Scientific Articles, Journal Supplements	Publication Program: Posters, Scientific Articles, Journal Supplements	Publication Program: Posters, Scientific Articles, Journal Supplements	\$1.2 MM
Other	NDMDA Ultra-Care & Patient Max Programs	NDMDA Ultra-Care & Patient Max Programs	NDMDA Ultra-Care & Patient Max Programs	\$0.3 MM

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**RISPERDAL – Bipolar
MEDICAL EDUCATION
ATTACHMENT 6c**

Medical Education Goals:

- To provide informative medical education programs to opinion leaders and high volume prescribers on the development and current data on the use of RISPERDAL in the treatment of bipolar disorder.
- To strengthen opinion leader and advocacy support for RISPERDAL as well as to differentiate RISPERDAL for appropriate patients.

Target Audiences:

- High Prescribing Psychiatrists
- Key Opinion Leaders

Key Messages:

RISPERDAL has a well known antipsychotic profile and superior properties: rapid onset of action, mood stabilizing properties, antidepressant activity, and low weight gain.

Rationale:

Medical education is a critical medium to educate decision-makers and influencers on the appropriate use of RISPERDAL in the treatment of bipolar disorders.

Key 2000 Tactics:

Millennium Leaders – The major objective of this program is to establish, develop, and strengthen our relationship with key opinion leaders. The program includes the development of a database to manage relationship with the top 100 opinion leaders in bipolar disorder, two National Advisory Boards meetings, five regional advisory board meetings, two medical education committee meetings, and five new leaders preceptor programs.

Regional CME Programs - The goal of these programs is to educate high prescribing psychiatrists on the benefits and appropriate use of RISPERDAL in bipolar disorder. Three tracks are planned, each providing physicians with a different topic on bipolar disorder. We expect an attendance of 3,000 high volume prescribers at a total of 60 one-day meetings.

CME Casexchange Meetings – The purpose of this program is to provide high volume prescribers with education on bipolar disorder. Each dinner meeting will include a lecture and a presentation of bipolar disorder cases. A total of 320 dinner meetings are planned (one per CNS sales representative) with at least 10 physicians attending each. The impact of this program on these physicians will be measured by feedback questionnaires and tracking prescribing trends post-meeting.

**RISPERDAL - Bipolar
PUBLIC RELATIONS
ATTACHMENT 8c**

Public Relations Goals:

Leverage trade, media, and investor media to grow RISPERDAL leadership position in schizophrenia and strengthen Janssen's position as a leader in CNS.

Target Audience(s):

- Providers (Psychiatrists, nurses, pharmacists)
- Patients, caregivers, and patient advocates
- Analysts
- Internal Janssen customers

Key Messages:

The key communication points will reflect our current sales message of superior efficacy, rapid onset of action, mood stabilizing activity, and low weight gain in the treatment of Bipolar Disorder. This message will be supported by the RIS-USA-102 and RIS-INT-46 study results.

Rationale:

- Disseminate positive data on RISPERDAL to target audience
- Expand reach into customer/caregiver market

2000 Tactics:

To be defined

**RISPERDAL – Bipolar
BRAND CONVENTIONS/MED MEETINGS
ATTACHMENT 10c**

Meeting Name	No. of Attendees	No. of Symposia	Major Messages	New Data	Entertainment	Total Budget
APA	15,000	1	Present available new data	RIS-102/46		\$0.2 MM
American College of Clinical Pharmacists, ACCP	3,000	1	Present available new data	RIS-102/46		\$0.2 MM
American College of Emergency Physicians, ACEP	7,000	1	Present available new data	RIS-102/46		\$0.2 MM
Institute on Psychiatric Services	3,000		Present available new data	RIS-102/46		
US Psych Congress	4,000		Present available new data	RIS-102/46	Social Event for Clinical Scholars	
ACNP	1,500		Present available new data	RIS-102/46	1 dinner	

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**RISPERDAL - Bipolar
MARKET RESEARCH
ATTACHMENT 13c**

2000 Brand Marketing Objective:

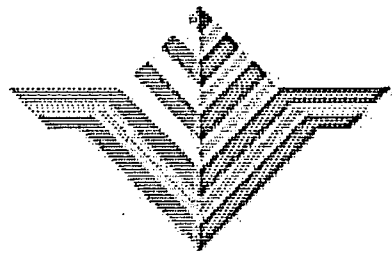
- Differentiate RISPERDAL and disseminate benefits for appropriate patients
- Strengthen opinion leader and advocacy support for RISPERDAL
- Improve compliance and optimize patient management

2000 Market Research Plan:

Objective	Rationale	Target	Timing (start/finish)
Understand spectrum for bipolar use	Develop RISPERDAL bipolar launch strategy	All	4Q'99/1Q
Understand current market perceptions	Track changes in competitive landscape; exploit opportunities	Psychs/ PCPs/ Opinion Leaders	4Q'99/1Q
Competitively pre-position vs. Zyprexa	Maintain/grow share of market	All	2Q
Develop/optimize RISPERDAL bipolar positioning	Distinguish vs. competition / grow share	Psychs/ PCPs	3Q
Develop and test promotional materials	Maximize RISPERDAL communication effectiveness	Psychs	3Q/4Q

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RISPERDAL®

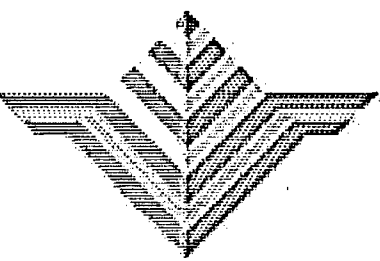
Growth Acceleration

Pharmaceutical Group Operating Committee

February 26, 2001

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Plaintiff Ex. 1552

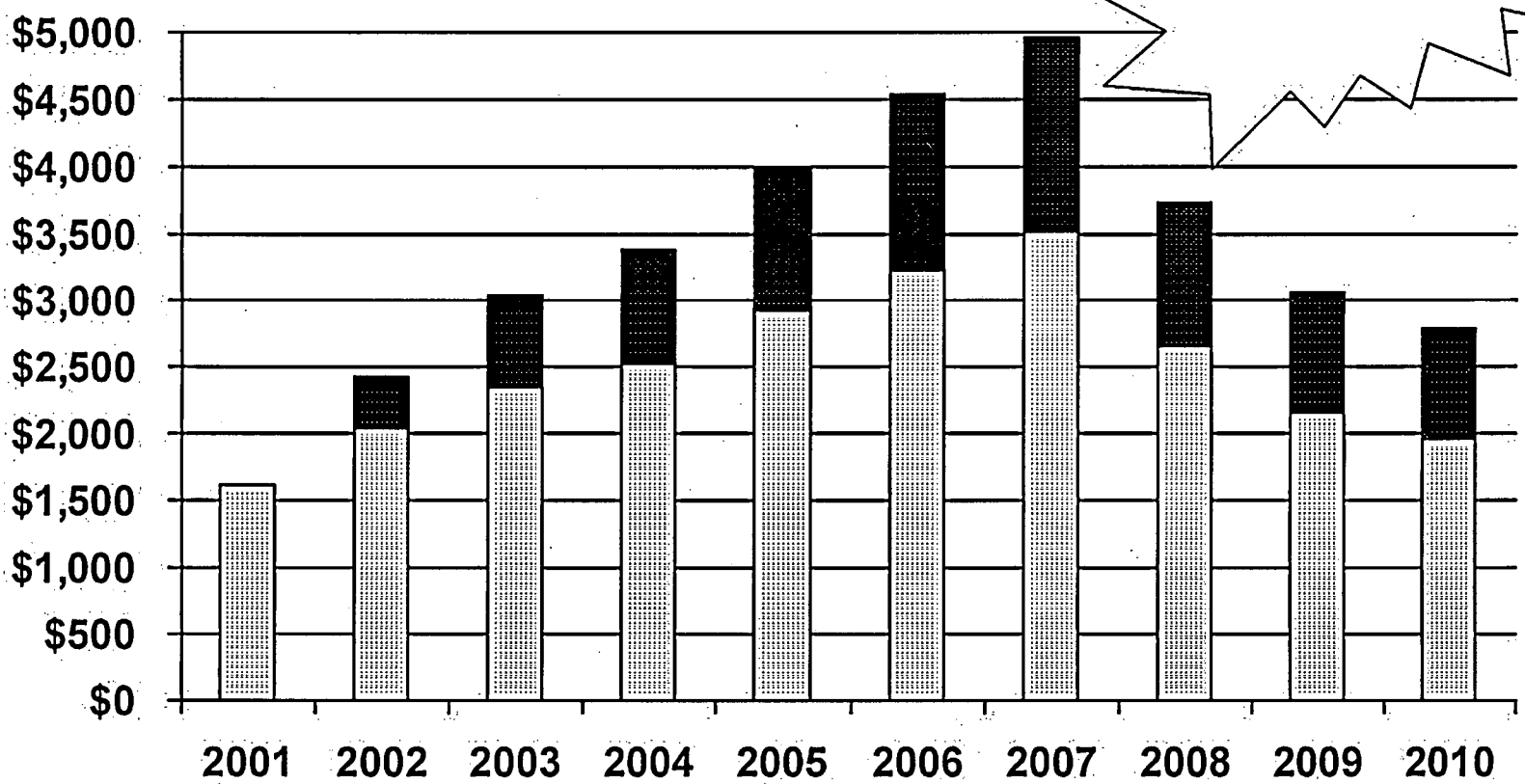


RISPERDAL

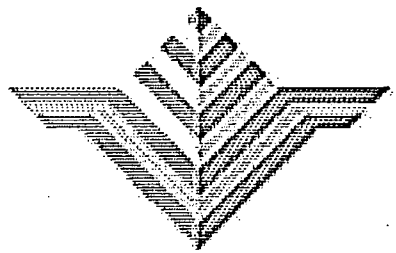
Worldwide Forecast

+\$9.8 Billion!!

NTS \$ Millions

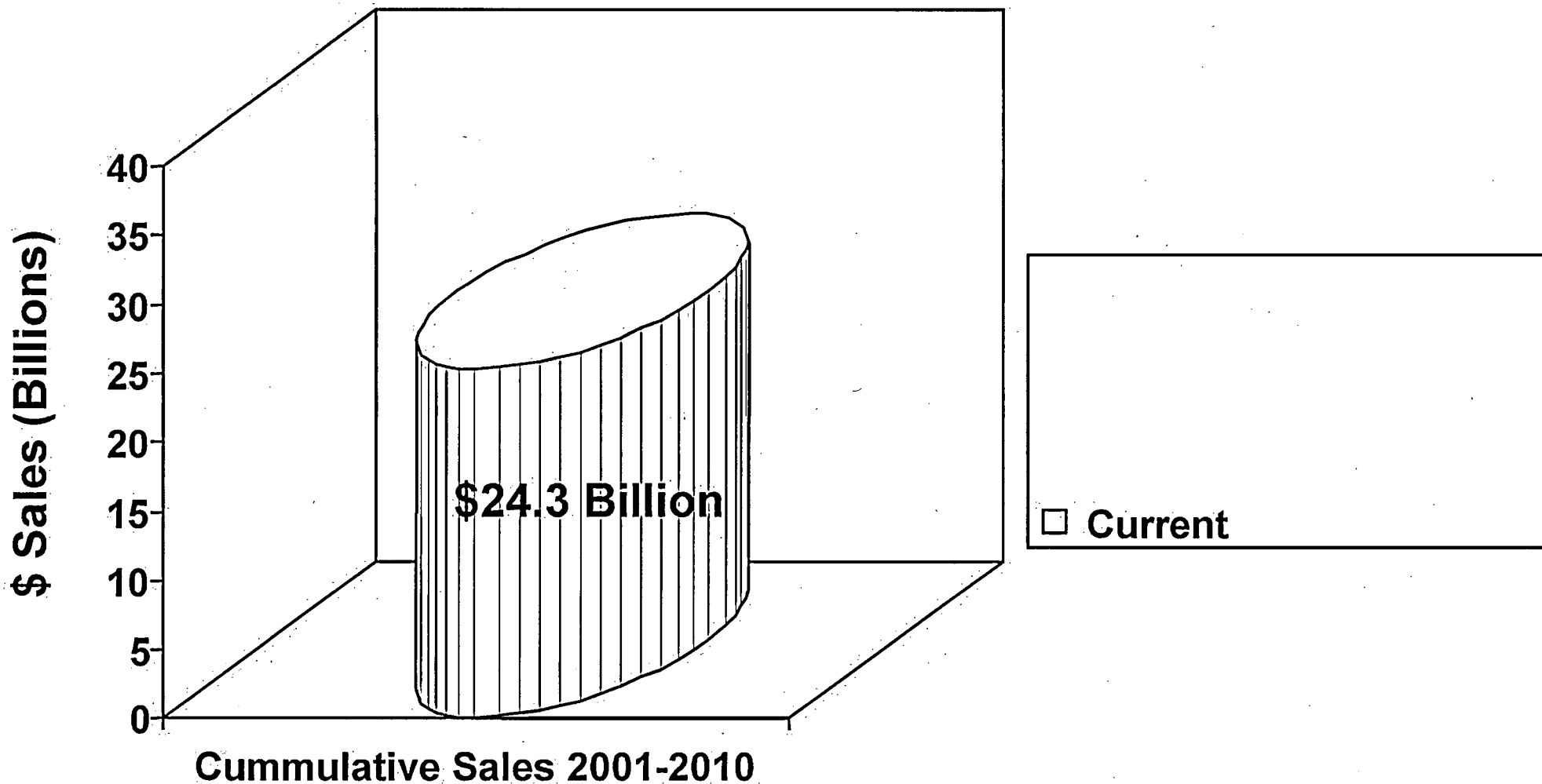


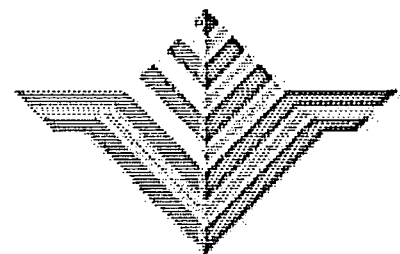
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Building a BIGGER Blockbuster

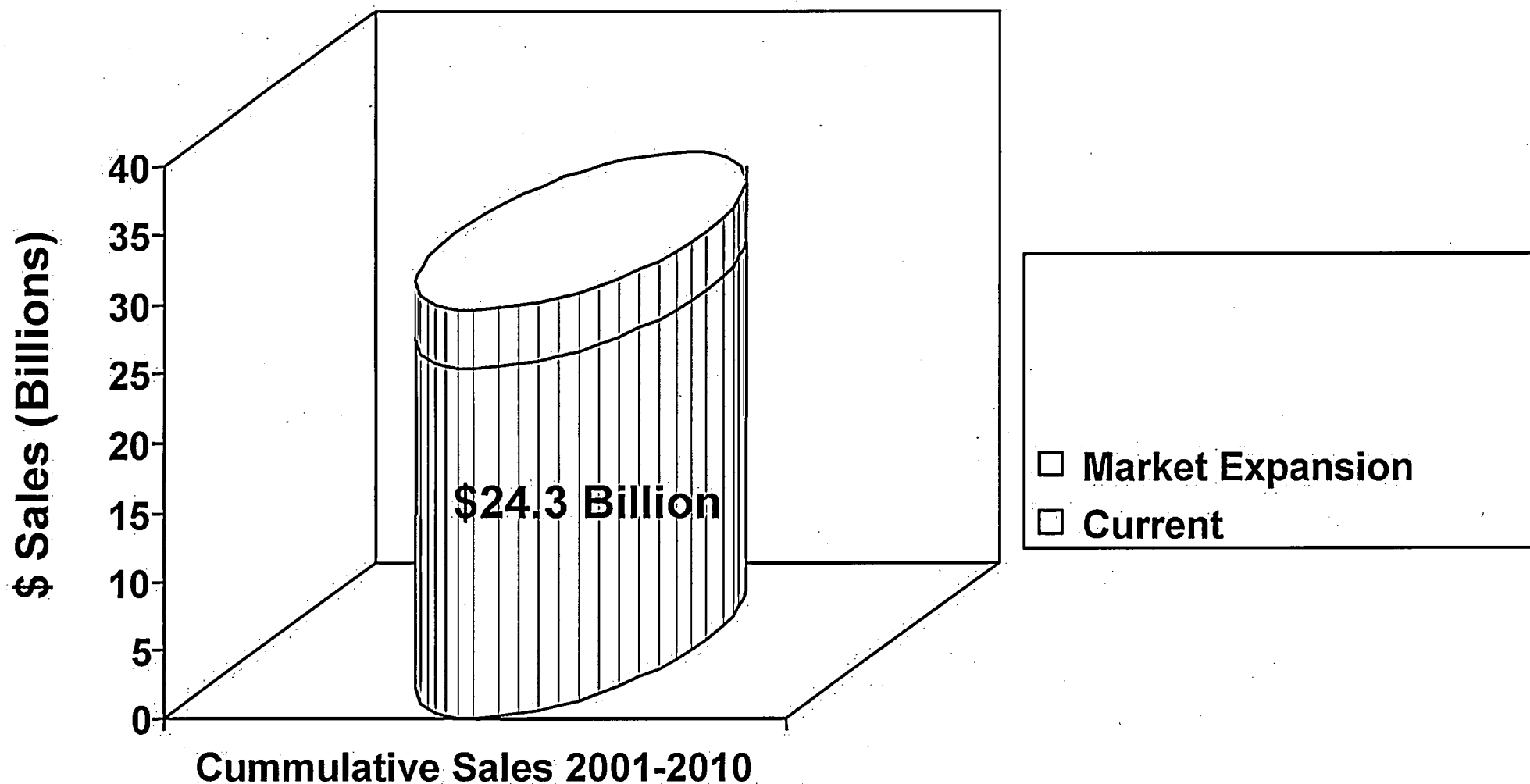
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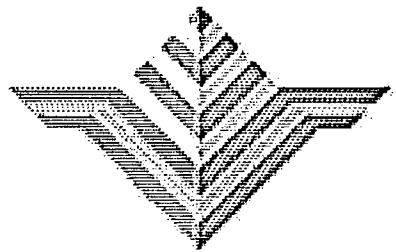




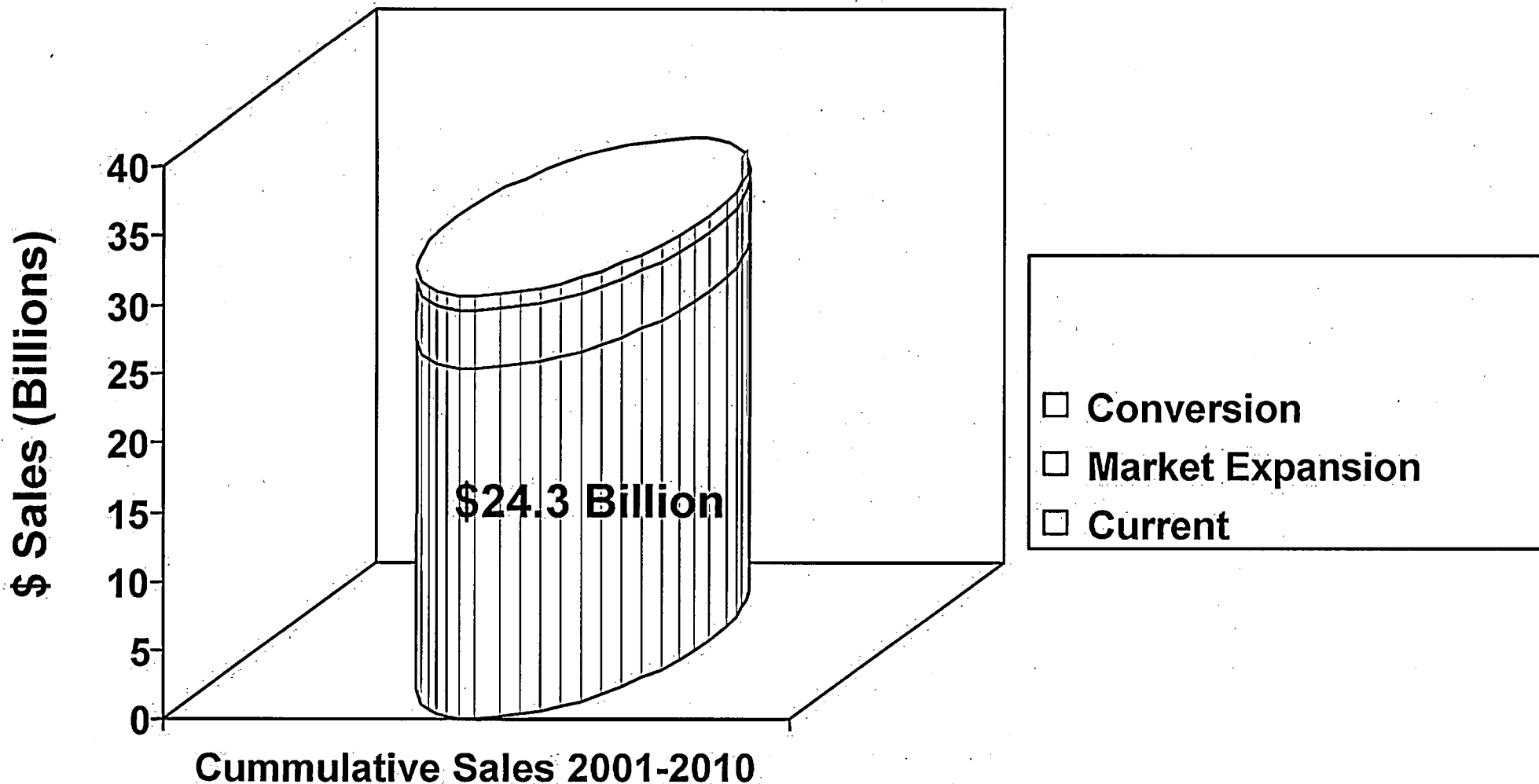
Building a BIGGER Blockbuster

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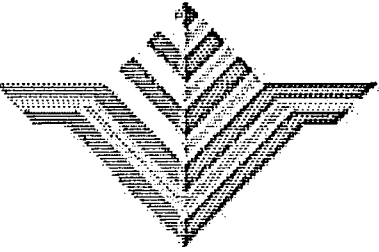




Building a BIGGER Blockbuster

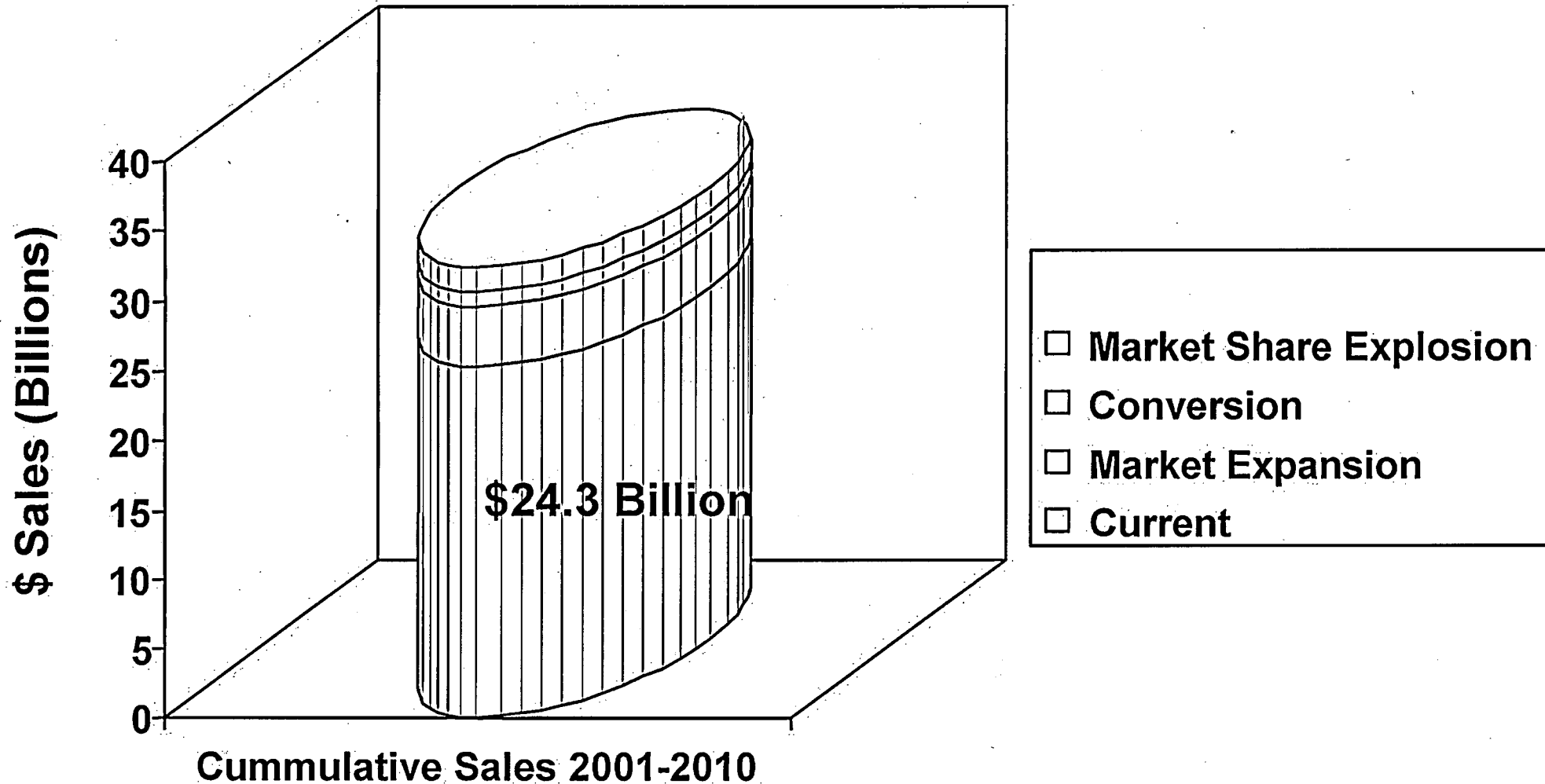


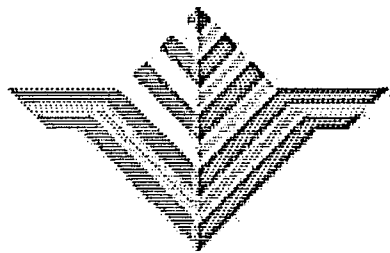
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Building a BIGGER Blockbuster

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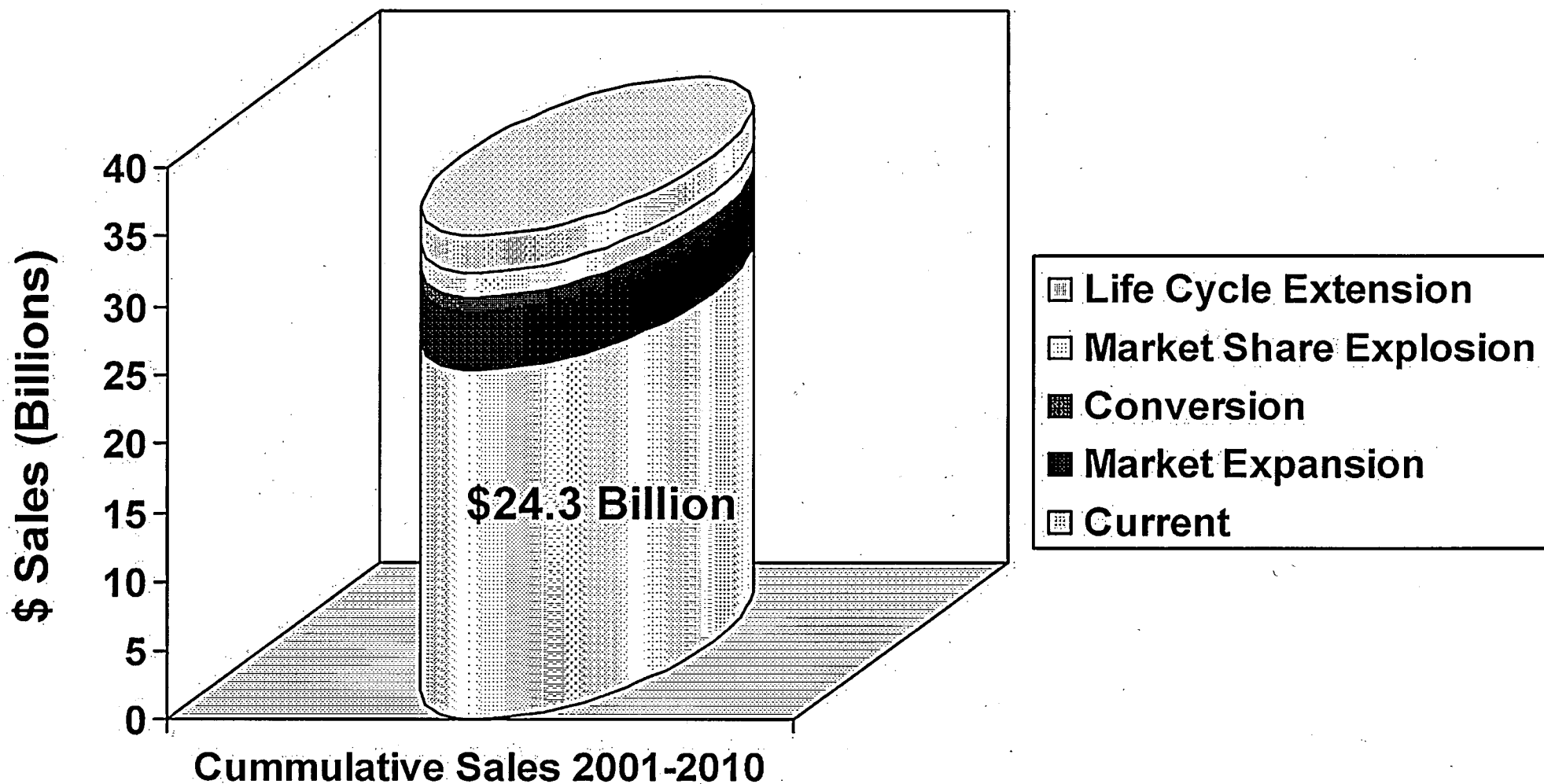


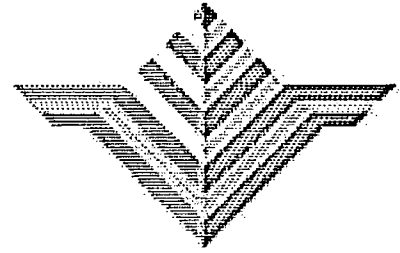


Building a BIGGER Blockbuster

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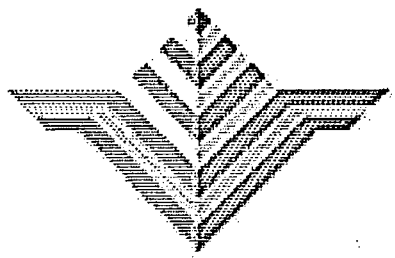


Why invest in RISPERDAL?

- > \$35 Billion cumulative sales*
- > Very high probability of success
- > Long patent life
- > 97% gross profit margin
- > 79% marketing contribution

*2001-2010

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RISPERDAL

Growth Acceleration Team

Christine Poon, Sponsor, Company Group Chairman, J&J Corporate

Sid Frank, Group Director, Public Sector & Institutional Business, JPI

Jane Griffiths, European Business Director, Janssen-Cilag, Europe

Fred Grossman, Director, Global Medical Leader, JRF

Ludwig Hantson, Director of Marketing, CNS Franchise, JPI

Larry Katz, Director, Strategic Life Cycle Management, PGSM

Ramy Mahmoud, Group Director, CNS Medical Affairs, JPI

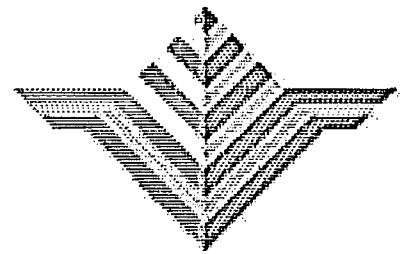
Kim Taylor, Vice President, Marketing & Medical, JC Asia Pacific

Margaret Theeuwes, GCL, Senior Director Psychiatry, PGSM

Janet Vergis, Vice President, CNS Franchise, JPI

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Additional Thanks to:

Yoshimi Awada

Raffele Balestra

Lynda Benton

Nadine Cohen

Juan Jose Colon

Tara Coyle

Sabind Dandiguan

Bob Decker

Alina Fridman

John Jacoppi

Alice Lex

Kai Martens

Kathy McCaffrey

Ken McDermott

Paul de Nijs

Patrice Noone

Luis Diaz Rubio

Toyoaki Shimada

Jean Marie Wajdowicz

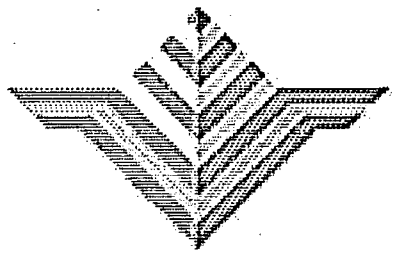
Debi Watson

Michele Wyluda

Weiyi Yang

Steve Wooding

R. 3561



Agenda

Introduction

J. Vergis

Market Expansion

F. Grossman

Conversion from Conventionals

J. Griffiths

Market Share Explosion

**L. Hantson/
R. Mahmoud**

Lifecycle Extension

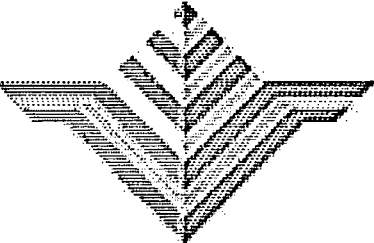
M. Theeuwes

Summary

J. Vergis

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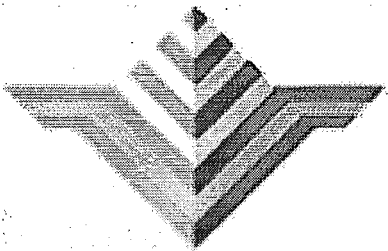
Market Expansion

Dementia

Refractory Depression

Bipolar

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Dementia (BPSD)

Situation:

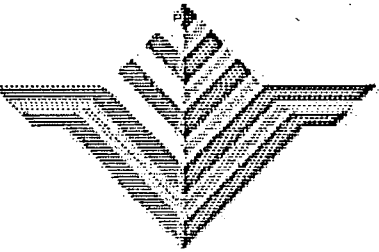
- > 15MM patients
- > \$4.3B Sales*
- > Increased competition
- > Registration program ongoing/approved



Objectives:

- > Maximize market preparation for label in dementia
- > Increase the number of patients treated and duration of treatment for dementia

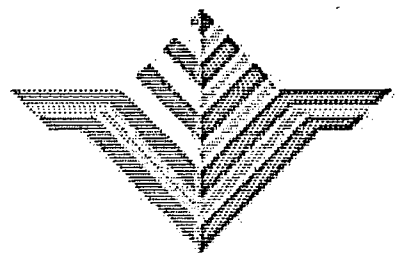
**Cumulative Sales 2001-2010*



Dementia (BPSD)

R. 3565

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
EMRP (investigator initiated trials)	2.0	0.7
Trial in secondary prophylaxis for psychosis early use (publication)	8.0	2.6
Experience trial	3.0	1.0
RISPERDAL/Seroquel trial	8.0	2.6
Medical marketing initiatives	<u>2.5</u>	<u>1.9</u>
TOTAL	\$23.5	\$8.8
 Headcount (Additional FTEs)	 9	

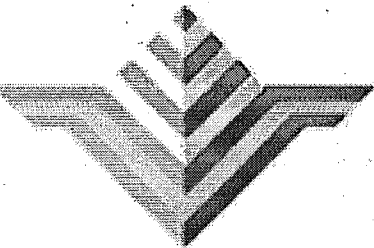


Worldwide Sales Impact Dementia

Incremental Revenue (\$MM)

R. 3566

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
\$ 5	\$ 12	\$ 23	\$ 25	\$ 29	\$ 30	\$ 32	\$ 17	\$ 12	\$ 9	\$177MM



Refractory Depression

Situation:

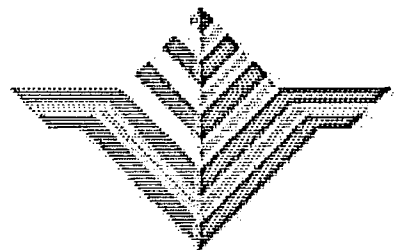
- > 110MM patients
- > \$4B Sales*
- > Highly dissatisfied market
 - > 30% treatment refractory
 - > 30% partial responders

Objectives:

- > Obtain indication for RISPERDAL add-on therapy to add-on for treatment refractory depression
- > Maximize market preparation for labeling in refractory depression

**Cumulative Sales 2001-2010*

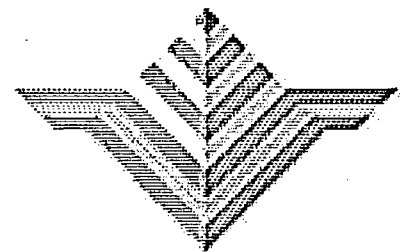




Refractory Depression

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
Tx Refractory (4-registration)	125.0	31.3
Partial responders	6.0	2.0
Psychotic depression (publication)	1.5	0.5
Extramural research	3.0	1.0
Experience trials	5.0	1.7
Medical marketing initiation	<u>2.5</u>	<u>1.9</u>
TOTAL	\$143.0	\$38.4
Headcount		
Additional FTEs (Medical Affairs)	9	
Additional FTEs (Registration)	20 - 30	

R. 3568

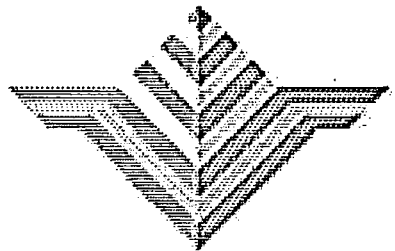


Worldwide Sales Impact Treatment Refractory Depression

Incremental Revenue (\$MM)

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
\$187	\$201	\$271	\$355	\$463	\$586	\$640	\$382	\$252	\$187	\$3,524MM

R. 3569

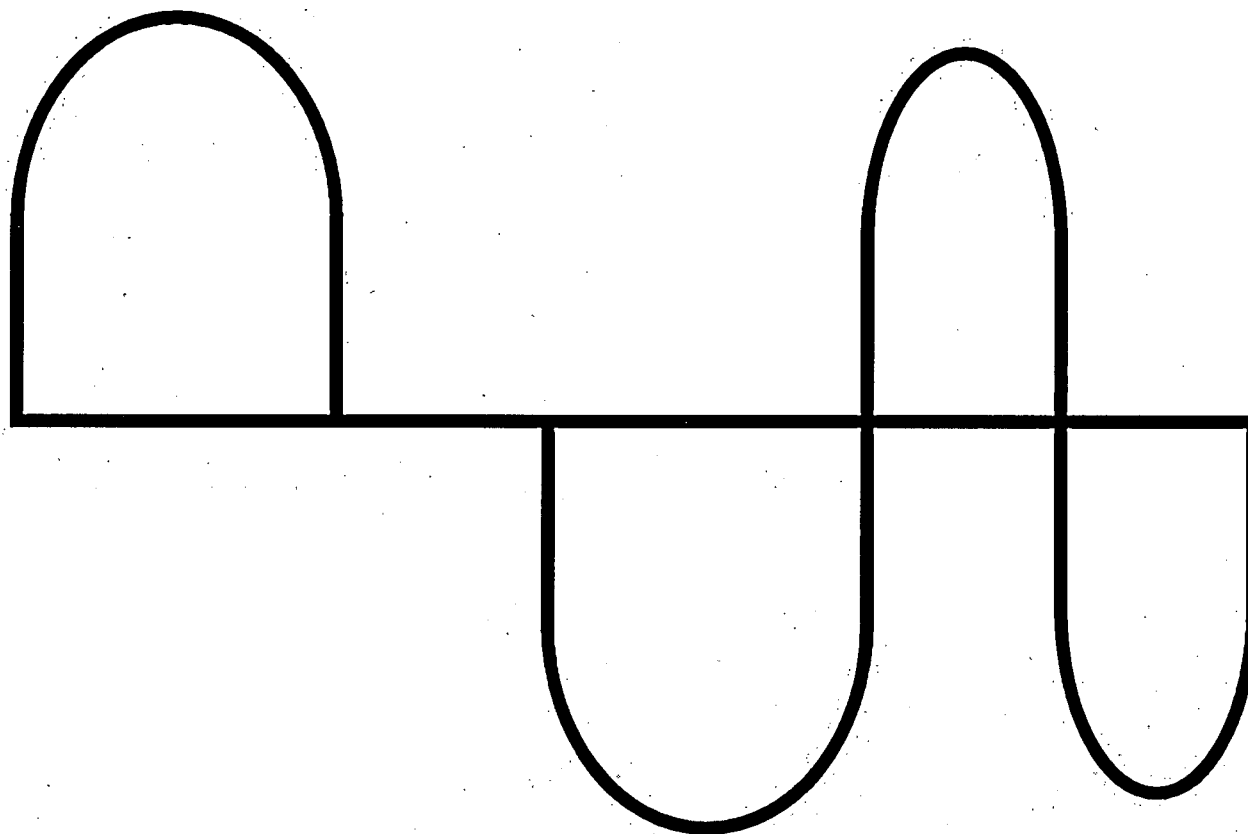


Bipolar Disorder

Mania

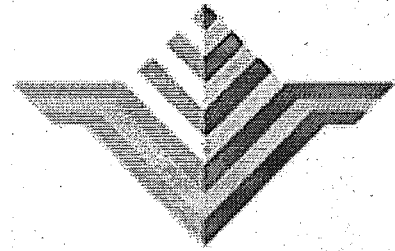
Stability

Depression

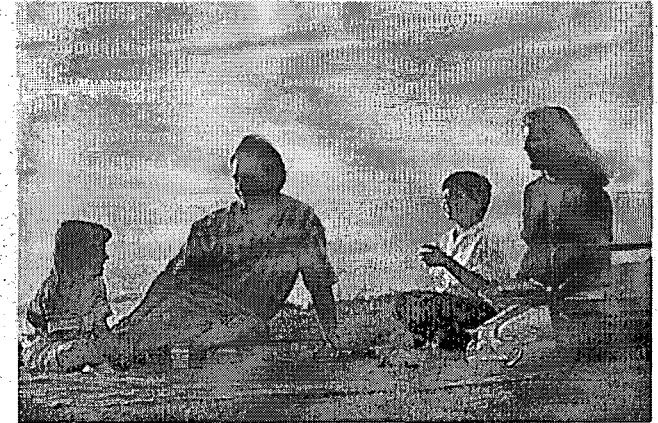


R. 3570

FILE 0610612



Bipolar Disorder



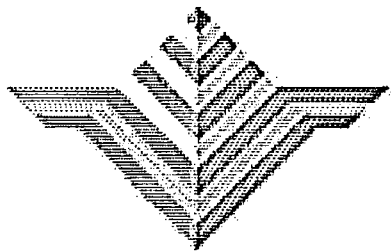
Situation:

- > 8MM patients
- > \$3B Sales*
- > Highly dissatisfied market
- > Competitive disadvantage
- > Registration program ongoing for monotherapy and add-on therapy for acute mania

Objectives:

- > Maximize market preparation for label in bipolar mania
- > Maximize long term use of RISPERDAL in bipolar disorder
- > Optimize message that RISPERDAL and TOPAMAX can be safely used as combination therapy

**Cumulative Sales 2001-2010*

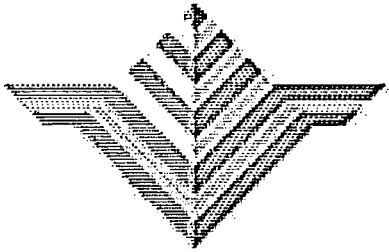


Bipolar Disorder

IRE 0610612

<u>Proposal:</u>	<u>Total Cost (\$)</u>	<u>2001 Cost (\$)</u>
Extramural research	3.5MM	1.2MM
Prospective longitudinal efficacy study	15.0MM	5.0MM
Study of RISPERDAL and TOPAMAX for safety	3.0MM	1.0MM
Medical marketing initiation	<u>2.5MM</u>	<u>1.9MM</u>
TOTAL	\$24.0MM	\$9.1MM
Headcount Additional FTEs	4	

R.3572

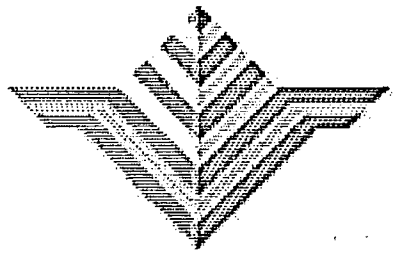


Worldwide Sales Impact Bipolar

Incremental Revenue (\$MM)

	<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
Bipolar-Maint	\$ 12	\$ 14	\$ 42	\$ 52	\$ 65	\$ 75	\$ 83	\$ 58	\$ 41	\$ 37	\$479MM
Bipolar-Ref Dep	\$ 3	\$ 3	\$ 5	\$ 18	\$ 24	\$ 29	\$ 31	\$ 17	\$ 10	\$ 9	<u>\$149MM</u> <u>\$628MM</u>

R. 3573

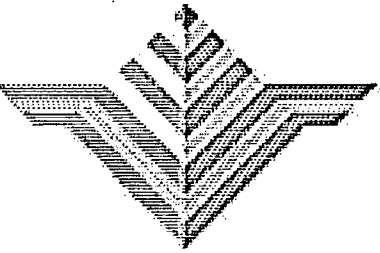


Requested Support Market Expansion

- > Increase resources for Dementia; Depression and Bipolar Programs
- > Initiate Process Excellence ASAP!
- > Future review of
 - > Child/Adolescent Markets
 - > Anxiety
 - > Delirium
 - > OCD
 - > Pacific Rim Opportunities

R.3574

TYPE NR1NR1Z



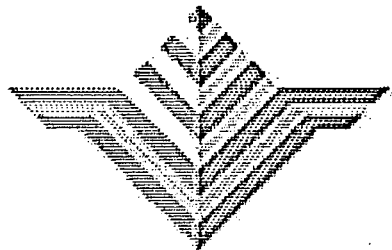
Conversion from Conventionals

Europe

US

Japan

R. 3575



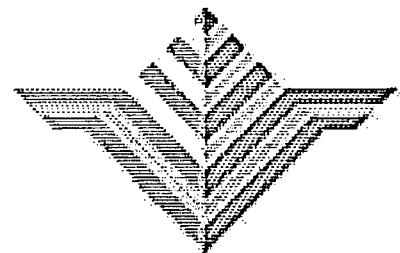
Conversion in the EU

Situation:

- > Typicals still occupy 70% of prescriptions
- > Efforts by Janssen Cilag, Lilly, and Astra Zeneca still result in slow switching rate

Objective:

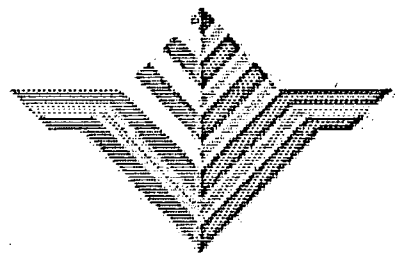
- > Increase patient demand for atypicals
- > Accelerate patient switch from conventionals to RISPERDAL



Conversion in the EU

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
Sales & Marketing Support		

R. 3577

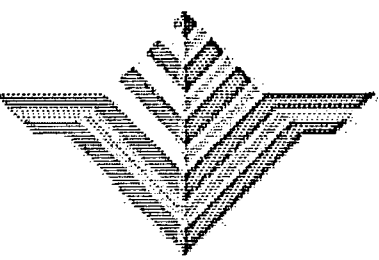


Worldwide Sales Impact Conversion in the EU

Incremental Revenue (\$MM)

R.3578

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$ MM



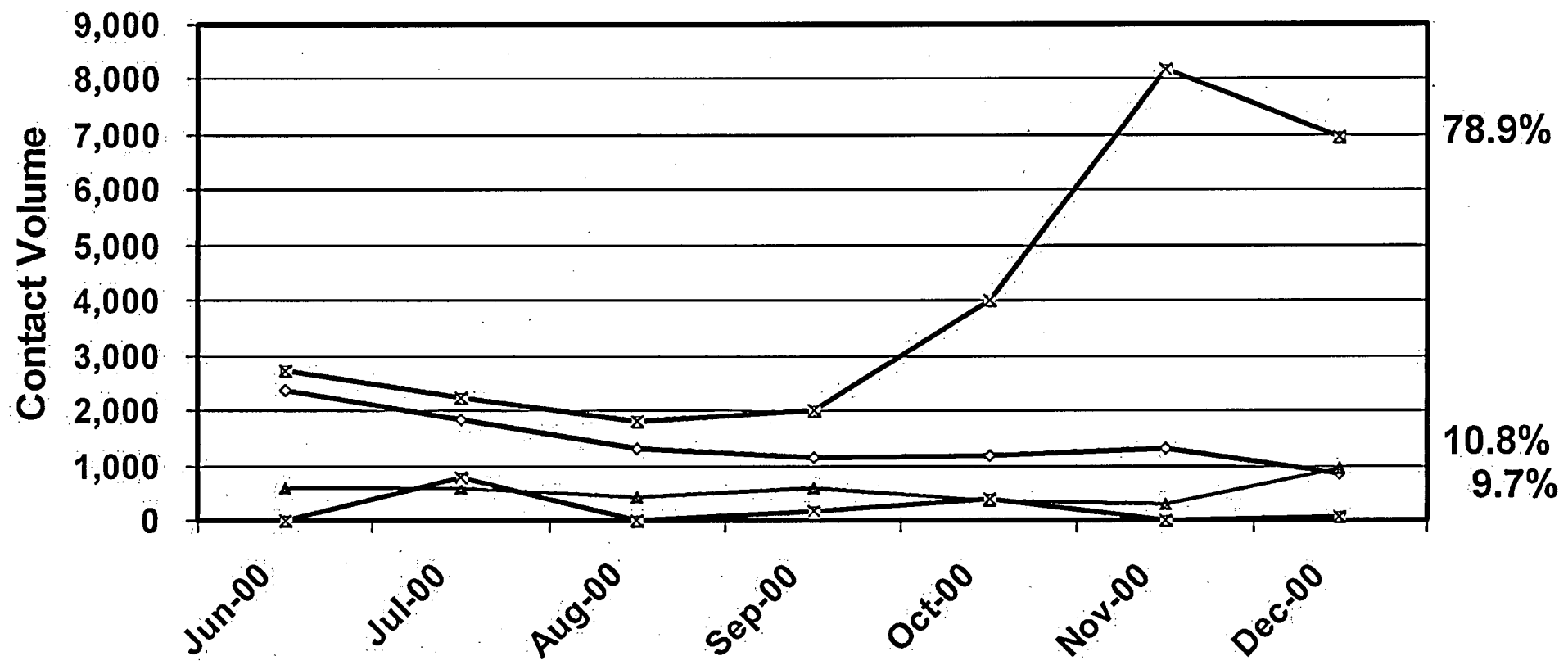
Conversion in the US Situation: Lilly PCP Launch

Primary Care Contacts in U.S.

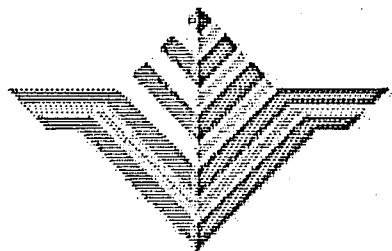
Share of
Contacts

—◇— Risperdal —x— Zyprexa —▲— Seroquel —x— All Others

R. 3579



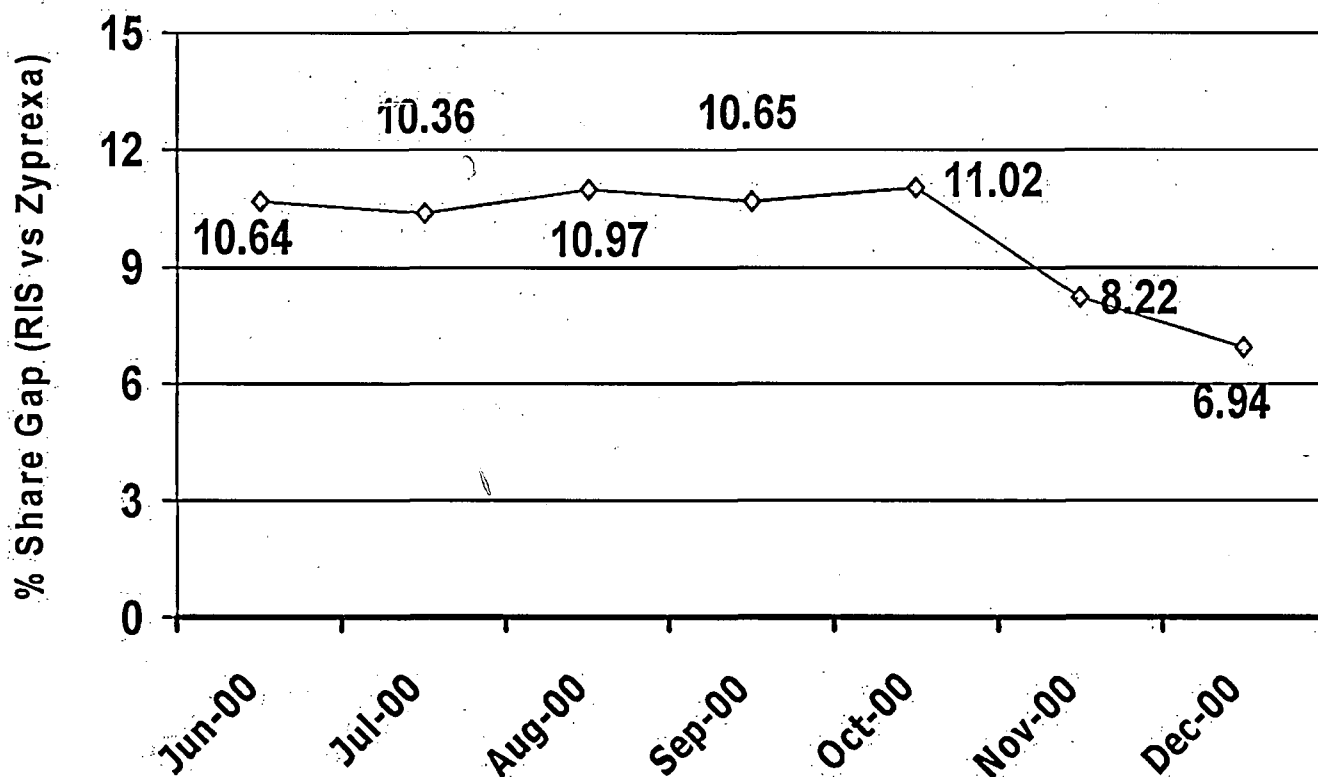
Source: IMS Health, IPS, 12/00



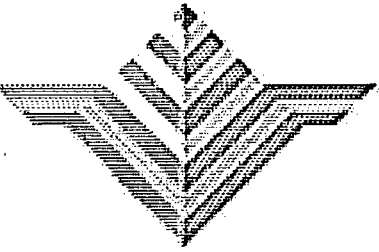
Conversion in the US

Situation: Decrease in Share Lead

FILE 061061F

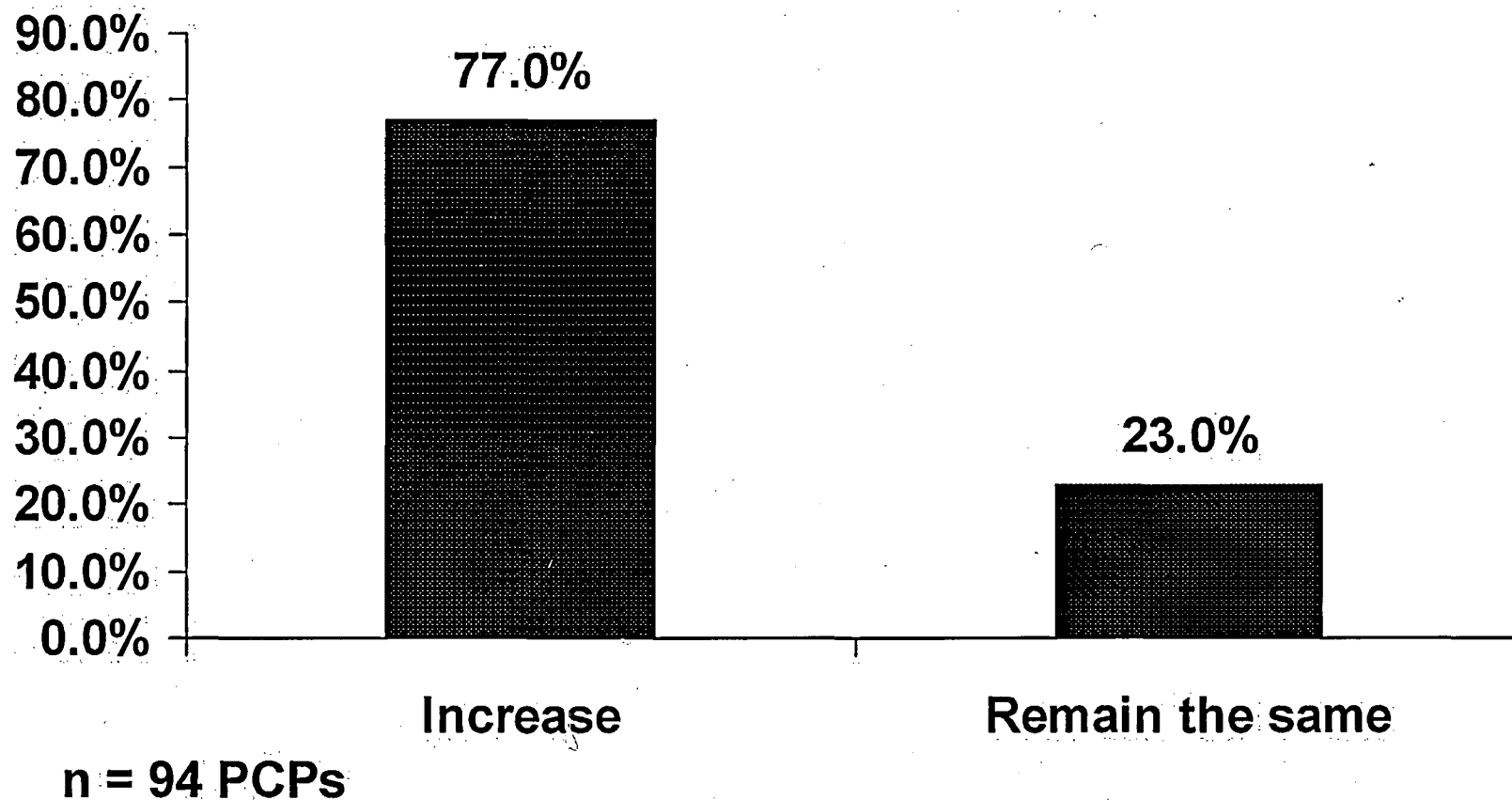


Source: IMS Health, All PCP Monthly NRx Share

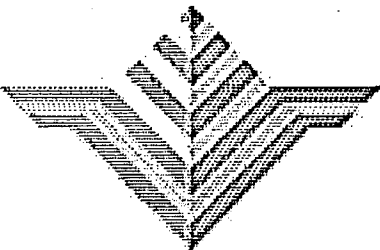


Conversion in the US

“How do you expect your prescribing of Zyprexa to Change”



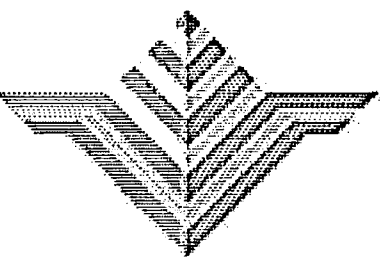
Source: Market Measures Fastape Study, 1/18/01



Conversion in the US

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
Sales & Marketing Support	3.0	1.7
Deploy existing Hospital reps	----	----
Headcount Additional FTEs (field)	100	100

R. 3582

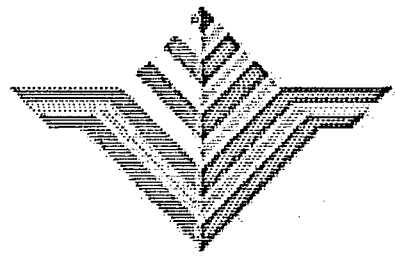


Worldwide Sales Impact Conversion in the US

Incremental Revenue (\$MM)

R. 3583

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
\$ 21	\$ 51	\$ 84	\$119	\$156	\$192	\$228	\$114	\$ 80	\$ 57	\$1,104MM

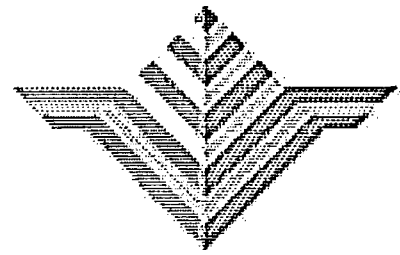


Requested Support Conversion from Conventionals

- > EU: Increase DTP and Clinical Support
- > US: Increase sales SOV in PCPs
- > Japan: Future review of pricing options

R.3584

1106061001



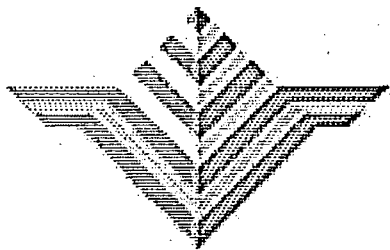
Market Share Explosion

Optimize PI

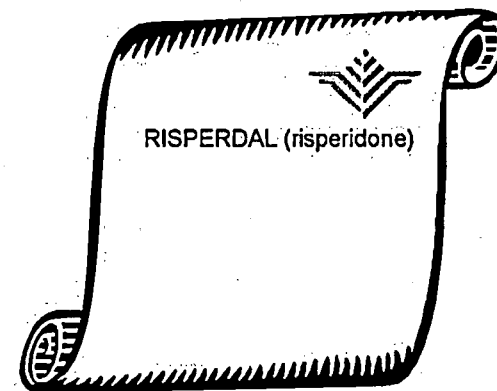
Diabetes Initiative

Zap Ziprasidone Program

R. 3585



Optimize PI

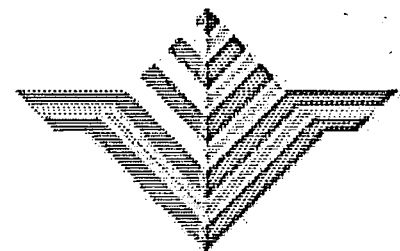


Situation:

- > Noncompetitive; not updated since launch
- > Does not reflect accurate titration, dosing and safety data
- > Lacks competitive information on efficacy

Objective:

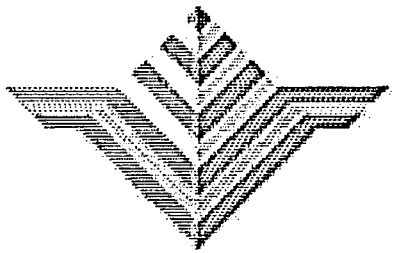
- > Optimize label using available clinical data



Proposed PI Changes

Program	Label Change	Data
> Titration & Dose	1) Slower titration 2) Lower max dose 3) Dosing for elderly	Czsernansky, Marder
> Aggression	In CD, AD, BP and and schizophrenia	Findling, Sachs, Marder and AUS-5
> Superiority	vs Haldol	Czernansky, Marder
> Safety	1) Change QT wording 2) Reflect accurate TD rate	Pfizer 054 Czernansky, Jeste

R. 3587

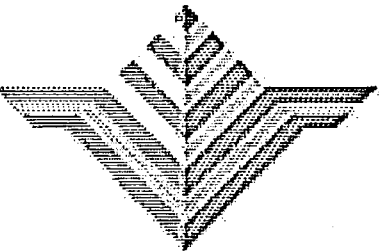


Optimize PI

110610611

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
Back-Up aggression study	15.0	5.0
Headcount Additional FTEs (9 Months)	4	

R.3588



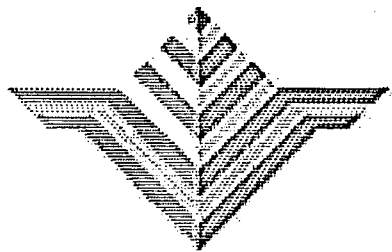
Worldwide Sales Impact

Optimize PI

Incremental Revenue (\$MM)

R. 3589

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
---	\$ 34	\$ 75	\$123	\$130	\$138	\$144	\$ 94	\$ 72	\$ 61	\$871MM



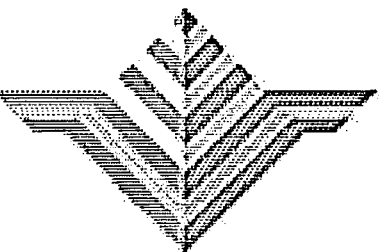
Diabetes Offensive

Situation:

- > Zyprexa appears to induce or worsen diabetic metabolism
- > Limited clinical data, low awareness
- > FDA submissions on glucose/diabetes (August 10, 2000)

Objective:

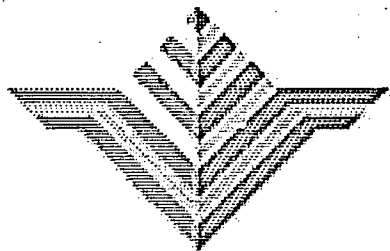
- > Generate/disseminate convincing differentiation data
- > Differentiate RISPERDAL's PI from Zyprexa's, prevent class label
- > Increase awareness and change prescribing behavior



Diabetes Offensive

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
Clinical		
2 Clin Pharm (schizo & bipolar)	4.0	1.6
Clinical comparison trials (vs. OLZ, vs. QUE)	7.0	2.8
EMRP	3.0	1.2
Outcomes		
Longitudinal database and chart review	2.5	1.2
Economic effects of dossier teams	0.8	0.3
Marketing Initiatives	<u>6.6</u>	<u>1.7</u>
TOTAL	\$23.9	\$8.8
Headcount Additional FTEs	9	

R. 3591



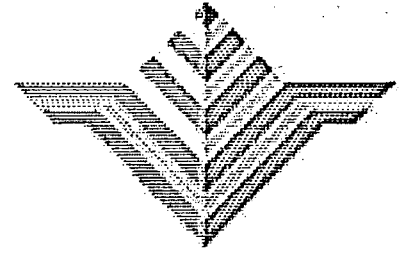
Worldwide Sales Impact Diabetes

IRE 061061f

Incremental Revenue (\$MM)

R.3592

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
---	\$ 64	\$ 68	\$ 71	\$ 74	\$ 78	\$ 80	\$ 40	\$ 28	\$ 20	\$523MM

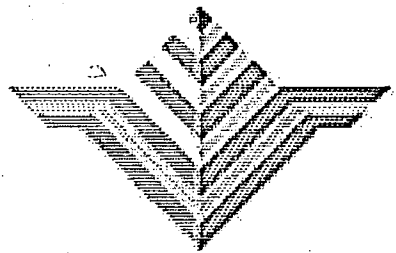


Zap Ziprasidone

Situation:

- > **Zeldox** (EU) in review; **Geodon** (US) approved
 - > Strengths: Maintenance, affective data, tolerability
 - > Weaknesses: QTc, bid, rash, schizophrenia only
- > Available tablets and short-acting IM
- > Well-established customer relationships in CNS, with strong PCP ties (Zoloft, Aricept)
- > History of significant investment

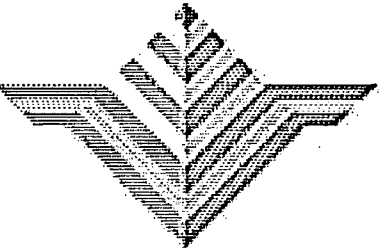
R. 3593



Zap Ziprasidone

Objectives:

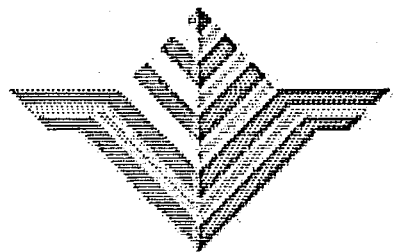
- > Provide evidence to counteract comparative data
- > Generate convincing safety (QT) differentiation data
- > Explore product's potentials to worsen diabetic metabolism
- > Increase awareness of safety issues



Zap Ziprasidone

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
Comparative study vs RISPERDAL	15.0	1.5
Safety comparison studies	<u>1.5</u>	<u>0.5</u>
Total	\$16.5	\$2.0
Headcount Additional FTEs	?	

R. 3595



Worldwide Sales Impact

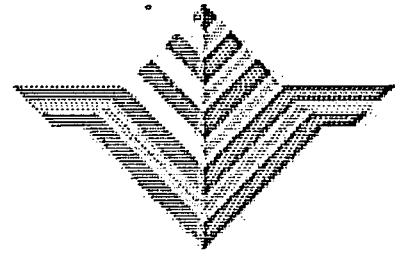
Zap Ziprasidone

11/16/06 06:10:06

Incremental Revenue (\$MM)

R. 3596

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
---	\$ 46	\$ 87	\$ 66	\$ 36	\$ 37	\$ 38	\$ 17	\$ 13	\$ 10	\$350MM

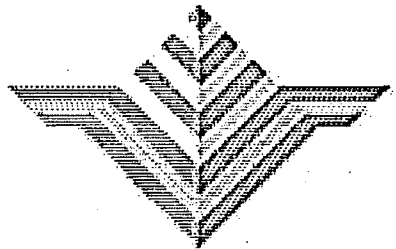


Support Requested Market Share Explosion

- > Increase priority funding of PI change
- > Fund Diabetes Initiative
- > Resource RISPERDAL-ziprasidone clinical trials

R. 3597

FILE 0610616



Lifecycle Extension

Patent Extension

Optimization of Microspheres Launch

REDACTED

Combination Products

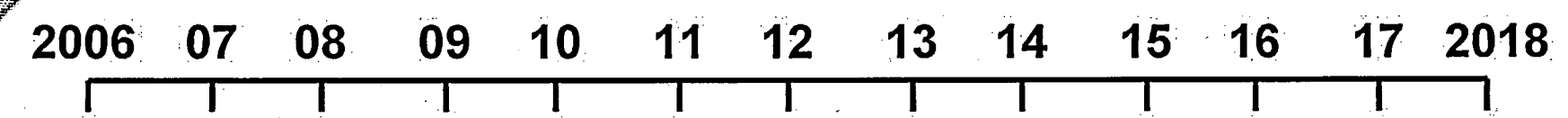
R. 3598

FILE 0610616

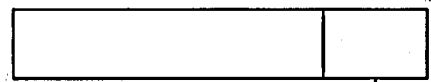


RISPERDAL Patents

R. 3599



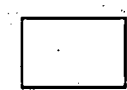
Tablets



\$632

\$833

Liquid



Compound Patent

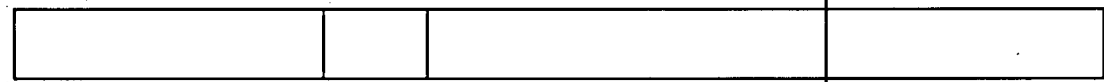


Pediatric Ext.
(of compound patent)



Formulation Patents
(can be circumvented)

QuickSolv



\$66

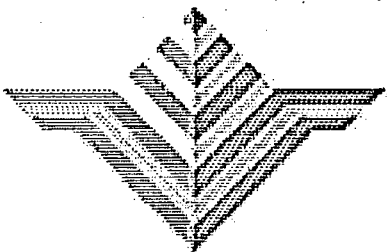
\$136

Alkermes Microspheres



\$293

\$1,730

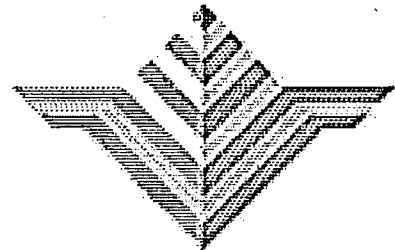


Worldwide Sales Impact Microspheres

FILE 0610617

R. 3600

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>
---	---	---	---	---	---	---	\$298	\$ 89	\$ 60 \$447MM



Optimize Microspheres Launch

Situation:

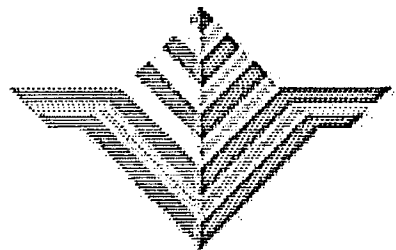
- > Current depot share of patient days of therapy 7 - 21%
- > Current market limited to refractory/non-compliant patients
- > 1st atypical long acting injectable to market
- > sNDA/IRF: 3Q01

Objectives:

- > Position Microspheres as superior to all other antipsychotic options
- > Expand market beyond refractory/non-compliant
- > Maximize revenue with new formulations and enhanced pricing

R. 3601

FILE 0610617

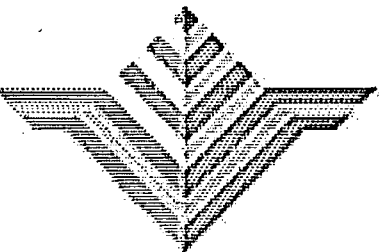


Optimize Microspheres Launch

110610617

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
Clinical		
Interval trial	TBD	TBD
Experience study	11.0	4.0
Bipolar long-term use	15.0	5.0
Large simple trial	4.0	2.0
Marketing Initiatives	<u>14.9</u>	<u>2.0</u>
TOTAL	\$44.9	\$13.0MM
Headcount Additional FTEs	5	

R. 3602

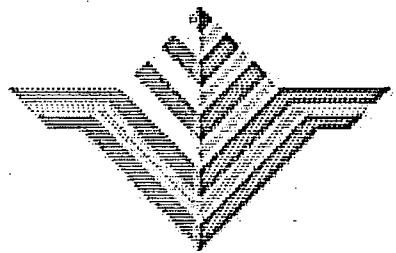


Worldwide Sales Impact Microspheres Launch - I

Incremental Revenue (\$MM)

R. 3603

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$ MM



Worldwide Sales Impact Microspheres Launch - II

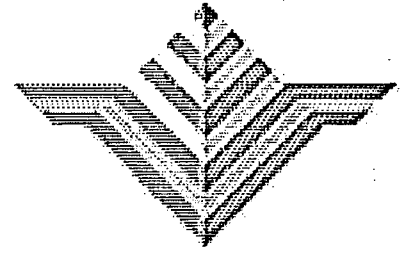
Pricing Optimization

- > Price Microspheres at 14 days x Zyprexa 15mg daily cost
- > Incremental vs original sales forecast: **2.7 Billion** 2001-2010

Incremental Revenue (\$MM)

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
---	\$ 20	\$112	\$155	\$245	\$334	\$399	\$447	\$473	\$498	\$2,683MM

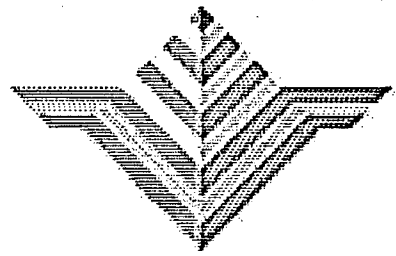
R. 3604



Additional Life Cycle Extension

- > Combination Therapy
 - > Risperidone and Galantamine
 - > Risperidone and Topiramate
 - > Risperidone and Antidepressants

R. 3605

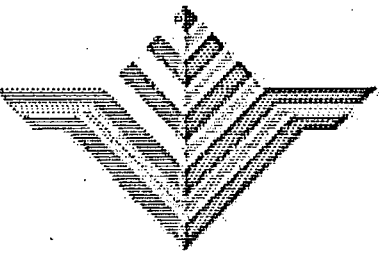


Support Requested Lifecycle Extension

- > Resource Microspheres to optimize launch
- > Future review of combination products and/or packaging

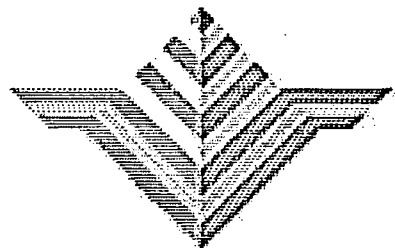
R. 3606

FILE 0610617



R. 3607

Summary



Additional Growth Opportunities

Market Expansion

- > Pharmacogenomics
- > New indications/use:
 - > Children/Adolescent
 - > Axis II
 - > Anxiety
 - > Delirium
 - > OCD
 - > PMDD
- > Pacific Rim Opportunities (Japan)
- > Corrections
- > Veterinary Use

Market Share Explosion

- > Seroquel blunting plan
- > J&J Foundation for the Mentally III
- > Label changes for Haldol

Lifecycle Extension

RED

- > New formulations (OS, HUD, patch)
- > Combination products and/or packaging: RIS + REM, TOP, ADPs

Pricing/Compliance

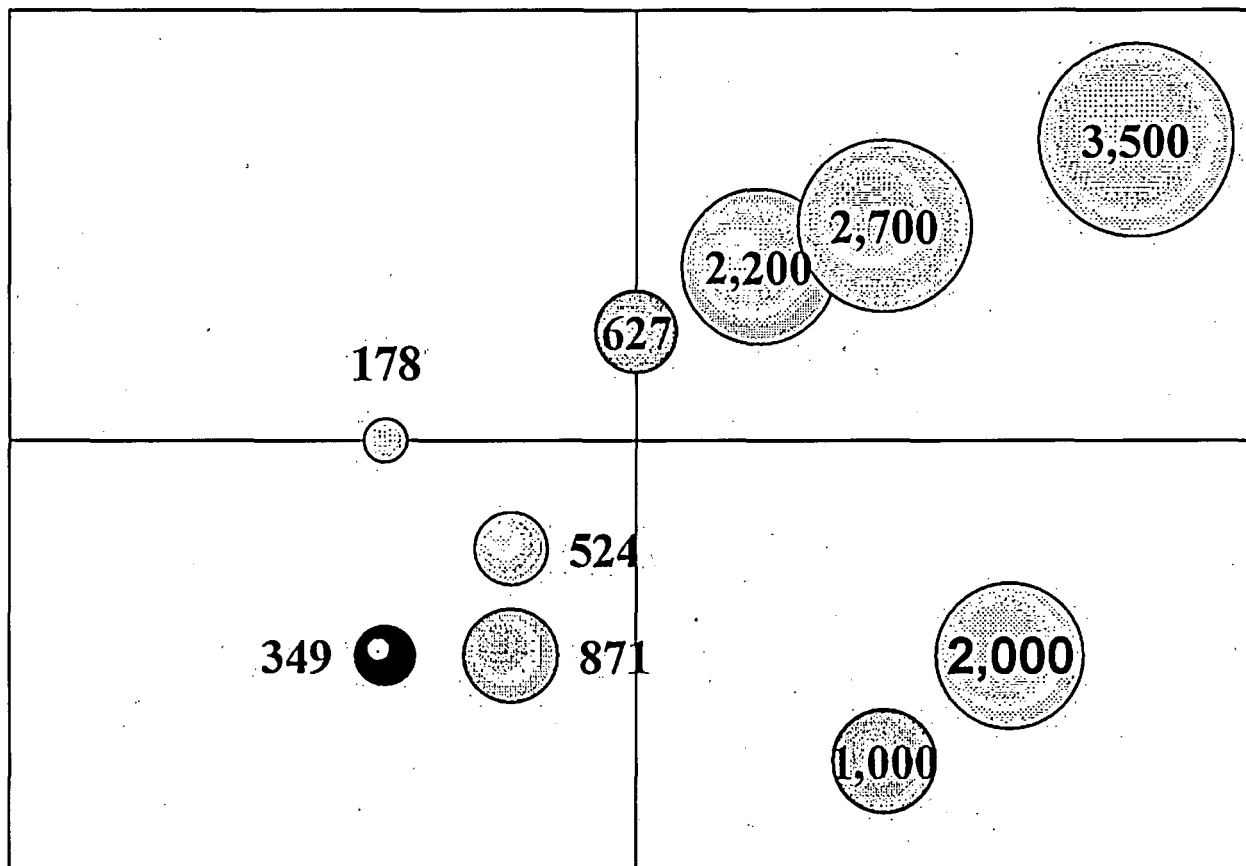
- > New strengths
- > Compliance pricing

R. 3608

Risperdal Opportunities

Expanded

NEW MARKETS



- Dementia
- Bipolar
- TR Depression
- Paediatrics
- Diabetes
- Zap Ziprasidone
- Label Optimisation
- Microspheres
- Conversion
- US PCP

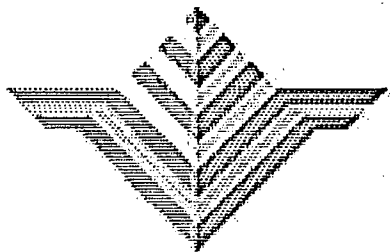
Entered

Protect \$ MS

Increase \$MS

EXISTING MARKETS

R. 3609

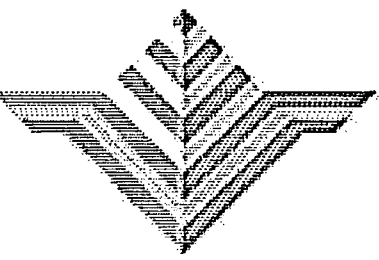


Summary Support Requested

IRE 0610615

	<u>Total</u>	<u>2001</u>
Clinical trials	\$133.0MM	\$74.0MM
Sales & Marketing Support	\$ 32.0MM	\$11.1MM
FTEs		
- Internal	60	60
- Field	100	100
Optimization of structure & processes		
Future review of incremental opportunities		

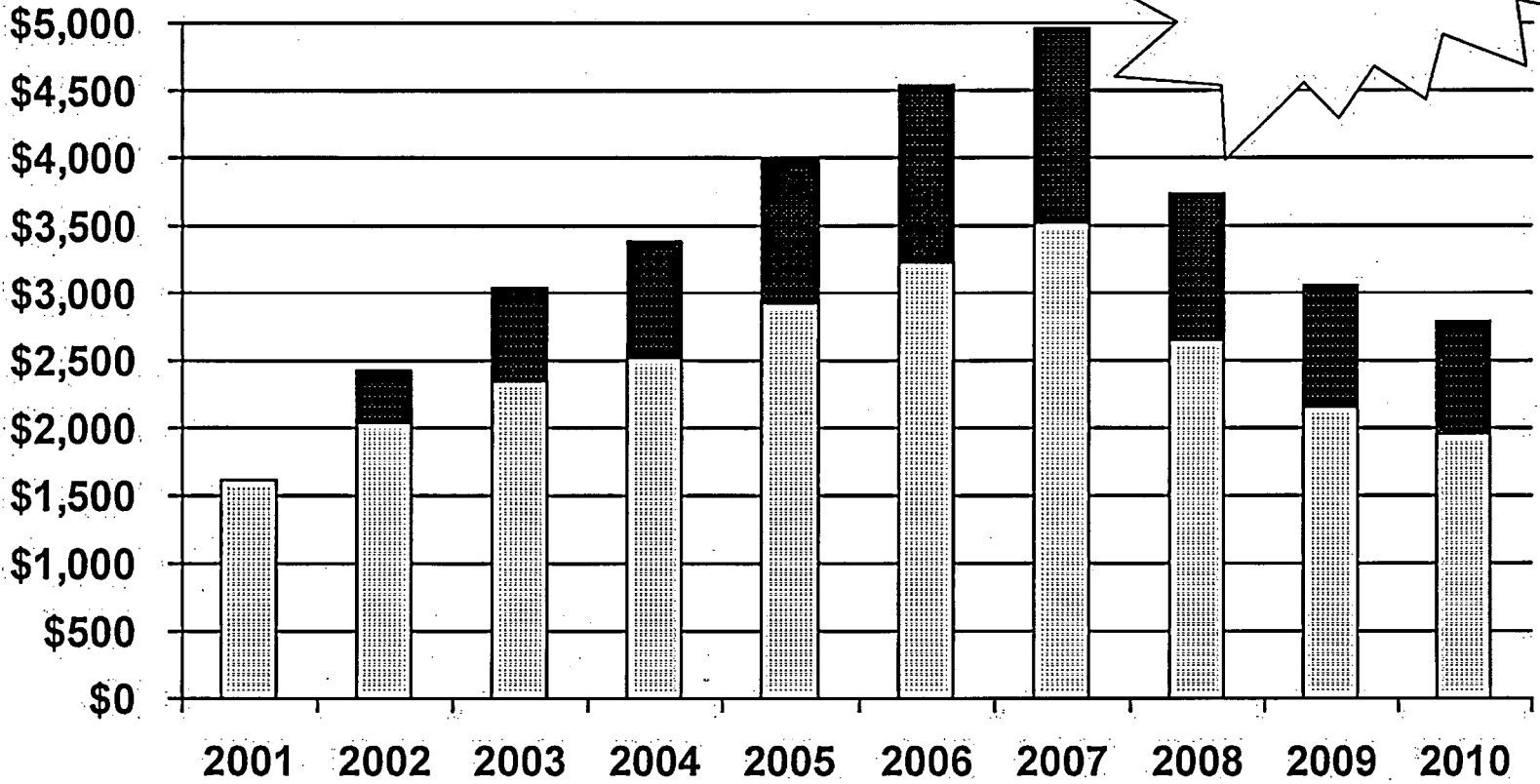
R.3610



RISPERDAL

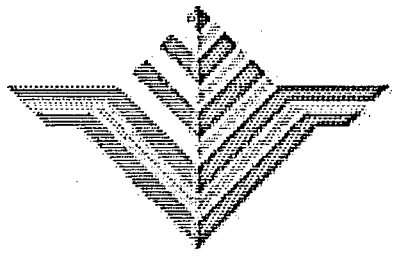
Worldwide Forecast

NTS \$ Millions



+\$9.8 Billion!!

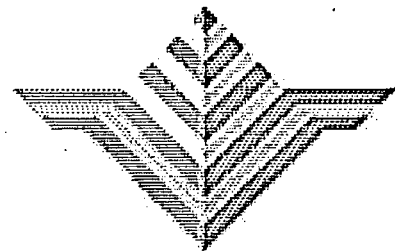
R. 3611



Why invest in RISPERDAL?

- > \$35 Billion cumulative sales*
- > Very high probability of success
- > Long patent life
- > 97% gross profit margin
- > 79% marketing contribution

*2001-2010



RISPERDAL®

Growth Acceleration

R. 3613

Pharmaceutical Group Operating Committee

February 26, 2001



RISPERDAL®
Growth Acceleration

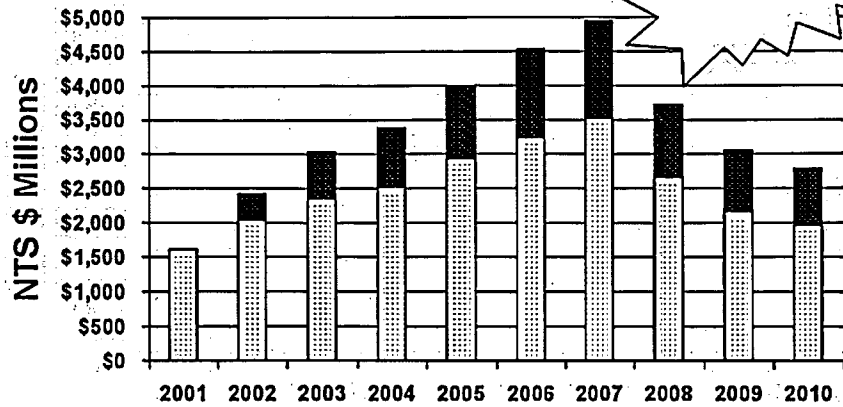
Pharmaceutical Group Operating Committee

February 26, 2001

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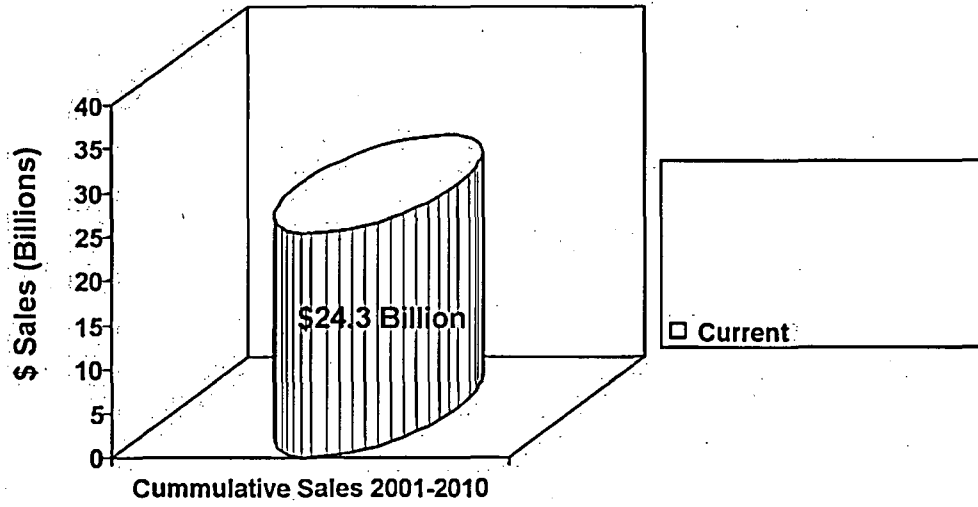
RISPERDAL Worldwide Forecast



The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



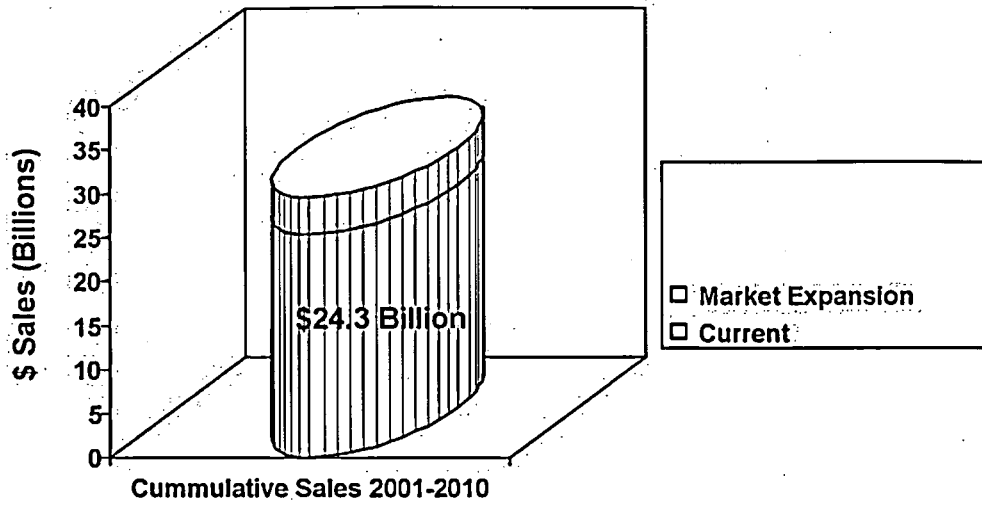
Building a BIGGER Blockbuster



The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



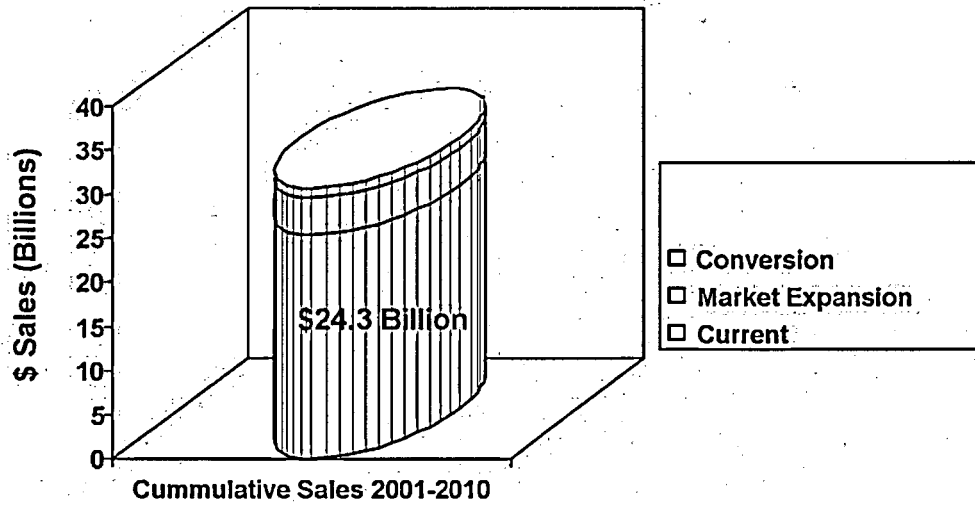
Building a BIGGER Blockbuster



The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



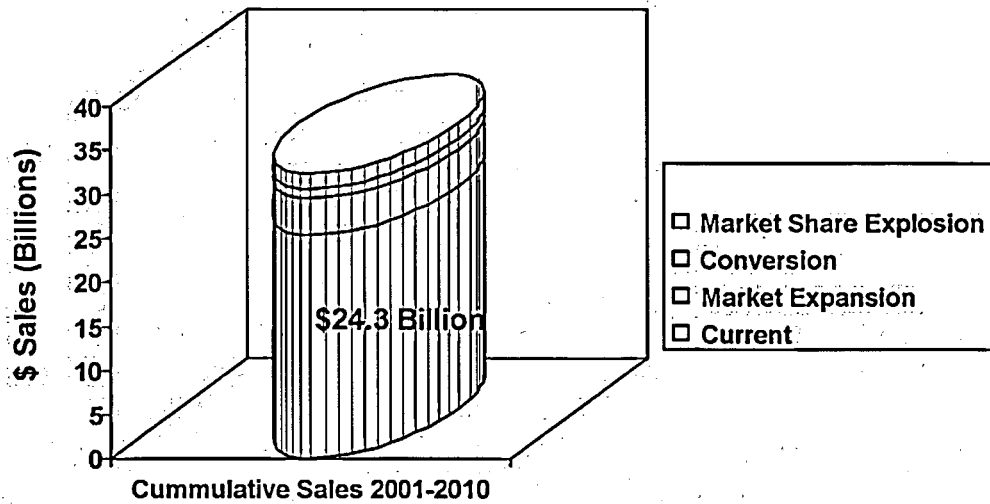
Building a BIGGER Blockbuster



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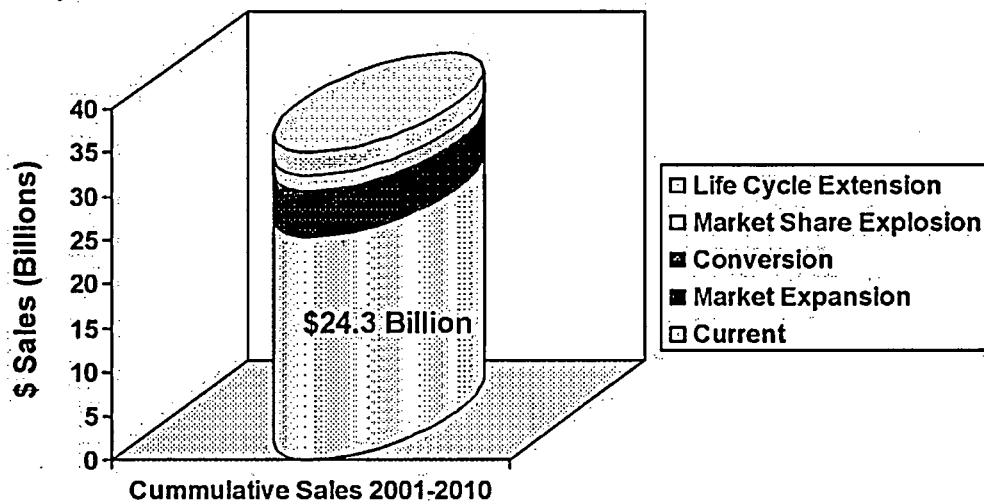
Building a BIGGER Blockbuster



The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Building a BIGGER Blockbuster



This material is that future have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Why invest in RISPERDAL?

- > \$35 Billion cumulative sales*
- > Very high probability of success
- > Long patent life
- > 97% gross profit margin
- > 79% marketing contribution

**2001-2010*

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



RISPERDAL **Growth Acceleration Team**

Christine Poon, Sponsor, Company Group Chairman, J&J Corporate

Sid Frank, Group Director, Public Sector & Institutional Business, JPI

Jane Griffiths, European Business Director, Janssen-Cilag, Europe

Fred Grossman, Director, Global Medical Leader, JRF

Ludwig Hantson, Director of Marketing, CNS Franchise, JPI

Larry Katz, Director, Strategic Life Cycle Management, PGSM

Ramy Mahmoud, Group Director, CNS Medical Affairs, JPI

Kim Taylor, Vice President, Marketing & Medical, JC Asia Pacific

Margaret Theeuwes, GCL, Senior Director Psychiatry, PGSM

Janet Vergis, Vice President, CNS Franchise, JPI

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.

Good let's just bold the names (not the titles) and perhaps italicize Chris.



Additional Thanks to:

Yoshimi Awada

Raffele Balestra

Lynda Benton

Nadine Cohen

Juan Jose Colon

Tara Coyle

Sabind Dandiguan

Bob Decker

Alina Fridman

John Jacoppi

Alice Lex

Kai Martens

Kathy McCaffrey

Ken McDermott

Paul de Nijs

Patrice Noone

Luis Diaz Rubio

Toyoaki Shimada

Jean Marie Wajdowicz

Debi Watson

Michele Wyluda

Weiyi Yang

Steve Wooding

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.

Can we bold?



Agenda

Introduction

J. Vergis

Market Expansion

F. Grossman

Conversion from Conventional

J. Griffiths

Market Share Explosion

L. Hantson/

R. Mahmoud

Lifecycle Extension

M. Theeuwes

Summary

J. Vergis

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.

Let's delete the times. Let's bold



Market Expansion

Dementia

Refractory Depression

Bipolar

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Dementia (BPSD)



Situation:

- > 15MM patients
- > \$4.3B Sales*
- > Increased competition
- > Registration program ongoing/approved

Objectives:

- > Maximize market preparation for label in dementia
- > Increase the number of patients treated and duration of treatment for dementia

**Cumulative Sales 2001-2010*

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Dementia (BPSD)

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
EMRP (investigator initiated trials)	2.0	0.7
Trial in secondary prophylaxis for psychosis early use (publication)	8.0	2.6
Experience trial	3.0	1.0
RISPERDAL/Seroquel trial	8.0	2.6
Medical marketing initiatives	<u>2.5</u>	<u>1.9</u>
TOTAL	\$23.5	\$8.8
 Headcount (Additional FTEs)	 9	

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Worldwide Sales Impact Dementia

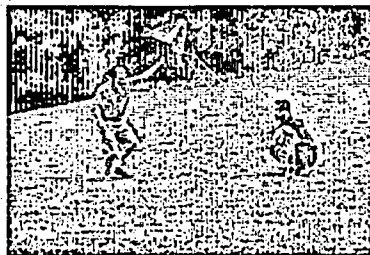
Incremental Revenue (\$MM)

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
\$ 5	\$ 12	\$ 23	\$ 25	\$ 29	\$ 30	\$ 32	\$ 17	\$ 12	\$ 9	\$177MM

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Refractory Depression



Situation:

- > 110MM patients
- > \$4B Sales*
- > Highly dissatisfied market
 - > 30% treatment refractory
 - > 30% partial responders

Objectives:

- > Obtain indication for RISPERDAL add-on therapy to add-on for treatment refractory depression
- > Maximize market preparation for labeling in refractory depression

**Cumulative Sales 2001-2010*

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Refractory Depression

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
Tx Refractory (4-registration)	125.0	31.3
Partial responders	6.0	2.0
Psychotic depression (publication)	1.5	0.5
Extramural research	3.0	1.0
Experience trials	5.0	1.7
Medical marketing initiation	<u>2.5</u>	<u>1.9</u>
TOTAL	\$143.0	\$38.4
Headcount		
Additional FTEs (Medical Affairs)	9	
Additional FTEs (Registration)	20 - 30	

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Worldwide Sales Impact Treatment Refractory Depression

Incremental Revenue (\$MM)

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
\$187	\$201	\$271	\$355	\$463	\$586	\$640	\$382	\$252	\$187	\$3,524MM

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.

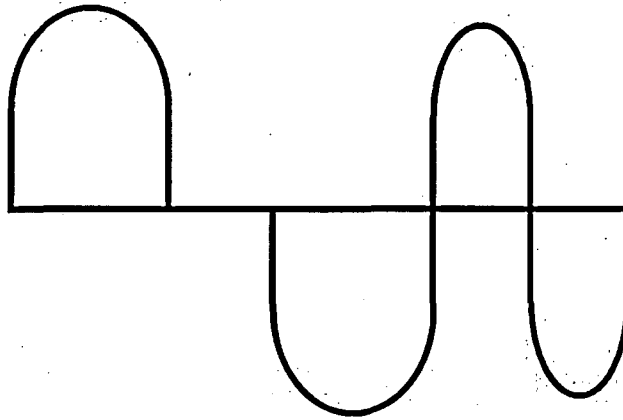


Bipolar Disorder

Mania

Stability

Depression



The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Bipolar Disorder



Situation:

- > 8MM patients
- > \$3B Sales*
- > Highly dissatisfied market
- > Competitive disadvantage
- > Registration program ongoing for monotherapy and add-on therapy for acute mania

Objectives:

- > Maximize market preparation for label in bipolar mania
- > Maximize long term use of RISPERDAL in bipolar disorder
- > Optimize message that RISPERDAL and TOPAMAX can be safely used as combination therapy

**Cumulative Sales 2001-2010*

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Bipolar Disorder

<u>Proposal:</u>	<u>Total Cost (\$)</u>	<u>2001 Cost (\$)</u>
Extramural research	3.5MM	1.2MM
Prospective longitudinal efficacy study	15.0MM	5.0MM
Study of RISPERDAL and TOPAMAX for safety	3.0MM	1.0MM
Medical marketing initiation	2.5MM	1.9MM
TOTAL	\$24.0MM	\$9.1MM
Headcount Additional FTEs	4	

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Worldwide Sales Impact Bipolar

Incremental Revenue (\$MM)

	<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
Bipolar-Maint	\$ 12	\$ 14	\$ 42	\$ 52	\$ 65	\$ 75	\$ 83	\$ 58	\$ 41	\$ 37	\$479MM
Bipolar-Ref Dep	\$ 3	\$ 3	\$ 5	\$ 18	\$ 24	\$ 29	\$ 31	\$ 17	\$ 10	\$ 9	<u>\$149MM</u> <u>\$628MM</u>

This materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Requested Support Market Expansion

- > Increase resources for Dementia;
Depression and Bipolar Programs
- > Initiate Process Excellence ASAP!
- > Future review of
 - > Child/Adolescent Markets
 - > Anxiety
 - > Delirium
 - > OCD
 - > Pacific Rim Opportunities

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Conversion from Conventionals

Europe

US

Japan

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Conversion in the EU

Situation:

- > Typicals still occupy 70% of prescriptions
- > Efforts by Janssen Cilag, Lilly, and Astra Zeneca still result in slow switching rate

Objective:

- > Increase patient demand for atypicals
- > Accelerate patient switch from conventionals to RISPERDAL

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Conversion in the EU

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
Sales & Marketing Support		

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Worldwide Sales Impact Conversion in the EU

Incremental Revenue (\$MM)

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$ MM

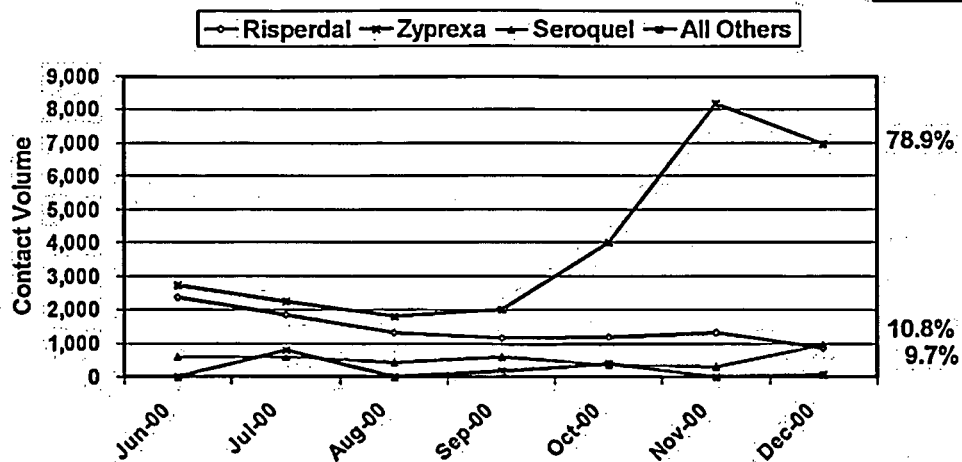
This materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Conversion in the US Situation: Lilly PCP Launch

Primary Care Contacts in U.S.

Share of
Contacts



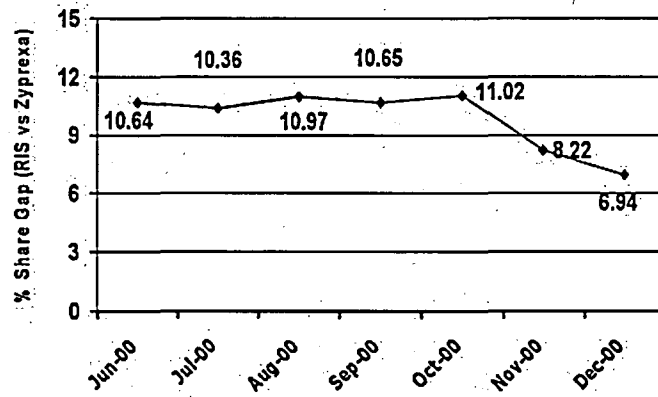
Source: IMS Health, IPS, 12/00

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Conversion in the US

Situation: Decrease in Share Lead



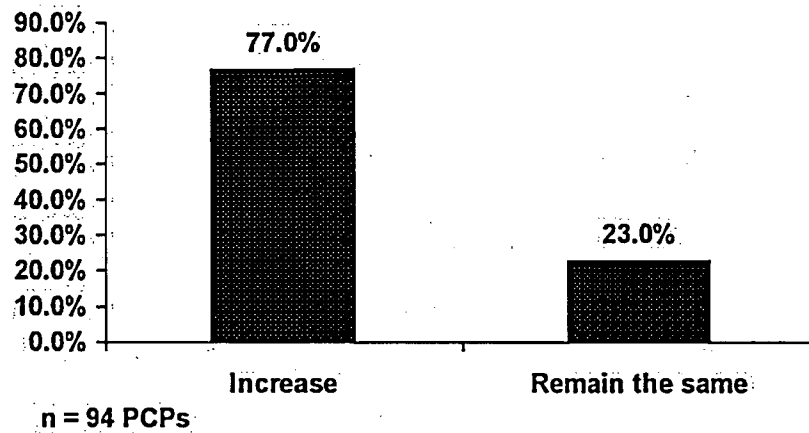
Source: IMS Health, All PCP Monthly NRx Share

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Conversion in the US

"How do you expect your prescribing of Zyprexa to Change"



Source: Market Measures Fastape Study, 1/18/01

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Conversion in the US

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
Sales & Marketing Support	3.0	1.7
Deploy existing Hospital reps	—	—
Headcount Additional FTEs (field)	100	100

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Worldwide Sales Impact Conversion in the US

Incremental Revenue (\$MM)

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>
\$ 21	\$ 51	\$ 84	\$119	\$156	\$192	\$228	\$114	\$ 80	\$ 57 \$1,104MM

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Requested Support Conversion from Conventionals

- > EU: Increase DTP and Clinical Support
- > US: Increase sales SOV in PCPs
- > Japan: Future review of pricing options

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



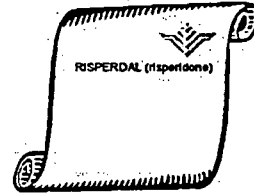
Market Share Explosion

Optimize PI Diabetes Initiative Zap Ziprasidone Program

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Optimize PI



Situation:

- > Noncompetitive; not updated since launch
- > Does not reflect accurate titration, dosing and safety data
- > Lacks competitive information on efficacy

Objective:

- > Optimize label using available clinical data

This material has not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Proposed PI Changes

Program	Label Change	Data
> Titration & Dose	1) Slower titration 2) Lower max dose 3) Dosing for elderly	Czsemansky, Marder
> Aggression	In CD, AD, BP and and schizophrenia	Findling, Sachs, Marder and AUS-5
> Superiority	vs Haldol	Czemansky, Marder
> Safety	1) Change QT wording 2) Reflect accurate TD rate	Pfizer 054 Czemansky, Jeste

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Optimize PI

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
Back-Up aggression study	15.0	5.0
Headcount Additional FTEs (9 Months)	4	

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Worldwide Sales Impact Optimize PI

Incremental Revenue (\$MM)

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
—	\$ 34	\$ 75	\$123	\$130	\$138	\$144	\$ 94	\$ 72	\$ 61	\$871MM

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Diabetes Offensive

Situation:

- > Zyprexa appears to induce or worsen diabetic metabolism
- > Limited clinical data, low awareness
- > FDA submissions on glucose/diabetes (August 10, 2000)

Objective:

- > Generate/disseminate convincing differentiation data
- > Differentiate RISPERDAL's PI from Zyprexa's, prevent class label
- > Increase awareness and change prescribing behavior

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Diabetes Offensive

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
Clinical		
2 Clin Pharm (schizo & bipolar)	4.0	1.6
Clinical comparison trials (vs. OLZ, vs. QUE)	7.0	2.8
EMRP	3.0	1.2
Outcomes		
Longitudinal database and chart review	2.5	1.2
Economic effects of dossier teams	0.8	0.3
Marketing Initiatives	<u>6.6</u>	<u>1.7</u>
TOTAL	\$23.9	\$8.8
Headcount Additional FTEs	9	

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Worldwide Sales Impact Diabetes

Incremental Revenue (\$MM)

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
—	\$ 64	\$ 68	\$ 71	\$ 74	\$ 78	\$ 80	\$ 40	\$ 28	\$ 20	\$523MM

This material that follows have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Zap Ziprasidone

Situation:

- > Zeldox (EU) in review; Geodon (US) approved
 - > Strengths: Maintenance, affective data, tolerability
 - > Weaknesses: QTc, bid, rash, schizophrenia only
- > Available tablets and short-acting IM
- > Well-established customer relationships in CNS, with strong PCP ties (Zoloft, Aricept)
- > History of significant investment

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Zap Ziprasidone

Objectives:

- > Provide evidence to counteract comparative data
- > Generate convincing safety (QT) differentiation data
- > Explore product's potentials to worsen diabetic metabolism
- > Increase awareness of safety issues

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Zap Ziprasidone

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
Comparative study vs RISPERDAL	15.0	1.5
Safety comparison studies	<u>1.5</u>	<u>0.5</u>
Total	\$16.5	\$2.0
Headcount Additional FTEs	?	

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Worldwide Sales Impact Zap Ziprasidone

Incremental Revenue (\$MM)

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
--	\$ 46	\$ 87	\$ 66	\$ 36	\$ 37	\$ 38	\$ 17	\$ 13	\$ 10	\$350MM

The materials that Edine have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Support Requested Market Share Explosion

- > Increase priority funding of PI change
- > Fund Diabetes Initiative
- > Resource RISPERDAL-ziprasidone clinical trials

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



Lifecycle Extension

Patent Extension

Optimization of Microspheres Launch

REDACTED

Combination Products

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



RISPERDAL Patents

2006 07 08 09 10 11 12 13 14 15 16 17 2018

Tablets



Liquid



QuickSolv



Alkermes Microspheres



- ☐ Compound Patent
- ☐ Pediatric Ext. (of compound patent)
- ☐ Formulation Patents (can be circumvented)

\$632

\$833

\$66

\$136

\$293

\$1,730

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Worldwide Sales Impact Microspheres

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>
—	—	—	—	—	—	—	\$298	\$ 89	\$ 60 \$447MM

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Optimize Microspheres Launch

Situation:

- > Current depot share of patient days of therapy 7 - 21%
- > Current market limited to refractory/non-compliant patients
- > 1st atypical long acting injectable to market
- > sNDA/IRF: 3Q01

Objectives:

- > Position Microspheres as superior to all other antipsychotic options
- > Expand market beyond refractory/non-compliant
- > Maximize revenue with new formulations and enhanced pricing

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Optimize Microspheres Launch

<u>Proposal:</u>	<u>Total Cost (\$MM)</u>	<u>2001 Cost (\$MM)</u>
Clinical		
Interval trial	TBD	TBD
Experience study	11.0	4.0
Bipolar long-term use	15.0	5.0
Large simple trial	4.0	2.0
Marketing Initiatives	<u>14.9</u>	<u>2.0</u>
TOTAL	\$44.9	\$13.0MM
Headcount Additional FTEs	5	

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Worldwide Sales Impact Microspheres Launch - I

Incremental Revenue (\$MM)

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$ MM

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Worldwide Sales Impact Microspheres Launch - II

Pricing Optimization

- > Price Microspheres at 14 days x Zyprexa 15mg daily cost
- > Incremental vs original sales forecast: **2.7 Billion** 2001-2010

Incremental Revenue (\$MM)

<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>	
—	\$ 20	\$112	\$155	\$245	\$334	\$399	\$447	\$473	\$498	\$2,683MM

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Additional Life Cycle Extension

- > Combination Therapy
 - > Risperidone and Galantamine
 - > Risperidone and Topiramate
 - > Risperidone and Antidepressants

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Support Requested Lifecycle Extension

- > Resource Microspheres to optimize launch
- > Future review of combination products and/or packaging

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Summary

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Additional Growth Opportunities

Market Expansion

- > Pharmacogenomics
- > New indications/use:
 - > Children/Adolescent
 - > Axis II
 - > Anxiety
 - > Delirium
 - > OCD
 - > PMDD
- > Pacific Rim Opportunities (Japan)
- > Corrections
- > Veterinary Use

Market Share Explosion

- > Seroquel blunting plan
- > J&J Foundation for the Mentally Ill
- > Label changes for Haldol

Lifecycle Extension

REDACTED

- > New formulations (OS, HUD, patch)
- > Combination products and/or packaging: RIS + REM, TOP, ADPs

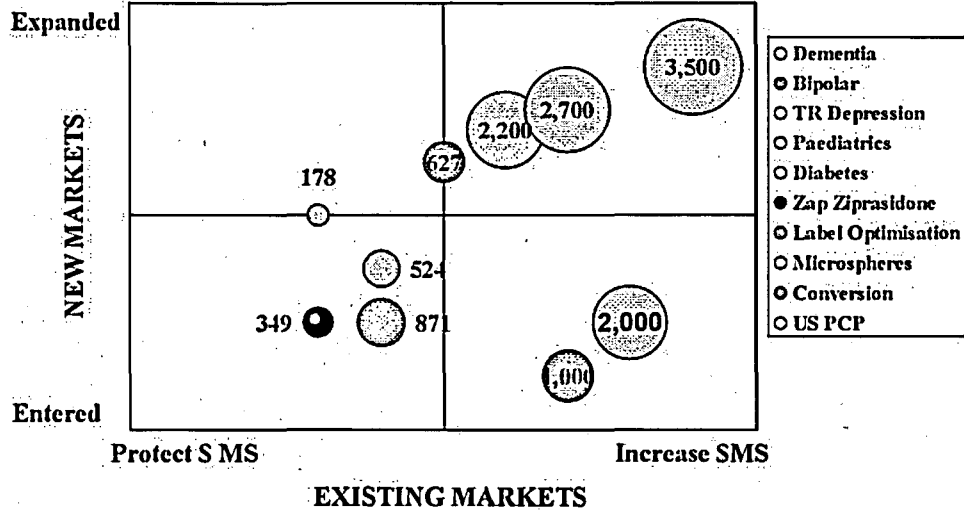
Pricing/Compliance

- > New strengths
- > Compliance pricing

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Risperdal Opportunities



The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued



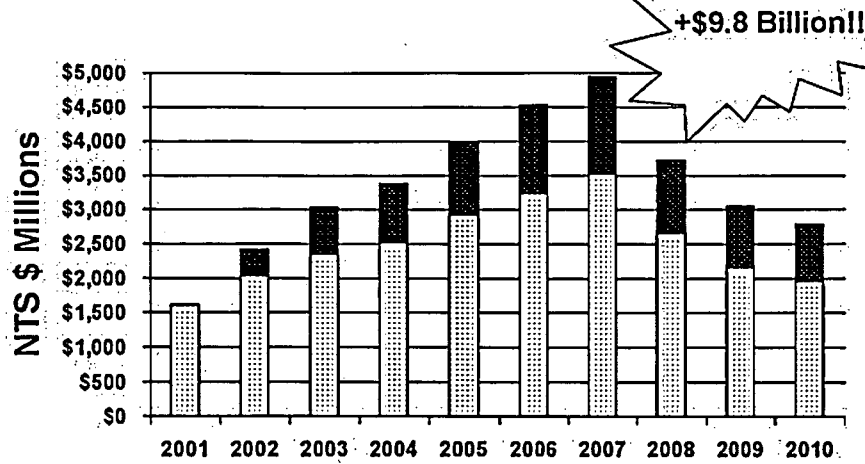
Summary Support Requested

	<u>Total</u>	<u>2001</u>
Clinical trials	\$133.0MM	\$74.0MM
Sales & Marketing Support	\$ 32.0MM	\$11.1MM
FTEs		
- Internal	60	60
- Field	100	100
Optimization of structure & processes		
Future review of incremental opportunities		

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



RISPERDAL Worldwide Forecast



The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



Why invest in RISPERDAL?

- > \$35 Billion cumulative sales*
- > Very high probability of success
- > Long patent life
- > 97% gross profit margin
- > 79% marketing contribution

**2001-2010*

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.



RISPERDAL®

Growth Acceleration

Pharmaceutical Group Operating Committee

February 26, 2001

The materials that follow have not yet been reviewed with the Law Department for legal sufficiency. Such review will be required for any proposals that are pursued.

DIFFERENTIAL EFFECTS OF ANTIPSYCHOTICS ON TYPE II DIABETES: FINDINGS FROM A LARGE HEALTH PLAN DATABASE

Frank Gianfrancesco,¹ Amy Grogg,² Ramy Mahmoud,²
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This study was supported by Janssen Pharmaceutica Products, LLP, Titusville, New Jersey

INTRODUCTION

Several reports suggest that some antipsychotics may induce or exacerbate type II diabetes. Mechanisms by which atypical agents may induce type II diabetes include their propensity to cause weight gain and their antagonism of 5-HT_{1A} receptors. The evidence, however, is still inconclusive.

In the present study we measured the onset or exacerbation of type II diabetes among patients treated with antipsychotics in a large managed care population. Logistic regression models compared the odds of reported diabetes based on exposure to each of the antipsychotics.

ABSTRACT

BACKGROUND: Case series suggest that some antipsychotics may induce or exacerbate type II diabetes and play a potential role in developing diabetic ketoacidosis. This study measured the association of antipsychotic treatments with diabetes at a population level.

METHODS: Claims data for psychosis patients within health plans encompassing 2.5 million lives were analyzed. Patients reporting pre-existing type II diabetes up to 8 months prior to observation were excluded. The frequency of newly reported type II diabetes in untreated patients and among patients treated with five antipsychotic categories (risperidone, olanzapine, clozapine, high potency conventionals and low potency conventionals) was compared. Logistic regression models compared the odds of reporting diabetes based on exposure to each of the antipsychotic categories.

RESULTS: The odds of reporting type II diabetes over one year for risperidone patients (OR=0.88 95% CI=0.37-2.07) was not significantly different from untreated patients. The other antipsychotics had a significantly greater risk of reporting diabetes than untreated ($p < 0.05$). Odds ratios based on 12 months of exposure were: olanzapine 3.10 (95% CI=1.62-5.93); clozapine 7.44 (95% CI=1.60-34.75); high potency conventionals 2.13 (95% CI=1.10-4.13); and low potency conventionals 3.46 (95% CI=1.52-7.79). Older age and greater use of non-antipsychotic psychotropic medications also contributed to risk of type II diabetes.

CONCLUSION: Consistent with previously published literature, these data suggest that some antipsychotics may increase the risk of acquiring or exacerbating type II diabetes, and that the effect may vary by drug. In contrast to clozapine and olanzapine, risperidone was not associated with risk of type II diabetes.

METHODS

Data collection

- Claims data were collected from two large mixed indemnity and managed care health plans, one in the Northeast and the other in the Southeast of the United States.
- Claims data for the period from January 1996 through December 1997 were analyzed.
- Some form of psychosis was identified in 7,933 patients.
- Of the 7,933 patients with psychosis, 4,308 received an antipsychotic therapy for 60 or more days. No antipsychotics were received by the remainder ($N = 3,625$).
- Psychosis patients were screened for preexisting type II diabetes for periods of 4 and 8 months before the observation period.
- Type II diabetes was identified using ICD-CM-9 diagnostic criteria and use of antidiabetic medications.

Antipsychotic treatment/Observation periods

- Episodes of treatment with an antipsychotic provided the basis for observation.
- Identification of a prescription for an antipsychotic as the first prescription in a treatment episode required that it not be preceded by another prescription for that antipsychotic for at least 90 days.
- Treatment episodes were measured from the date of the first prescription for an antipsychotic to the final date of treatment.
- Number of treatment episodes for each antipsychotic were (prior to prescreening):
 - Risperidone, 1591
 - Olanzapine, 1178
 - Clozapine, 81
 - High-potency conventional antipsychotics, 1681
 - Low-potency conventional antipsychotics, 556

Presented at the Annual Meeting of the Society of Biological Psychiatry, May 3-5, 2001, New Orleans, LA

Logistic regression analyses

- Logistic regression was used to control for differences between groups.
- Two sets of logistic regressions were estimated excluding patients with preexisting type II diabetes at 4 and 8 months before observation.
- Two models were specified to capture the diabetic effects:
 - Antipsychotic treatment duration: Each variable (treatment group) equaled the length of treatment in months if the observed patient used that therapy
 - Antipsychotic dose: Each variable (treatment group) equaled the amount of antipsychotic used in risperidone equivalent milligrams per day.
- Doses of all of the antipsychotics were expressed in milligrams per day of risperidone equivalents.
- The following control variables were also specified in the models:
 - Concurrent use of antipsychotics
 - Age and sex
 - Observation period (months)
 - Concomitant use of other psychotropic drugs
 - Type of health care coverage: managed care or indemnity
 - Psychosis diagnoses (schizophrenia, bipolar and mania, major depression, dementia, other psychoses)

RESULTS

Background information on patients in each of the treatment groups is shown in Table 1:

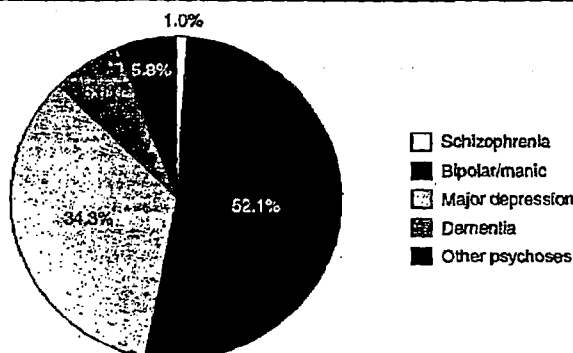
- Most of the patients in each treatment group were women. Patients receiving the atypical agents (risperidone, olanzapine, and clozapine) tended to be younger than those treated with conventional agents.
- More than half of the untreated patients (52%) had diagnoses of bipolar or manic disorder (Figure 1). Among all the treated patients (Figure 2) and in four of the five antipsychotic groups, major depression was the most common psychotic disorder. Among patients receiving clozapine, schizophrenia was the diagnosis in more than half (57%) and the duration of antipsychotic treatment was the longest (9.4 ± 5.5 months).
- The daily dose of olanzapine was higher than that of the other antipsychotics and concurrent use of other antipsychotics was more common in the clozapine group than in the other patient groups.

Table 1. Characteristics of Patient Episodes with Psychosis and No Type II Diabetes at Four Months Prior to Observation

	Untreated Patients (N = 3061)	Treated Patients (N = 4334)	Risperidone (N = 1368)	Olanzapine (N = 1047)	Clozapine (N = 63)	High-Potency Conventionals (N = 1376)	Low-Potency Conventionals (N = 480)
Women, % patients	59.6	63.4	59.8	62.2	58.7	66.2	68.5
Age, mean (SD) years	41.9 (14.8)	45.3 (19.3)	43.0 (20.7)	43.1 (16.9)	39.4 (14.1)	48.4 (18.7)	48.3 (20.5)
Diagnosis, % patients							
Schizophrenia	1.0	17.2	14.0	22.4	57.1	16.6	11.2
Bipolar and manic	52.1	21.5	19.7	24.8	19.0	20.1	23.5
Major depression	34.3	38.8	42.3	37.8	14.3	36.9	39.4
Dementia	6.8	6.4	6.3	2.1	0.0	8.6	10.2
Other psychoses	5.8	16.2	17.7	12.8	9.5	17.7	15.6
Observation period, mean (SD) months	13.8 (4.8)	6.4 (4.6)	6.4 (4.7)	5.6 (3.5)	8.8 (5.4)	6.7 (4.9)	6.8 (5)
Duration of antipsychotic treatment, mean (SD) months	na	6.8 (4.7)	6.9 (4.8)	6.1 (3.6)	9.4 (5.5)	7 (5.1)	7.1 (5.2)
Antipsychotic dose, mean (SD) mg/day*	na	2.4 (2.1)	2.3 (1.8)	3.6 (2.0)	2.5 (1.9)	1.7 (1.9)	1.7 (2.7)
Concurrent use of other antipsychotics, % patients	na	20.8	19.6	24.6	34.9	17.9	22.1
Use of other psychotropics, mean (SD) \$/month	46.29 (72.91)	66.42 (90.51)	69.76 (84.09)	77.26 (107.34)	76.16 (175.52)	56.61 (79.97)	60.11 (76.19)

*Milligrams of risperidone equivalents.

Figure 1. Diagnoses in Untreated Patients



Frequency of Type II Diabetes

- Risperidone consistently had the lowest percentage of patients reporting type II diabetes (Figure 3). Among patients receiving clozapine the frequency of type II diabetes was 13.3% in patients prescreened at 4 months and 25.0% in patients prescreened at 8 months (data not included in Figure 3).
- Untreated and risperidone patients had similar rates of reporting diabetes (Figure 3).

Figure 2. Diagnoses in Treated Patients

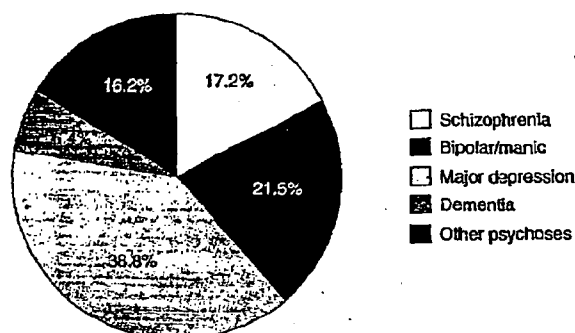
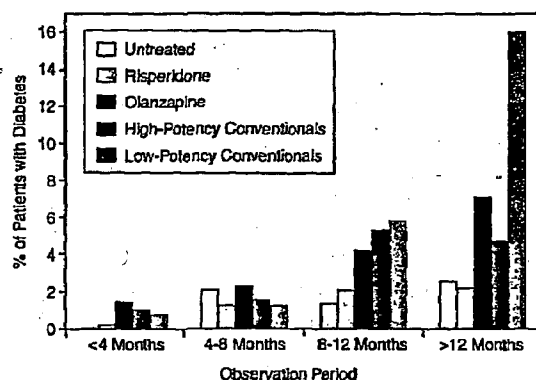


Figure 3. Frequency of Type II Diabetes in Patients Prescreened at 8 Months Before Observation



Logistic Regression Results

- Results of logistic regression based on prescreening for type II diabetes at 4 and 8 months were similar; all of the antipsychotics except risperidone were associated with type II diabetes.
- Odds ratios for treatment duration indicated that olanzapine and high- and low-potency conventionals were significantly associated with type II diabetes among patients with no diabetes at 4 and 8 months before observation (Table 2).

Table 2. Odds of Type II Diabetes in Patients with Psychosis: Results of Logistic Regression

Variable	No Type II Diabetes at 4 Months Before Observation <i>Diabetes reported in 206 of 7395 observations</i>		No Type II Diabetes at 8 Months Before Observation <i>Diabetes reported in 101 of 4979 observations</i>	
	Odds Ratio	P Value	Odds Ratio	P Value
Treatment duration (months)*				
Risperidone	1.021	0.263	0.989	0.765
Olanzapine	1.082	0.0008†	1.099	0.0006†
High-potency conventionals	1.047	0.003†	1.065	0.025*
Low-potency conventionals	1.058	0.009†	1.109	0.003†
Clozapine	1.079	0.071	1.182	0.01*
Age	1.028	0.0001†	1.025	0.0004†
Sex (male=1)	1.079	0.617	0.822	0.382
Observation period (months)	1.081	0.0001†	1.125	0.0001†
Other psychotropic drugs (\$10 units per month)	1.021	0.0003†	1.021	0.008†
Concurrent antipsychotic (ratio of days supply)	1.06	0.857	1.425	0.401
Coverage (managed care=1; indemnity=0)	1.085	0.614	0.99	0.968
Schizophrenia (yes=1; no=0)	1.534	0.166	0.994	0.990
Bipolar/manic (yes=1; no=0)	1.157	0.589	1.159	0.699
Major depressive (yes=1; no=0)	1.192	0.501	1.151	0.701
Dementia (yes=1; no=0)	1.243	0.508	1.449	0.402

*P<0.05 by chi-square test. †P<0.01. ‡P<0.001.

*Patients not treated with antipsychotics are represented by zeros for each of the five specified antipsychotic categories

- Significant associations between clozapine and diabetes were observed in some populations (those prescreened for diabetes at 8 months before observation), with an 18.2% increased odds of diabetes per month of treatment ($p = 0.0104$). However, a definite association between clozapine and diabetes cannot be determined from this study because of the limited sample size for clozapine.
- Age, observation period length, and use of other psychotropics were also significant predictors of diabetes.
- One month of treatment with olanzapine increased the odds of type II diabetes by 9.9% versus no treatment.
- The odds ratios for dose were also calculated using all variables. Dose was a significant predictor of type II diabetes only with olanzapine. As the olanzapine dose increased, the likelihood of newly reported type II diabetes increased 22.2% per 2.6 mg of olanzapine.

Conversion to 12 Months

The odds ratios for antipsychotic treatment duration were converted to 12 months (Table 3, Figure 4).

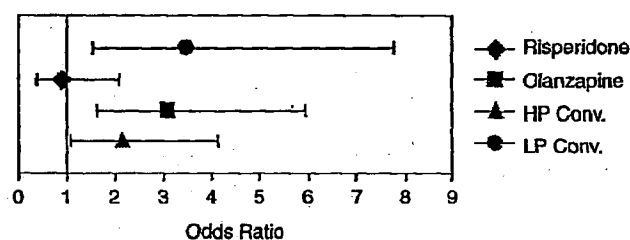
Table 3. Odds of Type II Diabetes During 12 Months of Antipsychotic Treatment in Patients with No Type II Diabetes at Eight Months Before Observation

	Odds Relative to Untreated	95% Confidence Intervals	Odds Relative to Risperidone
Risperidone	0.88	0.372-2.070	na
Olanzapine	3.10	1.620-5.934 [†]	3.53*
High-potency conventionals	2.13	1.097-4.134 [†]	2.42
Low-potency conventionals	3.46	1.522-7.785 [†]	3.93*
Clozapine	7.44	1.603-34.751 [†]	8.45*

[†] Odds ratio of 1.00, meaning effect is no different from untreated, falls outside of 95% confidence interval.

* $P < 0.05$

Figure 4. Odds of Newly Reported Type II Diabetes with Antipsychotics in Psychosis Patients During 12 Months Relative to No Treatment



- Risperidone's ratio of 0.88 implies that patients treated for 12 months have odds of newly reported type II diabetes that are 12% below baseline (not significant).
- In contrast, the 12-month ratios for the other antipsychotics are greater than 1. All have significantly higher odds of inducing newly reported diabetes than no treatment.
- Olanzapine's odds ratio of 3.10 relative to untreated indicates that 12 months of treatment increases the odds of diabetes by 210% over no treatment.
- Olanzapine's odds ratio of 3.53 relative to risperidone indicates that its diabetic effect is 2.5 times greater than that of risperidone.
- Olanzapine, low-potency conventionals and clozapine were all significantly different from risperidone.

CONCLUSIONS

- According to frequency tables and logistic regression, patients with psychosis treated with risperidone were no more likely to newly report type II diabetes than untreated patients.
- In contrast, olanzapine, clozapine, and conventional agents had a significant diabetic effect versus no treatment.
- Among atypical antipsychotics analyzed, the dibenzodiazepines (clozapine and olanzapine) had a greater association with diabetes than the benzisoxazole (risperidone).
- Olanzapine was the only agent to demonstrate a significant dose response: as the dose increased, the odds of newly reported diabetes increased.



Janssen

CONFIDENTIAL

First Cycle
1999

EXHIBIT 23
WIT: BRANN
DATE: 4.28.10
TERRI SAPP

SALES DIRECTION

CONFIDENTIAL

R. 3681

J-TXCID1673025

Sales Direction 1st Cycle 1999

Welcome to the 1st cycle of 1999 and your first District Meeting of the year. On behalf of the entire sales team, I would like thank you for your efforts last year and recognize your impact on helping Janssen exceed the sales forecast! There were a number of challenges in 1998, including the competition, relabeling, and the launching of new sales forces (425, ElderCare). Throughout the year, the sales team rose to meet and effectively handle those challenges head on. Congratulations, and thanks again for all your efforts.

For 1999, our sales goals and objectives will be just as aggressive as we look toward continued growth of the promoted brands. To support the growth of our current and future products, Janssen will undertake an expansion of the sales force that will increase our focus, reach, and frequency with all of the key customers and accounts. The additional focus achieved from the new sales forces will allow us to be more competitive and achieve greater penetration of all competed markets.

Throughout the year we will continue to focus on the fundamental skills and competencies that are critical to driving our business. Let's take a moment to review those keys to success:

- ✓ **The Right Physician :** If you are a 500, 425, ElderCare or Hospital representative, targeting of the key customers and accounts is critical to your short and long term success. Utilization of your decile data to target, trend, and evaluate your business is the cornerstone of successful territory management. The application of your selling time against the highest potential customers will drive your business results.
- ✓ **The Right Frequency:** It's important that each targeted physicians is seen a minimum of 1X per month by each of the sales forces. Greater frequency on our targeted high decile physicians has proven to increase sales results, as well as improve our customer satisfaction scores. It's essential that we coordinate and maximize our T.O.P's to drive frequency of calls on our key customers. In order to achieve our production goals though, it is important to achieve a minimum of 8 physician calls per day, 3 retail pharmacy calls, and more than 2 presentations per call.
- ✓ **The Right Message :** Consistency of sales message is an important component of each and every sales call. At each District meeting we spend time practicing and refining our sales message, and it's important that we execute this consistent message on every call with the customer.

The 1st cycle sales directions for the individual brands are as follows:

PROPULSID® Tablets, Suspension

The GI market at over \$6.0 billion in annual sales is one of the largest U.S. therapeutic categories and has been growing at a rate of over 10% per year. PROPULSID remains the cornerstone of our GI franchise, and finished 1998 at over \$500 million in sales with a 15% increase over the previous year. The growing GI marketplace still presents a tremendous opportunity to grow our PROPULSID business in all of our key customer segments (Primary Care, Gastroenterology, Institutions and Long Term Care).

The 500, 425, HSR and ElderCare sales forces will all sell PROPULSID this cycle. In the 500 sales force PROPULSID will be in the 1st selling position, and with the 425 sales force it will be in the 2nd selling position. The HSRs will sell PROPULSID in the first product position with Primary Care, IM,

CONFIDENTIAL

GI fellows and staff. ElderCare will have PROPULSID in the 3rd selling position with Medical Directors, Directors of Nursing, Consultant Pharmacists and PC/IM targets.

The objectives for this cycle are as follows:

- Making the link from motility disorders to GERD to patient symptoms
- Reinforce that PROPULSID is the only medication that can effectively relieve heartburn and the motility related symptoms
- Continue to ensure proper patient selection for PROPULSID

This cycle the brand team has provided new materials including CME Experts on Tape Part II in both video/ CD-Rom format. Use of these materials in conjunction with teletopics and speaker programs provide excellent opportunities for Peer-to-Peer selling. The new Gastro Wellness materials should be distributed in all physician offices, pharmacies and hospitals.

SPORANOX® Capsules

Due to the selling efforts of the sales force, SPORANOX showed a continuous growth in sales throughout the year and exceeded the forecast for 1998! In addition to growing sales, *PulsePak* prescriptions continue to be strong and account for almost one-half of all SPORANOX prescriptions.

For the 425 Sales Force, SPORANOX will be in the 1st selling position to all targeted physicians. For the 500 Sales Force NOT trained on DURAGESIC, SPORANOX will be in the 2nd selling position. If you are a DURAGESIC trained representative, SPORANOX will be in the 3rd selling position. *In addition, both sales forces will again be calling on Dermatologist and Podiatrists.*

The objectives for the cycle are as follows:

- Sell against Lamisil
- Sell the Benefits of SPORANOX *PulsePak*
 - PulsePak* is easier to prescribe
 - PulsePak* is easier for patients to use
- Sell the Benefits of Pulse Dosing
 - Less drug
 - Less cost
 - Fewer treatment days
 - Patient preferred
- Target High Volume Physicians
 - Use samples with HVP physicians
 - Allocate resources with targeted physicians

For 1999, the market definition for SPORANOX has been changed to include SPORANOX and Lamisil only. This change will allow you to focus your efforts on Lamisil, and grow SPORANOX

market share by taking it away from Novartis! For targeting purposes (decile), you will still call on AFO 7-9 physicians who may be prescribing other oral antifungals, such as Diflucan or griseofulvin. This change in market definition will take effect as of the January incentive reports.

DURAGESIC®

For 1998, DURAGESIC had another year of tremendous sales growth, DURAGESIC sales increased over 30% versus the previous year! The efforts of the sales force play a paramount role in the growth and overall success of this brand. In 1999, we expect DURAGESIC to have another banner year of growth with sales reaching \$300 million in sales.

For 1999, we will be redefining the market definition for DURAGESIC to include Percocet, along with OxyContin, MS Contin, Kadian and Oramorph. Demerol, Dilaudid and IR Morphine will be removed from the market definition. This change in market definition will expand the number of chronic pain 8s & 9s per territory, and will offer an increased opportunity to sell DURAGESIC in all targeted territories. The addition of these new products to the market definition will allow you focus your efforts on driving DURAGESIC market share and regaining market leadership from OxyContin!

DURAGESIC will be sold by the HSR, ElderCare and 500 sales force this cycle. For the DURAGESIC targeted 500 sales force, DURAGESIC will be in the 2nd selling position. ElderCare will sell DURAGESIC in the 2nd selling position to all targeted customers, and HSR will sell DURAGESIC to all pain clinics, PC/IM/GE, residents and fellows.

Below are the objectives for the cycle:

- Initiate DURAGESIC as soon as around the clock opioid therapy is required to treat chronic pain
- Expand use of DURAGESIC among physicians who only use DURAGESIC to treat cancer pain
- Differentiate DURAGESIC from short-acting opioids that are used around the clock

In order to achieve our cycle objectives, it's imperative that we incorporate the brand key communication points (The Right Message):

"For any chronic pain state that requires around the clock opioid treatment, DURAGESIC should be the first choice."

- Only DURAGESIC provides 72 hours of continuous pain relief
- DURAGESIC has less side effects
- DURAGESIC is patient preferred

RISPERDAL®

RISPERDAL sales showed continued growth despite a very competitive marketplace and fierce competition. Brand sales exceeded \$700 million and posted a greater than 20% increase versus last year. This tremendous growth in sales is due to the dedication and efforts of the sales team with the brand. Congratulations on a great year!

RISPERDAL is and continues to be the #1 antipsychotic in the United States. Brand market share in the base psychosis and Long Term Care markets are both at all time highs! Our goal needs to be to

continue to grow our brand market share, while continuing to stop the competition. RISPERDAL is and will remain the #1 product in the base psychosis and Long Term Care markets during 1999.

Below please find the brand objectives and key communication points by sales force and market segment.

Hospital Sales

The key communication points for RISPERDAL with the hospital sales force are:

➤ Emphasis on Efficacy

- RISPERDAL is the only APS proven superior to Haldol in neg. and pos. symptoms
- RISPERDAL is rarely co-prescribed with other antipsychotics (3x less than OLZ)

➤ Stress Low Weight Gain

- Recent data suggests 1 lb. per week with OLZ

➤ Ensure Appropriate Dosing

- Average dose for schizophrenia is 4.6 mg / day
- RISPERDAL also has convenient QD dosing (30ml bottles)

The HSR will continue to sell RISPERDAL in the 1st product position to all psychs and psych residents. For 1999, the 50% weighting on RISPERDAL has been removed. As of January, all products in the hospital will weight themselves according to the current business potential. This removal of the weighting will allow a more balanced approach to the management of the hospital business and the pursuit of brand potential.

ELDERCARE

The RISPERDAL key communication points for ElderCare are as follows:

➤ RISPERDAL improves a broad range of psychotic symptoms

➤ RISPERDAL has a low incidence of side effects:

- EPS
- Sedation
- Anticholinergic side effects

➤ RISPERDAL dosing fits patient and caregiver lifestyles

- BID and QD dosing
- Tablets and Solution (30ml bottles)

The ElderCare sales team has gotten off to a fantastic start in 1998, and your efforts are helping to drive RISPERDAL market share to new heights in the Long Term Care market. For the first cycle, RISPERDAL will be in the 1st selling position with ElderCare with all targeted customers. Your continued efforts in developing your accounts, customers, and driving your market share will make ElderCare a tremendous success in 1999.

This first cycle is a tremendous opportunity for the sales team to set the tone and the momentum for the remainder of the year. Our ability to drive brand market share and take business away from the competition will be the cornerstone of our success for 1999. I think you will find the brand market redefinitions and HSR weighting change will allow you to focus on the competition and the opportunities that exist in your individual territories.

Our success as a sales team is dependent upon our ability to PRIORITIZE, FOCUS and EXECUTE against the plans we make at your District Meetings. We've proven we have the right sales team, products and brand message to be successful. Let's all commit to making 1999 another banner year for the sales force and Janssen overall!

Good luck and GOOD SELLING!!

Stephen A. Zollo
Vice President, Sales

/jen

CALL PLAN

1999 1st Cycle Priorities Janssen 500SF

- Territory Representatives in the 500 Sales Force will focus on these strategic brands: **PROPULSID**, **DURAGESIC** and **SPORANOX**.

SELLING PRIORITIES

w/DURAGESIC

1. PROPULSID

2. DURAGESIC

3. SPORANOX

w/o DURAGESIC

1. PROPULSID

2. SPORANOX

- **DURAGESIC** is to be sold only to physicians who are Chronic Pain decile (8 - 9).
- Dermatologists and Podiatrists will be seen by both the 500 and 425 Sales Forces. Sporanox will be sold in 1st position.
- Three Pharmacy calls per day are required.

1999 1st Cycle Call Plan

Janssen 500SF Territory Representatives

TARGETS / PRESENTATIONS

<u>Physicians</u>	<u>#1</u> <u>All GE</u>	<u>#2</u> <u>Crossmatch</u> <u>GI8-9/CP 8-9</u>	<u>#3</u> <u>Remaining</u> <u>GI8-9</u>	<u>#4</u> <u>AFO 7-9</u>	<u>#5</u> <u>Remaining</u> <u>DERMs & PODs</u>
Presentation #1	PRO	PRO	PRO	SPX	SPX
Presentation #2		DUR	SPX	PRO	
Presentation #3		SPX			

- Targeted physicians/presentations are listed in order of importance.
- Physician target lists should be created on Navigator at your cycle meeting.
- Frequency goals are once per month on targeted physicians.
- Dermatologists and Podiatrists will be seen by both the 500 and 425 Sales Forces. Sporanox will be sold in 1st position.

1999 1st Cycle Priorities Janssen 425SF Territory Representatives

- **Territory Representatives in the 425 Sales Force will focus on these strategic brands: SPORANOX and PROPULSID.**

SELLING PRIORITIES

- 1. SPORANOX**
- 2. PROPULSID**
- 3. NIZORAL CREAM**

- **Dermatologists and Podiatrists will be seen by both the 500 and 425 Sales Forces. For the 425SF, Sporanox will be sold in 1st position, followed by Nizoral Cream.**
- **Three Pharmacy calls per day are required**

1999 1st Cycle Call Plan

Janssen 425SF Territory Representatives

TARGETS / PRESENTATIONS

<u>Physicians</u>	<u>#1</u> <u>AFO 7-9</u>	<u>#2</u> <u>Remaining</u> <u>PC/IM/D/PODs</u> <u>SPX 8-9</u>	<u>#3</u> <u>PC/IM GI9</u>	<u>#4</u> <u>PC/IM GI8</u>	<u>#5 Remaining</u> <u>DERMs & PODs</u>
Presentation #1	SPX	SPX	SPX	SPX	SPX
Presentation #2	PRO	PRO	PRO	PRO	NZC
Presentation #3	NZC	NZC	NZC	NZC	

- Targeted physicians/presentations are listed in order of importance.
- Physician target lists should be created on Navigator at your cycle meeting.
- Frequency goals are once per month on targeted physicians.
- Dermatologists and Podiatrists will be seen by both the 500 and 425 Sales Forces. For the 425SF, Sporanox will be sold in 1st position followed by ...

1999 1st Cycle Priorities

Janssen Hospital Representatives

- Hospital Representatives will continue to focus on our most important and influential teaching institutions.
- The primary effort is to represent and sell Janssen products to thought leaders, residents, attending & staff physicians.

PRODUCT MIX: **DURAGESIC**
 PROPULSID
 RISPERDAL
 SPORANOX

- Depending on the target audience and their potential use, the second product sold will vary.
- **NOTE:** The 50% weighting on Risperdal has been removed. Products will be self-weighted based on dollar potential.

1999 1st Cycle Call Plan

Janssen Hospital Representatives

TARGETS / PRESENTATIONS

PSYCHIATRY

RIS

PC / IM/GE

PRO

DUR

SPX

PAIN CLINICS

DUR

DERMs / PODs

SPX

NZC

- Hospital Representatives will continue to focus on our most important and influential teaching institutions. Selling efforts should be towards the clinics and departments associated with these specialties.
- Continued emphasis for 1998 has been placed on these strategic brands: DURAGESIC, PROPULSID, RISPERDAL and SPORANOX.

1999 1st Cycle Priorities Janssen ElderCare Representatives

- **ElderCare Representatives will focus on targeted physicians and nursing home facilities that treat elderly patients.**
- **The primary effort is to represent and sell Janssen products to physicians, Medical Directors, Director's of Nursing, Psychiatric Consultants, and Geriatric Psychiatrists.**
- **SELLING PRIORITIES:**
 - 1. RISPERDAL**
 - 2. DURAGESIC**
 - 3. PROPULSID**

1999 1st Cycle Call Plan

Janssen ElderCare Representatives

TARGETS / PRESENTATIONS

GERIATRIC PSYCHS

RIS

MEDICAL DIRECTORS

RIS
DUR
PRO

DIRECTOR'S OF NURSING

RIS
DUR
PRO

PC/IM* PHYSICIANS

APS 4-9

RIS
DUR
PRO

- The Nursing Home Pharmacy should be called on.
- Efforts should be coordinated between the LTC Manager and Pharmacy Provider.

DURAGESIC®

DURAGESIC® (fentanyl transdermal system) CII
1st Cycle 1999

Congratulations to the RAINMAKERS that drove DURAGESIC sales to the best year ever! We expect 1999 to be another banner year for DURAGESIC as we drive toward our sales goal of \$300 million! The materials and programs for this cycle are designed to make your efforts as successful as possible and to make 1999 the best year ever for DURAGESIC.

MARKET UPDATE

The market for long-acting opioids experienced tremendous TRx growth at 25% in 1998 with DURAGESIC and OxyContin leading the way. Sales representatives fueled this growth by teaching physicians about the advantages of long-acting opioids like DURAGESIC. Specifically, by convincing physicians to switch their patients from short-acting opioids that are dosed around the clock (ATC) to DURAGESIC, you drove this market expansion. New for 1999, the market definition has been expanded to include Percocet, along with OxyContin, MSContin, DURAGESIC, Kadian, and Oramorph. Demerol, Dilaudid, and IR Morphine will be removed from the market definition. This means that there will be more chronic pain decile 8 & 9 physicians per territory. You should have already received the decile data for these physicians in January. These new physicians offer an opportunity that is consistent with our key communication point:

"For any chronic pain state that requires around-the-clock opioid treatment, DURAGESIC should be the first choice."

- *Only DURAGESIC provides 72 hours of continuous pain relief*
- *DURAGESIC has less side effects*
- *DURAGESIC is patient preferred*

Our challenge is to position DURAGESIC as the preferred alternative for around-the-clock opioid therapy with all of our customer segments (primary care physicians, oncologists, pain specialists, and long-term care providers). We will accomplish this goal by deploying the following strategies:

I. INITIATE DURAGESIC AS SOON AS AROUND-THE-CLOCK OPIOID THERAPY IS REQUIRED TO TREAT CHRONIC PAIN

DURAGESIC is the best alternative when patients need "around-the-clock" opioids for the management of chronic pain. These patients are usually on short-acting opioids such as Percocet, Percodan, or Vicodin. DURAGESIC 25 mcg/hr patches are a much better option and will give these patients effective pain relief with less side effects and better quality of life than other opioids.

II. EXPAND USE OF DURAGESIC® AMONG PHYSICIANS WHO ONLY USE DURAGESIC TO TREAT CANCER PAIN

Our task is to convince physicians that DURAGESIC can provide their patients that suffer from chronic non-malignant pain the same benefits that their cancer pain patients have experienced. It is important to remind these physicians that the American Geriatric Society, the American Pain Society, and the Academy of Pain Medicine have all endorsed the appropriate use of opioids to treat chronic non-malignant pain.

III. DIFFERENTIATE DURAGESIC FROM SHORT-ACTING OPIOIDS THAT ARE USED AROUND THE CLOCK

"Only DURAGESIC offers an effective transdermal opioid analgesic patch for chronic pain that provides 72 hours of reliable delivery, improves patients' overall quality of life, has a better safety (constipation) profile than other opioids, and is patient preferred." By communicating this message on every call, you will differentiate DURAGESIC from the competition.

The Brand Team has provided many new materials that are designated for different customer segments. Updated and new leave-behinds are available; please refer to your JTMS system and the Resource Binders.

IV. NEW MATERIALS AVAILABLE FOR CYCLE I

A. Case Study for Osteoarthritis

Helping physicians picture appropriate patients for DURAGESIC will be made easier by using the case study for Osteoarthritis. This case study demonstrates clear advantages of DURAGESIC over short-acting opioids, such as Lorcet, that are commonly used to treat chronic non-malignant pain. This case demonstrates the benefits of the "patient-preferred" alternative for around-the-clock opioid therapy.

B. Case Study for Chronic Back Pain

Helping physicians picture appropriate patients for DURAGESIC will be made easier by using the case study for chronic back pain. It positions DURAGESIC as the optimal choice for patients when short-acting opioids, such as Percocet, prove ineffective or inconvenient. This case study outcome emphasizes the efficacious, patient-preferred therapy DURAGESIC can provide to patients with chronic back pain.

C. Dosing Conversion Chart

This convenient reference tool is designed to make it easy for physicians to convert any short-acting or long-acting opioids that are dosed around the clock to a DURAGESIC 25mcg/hr patch.

- D. **Teletopics: "Primary Care Approaches to the Management of Chronic Pain"**
A new Teletopics program featuring Dr. Matthew Lefkowitz will be available in the 1st cycle. The program will focus on the appropriate use of opioids for the treatment of non-malignant pain. Dr. Lefkowitz will review the cases of three patients whose primary care physician is managing their non-malignant pain safely and effectively with opioids.
- E. **Teletopics: "The Treatment of Non-malignant Pain in the Long-Term Care Setting"**
This new Teletopics program will feature Dr. Bruce Chamberlain discussing the use of opioids in the treatment of chronic moderate-to-severe non-malignant pain. The schedule for this case-based program is designed to make it most convenient and impactful in long-term care facilities. The program will debut in February.
- F. **CME Audio Forum III**
This is the third in a series of three audio forums. Feedback from the field has been very positive on these CME programs because physicians, nurses, and pharmacists can call in 24 hours a day (7 days a week) and receive CE credits. Please review the Audio Forum before distributing it to your customers so you can sell the content of the Audio Forum and tie it into a DURAGESIC[®] sales call.
- G. **"The Management of Chronic Pain in Older persons" Guidelines**
These guidelines which were recently published by the American Geriatrics Society documented that after a thorough assessment of pain, opioid drugs should be utilized in the treatment of older people if appropriate. These guidelines should be used to update your medical professional with the AGS position on the use of opioids in the elderly in an effort to improve their comfort level with these drugs.

V. **STILL CURRENT SALES MATERIALS FOR CYCLE I**

- A. **Primary Care Sales Aid**
The field sales force reports that this sales aid has been effective in educating physicians on how to prescribe DURAGESIC for the appropriate chronic pain patients. This is a comprehensive aid that should still be used as the primary sales aid.
- B. **Lunch and Learn Video Series: "Chronic Pain Management: Perspectives for the Primary Care Physicians"**
A three-video series of the extremely successful "Pain Free 2000 - Management of Chronic Non-malignant Pain" satellite symposia will be available. Each video is 15-20 minutes long and will feature various topics from the satellite symposia. Show a video, or two, over a lunch with physicians, then sell the features and

benefits of DURAGESIC®. Please preview the videos prior to showing them to your physicians so you will know the content and can bridge to the sales call.

- C. **Answers to your Questions about DURAGESIC Booklet—DR-350**
A patient booklet has been developed to help answer questions that patients commonly ask about DURAGESIC therapy. This leave-behind tool is a great resource that is indexed by topic for easy reference.
- D. **“Getting the Most Out of DURAGESIC” Video – DR-344**
A great tool for an in-service with physicians and nurses. Provide them with copies of this video to give to their patients because the proper application of the first patch is a key to patient satisfaction.
- E. **Simpson Chronic Back Pain Reprint Carrier – DR-345**
This is another positive study for DURAGESIC in chronic back pain. This study supports patient preference for DURAGESIC in non-malignant pain. This study was published in the *Journal of Pain and Symptom Management* in October 1997.
- F. **DURAGESIC Dosage Calculator – DR-348**
The Dosage Calculator has been revised specifically for the Primary Care Physicians. This version includes brand names of the short-acting opioids and a Visual Analog Scale that physicians can use for pain assessments.
- G. **Answers to your Questions about DURAGESIC Q&A Booklet – DR-274**
The updated booklet is geared to all physicians and provides answers to frequently asked questions. The booklet is a leave-behind and is organized by topic for easy reference.
- H. **“Chronic Pain in Geriatrics: Management” CME Video – ELD-008**
This CME video will be very useful to provide appropriate pain management goals for medical professionals treating elderly patients in the home, acute care, and long-term care settings. This video should be utilized for in-service, or it may be distributed to key nursing home accounts.
- I. **“Chronic Pain in Geriatrics: Assessment CME Video – ELD-007**
This CME video will be very useful for healthcare providers in the long-term care and acute or home settings to effectively assess the pain of their patient. It will also discuss how elderly patients with cognitive impairment can be reliably assessed for pain.

Good luck in your selling efforts for 1999. Please feel free to contact the DURAGESIC Brand Team with any questions or feedback, or better yet, provide your comments to:

DURAGESIC HOTLINE on the Aspen System spell “OUCH” (6824)

PROPULSID®

**PROPULSID® (cisapride)
1st Cycle 1999**

Market Opportunity

The GI market continues to show a healthy total prescription growth rate of 10.9% through September. Currently the prescription GI market is valued over \$6.0 billion dollars and PROPULSID is on track to reach the \$500 million dollar milestone for the first time in the U.S. Also, PROPULSID sales are on pace to exceed 1997 sales by 15%. PROPULSID NRx and TRx market shares have remained consistent through September at (8.8%) and (8.8%) respectively. Additionally, new prescription volume has averaged close to 300,000 Rx's per month YTD. The H2 prescriptions have decreased by 7.3% YTD compared to 1997.

Recently, the PROPULSID Patient Medication Guide and Unit-of-Use packaging were introduced to the marketplace. The sales force has done an outstanding job in pre-selling the benefit of the medication guide to all healthcare providers. Both physicians and pharmacists felt Janssen was being very proactive by introducing patient education material that would help to ensure proper patient selection for PROPULSID. Early feedback from pharmacists concerning the new packaging sizes has also been favorable. Pharmacists like the idea of unit-of-use dispensing since they know that every patient will now receive valuable patient education material with every new and refilled prescription. Please continue to inform physicians about both new programs as you continue to SELL PROPULSID. The brand objectives this cycle are as follows:

1. **Make The Link** from motility disorders to GERD to patient symptoms.
2. **Reinforce** that PROPULSID is the only medication that can effectively relieve heartburn and the motility-related symptoms.
3. **Continue** to ensure proper patient selection for PROPULSID.

PROPULSID POSITIONING

We must continue to position PROPULSID as a unique motility agent that effectively relieves heartburn and all the motility-related symptoms. In addition, we need to raise physician awareness of the number of patients with heartburn who continue to suffer from additional motility-related symptoms. To maximize our opportunities we must:

- Sell PROPULSID as the only therapy that effectively relieves a patient's heartburn as well as their motility-related symptoms.
- Utilize the Patient Letter along with the PACT Study to clearly demonstrate the superior efficacy of PROPULSID in patients with heartburn. Also, emphasize that these patients were on previous acid-suppression therapies that failed, which was due to the fact they were also experiencing some motility-related symptoms.
- Deliver a clear safety message when appropriate to ensure healthcare providers are comfortable in identifying the proper patients that will benefit from PROPULSID.

CYCLE MATERIAL

500/425 SF 1st Cycle Visual Aid: This cycle we need to convince physicians to make the link: Motility Disorders → GERD → Patient Symptoms → PROPULSID. Most physicians are aware that motility is the underlying problem in GERD, but they need to be reminded of the number of patients suffering from motility-related symptoms. Once you have linked symptoms to a motility problem, it should be easy to convince physicians that it makes sense to prescribe the best promotility agent -PROPULSID- rather than trying more acid-suppressant therapy. The actual Patient Letter is a way to get physicians thinking about where they can use PROPULSID safely and effectively. The cover is designed to facilitate physician probes so that you can learn which symptoms each physician links to motility. The quotes used on the front cover are from two highly respected physicians. Continue to use the PACT Data to emphasize that acid is not a problem in these patients. Use the bar graphs to illustrate that in all patients, even patients with severe symptoms of heartburn, PROPULSID provided significant symptom relief. Also, point out that most patients and physicians rated symptom relief with PROPULSID as excellent or good. Finally, continue to utilize the two pages in the brochure that stress proper patient selection. The bulleted format allows you to easily discuss the appropriate patients for PROPULSID. It is important to point out that PROPULSID is now offered only in new unit-of-use sizes for patient convenience: 10mg tablets in bottles of 120 and 20mg tablets in bottles of 60.

ElderCare SF 1st Cycle Visual Aid: This sales aid was developed with the intent of helping the ElderCare Representatives effectively position PROPULSID in the elderly population. The cover clearly outlines the percentage of patients over the age of 60 who experience the symptoms of GERD daily. It also highlights the fact that improving gastric motility is the primary goal of therapy. The case study depicted is a typical nursing home resident suffering from symptoms of GERD. This is a patient with other disease states as well as taking other medications. Also, the PACT data has been further analyzed to show the number of elderly patients that responded to PROPULSID therapy. This specific data should help the representatives drive home the message that PROPULSID is effective in treating a variety of motility disorders. Finally, continue to utilize the two pages in the brochure that stress proper patient selection. The bulleted format allows you to easily discuss the appropriate patients for PROPULSID.

CME Experts on Tape/CD-ROM: This is the second series of CME videos and CD-ROMs this cycle. The second video/CD-ROM is titled, "Dyspepsia: Diagnosis and Management." This 15-minute video will be moderated by Dr. Michael Camilleri, Division of Gastroenterology and Hepatology, Mayo Medical Center. The video will offer 1 Hour of Category 1 CME from the University of Nebraska. Physicians, Nurses, and Physician Assistants will all be eligible to earn credits. Each rep will be shipped a video and CD-ROM along with a supply of booklets that should be left with the participating physicians to complete in order to receive the CME. Janssen will pay for the credits upon completion by the physician. Dr. Camilleri will give a perspective on the disease of dyspepsia. The discussion will include examining all the related symptoms before initiating the appropriate therapy. Dr. Camilleri will also give a brief overview of the use of promotility agents in treating dyspepsia. This program will be offered on videotape as well as in CD-ROM. The same guidelines for a CME program apply whether you utilize the video or CD-ROM.

Rep Reference Binder: This reference binder is a tool that will help you consolidate all the information related to the GERD market. This reference is designed for you to be able to review the material throughout the day, even between sales calls. The reference binder will cover the market, suggested treatment protocols, a competitor comparison (in chart format), and PROPULSID support materials. You will receive the first section of the binder this cycle. Two subsequent sections will be sent throughout the first cycle to allow you time to read and become comfortable with the information. The Brand Team is confident you will find this Rep Reference Binder a great tool to help you prepare for your PROPULSID sales calls.

CME Teletopics: There will be two new exciting programs for this cycle. The first one is titled: "GERD Therapy, Step Up or Step Down?" This program will be moderated by Dr. Malcolm Robinson. The second program is titled: "Maintenance of GERD and Dysmotility, Long-Term Therapeutic Options." This program will be moderated by Dr. Donald Castell, current president of the AGA. Both programs will describe the relationship of dysmotility to GERD, and the importance of identifying and treating motility symptoms in both short and long-term therapy. Additionally, the current roundtable program titled: "Current Concepts in Prokinetic Therapy," will again be available this upcoming cycle. Please consult your booklet for dates and times.

ElderCare CME Teletopics: The program titled: "Motility And The Aging" moderated by Dr. Jean Saleh and Dr. Michael Fraser will continue through the upcoming cycle. This program has received very positive feedback, as it discusses the unique types of motility problems associated with the elderly in a nursing home or extended care environment. Please consult your booklet for new times and dates beginning in February.

Patient Medication Guides: The file card size medication guides will continue to be available for reorder. These guides should be left in the sample bins so physicians can distribute to patients along with PROPULSID samples. Also, continue to distribute them to pharmacists on your pharmacy calls as they request them.

Patient Medication Guide/Unit-of-Use Flashcard: This flashcard will still be made available if you need to explain both the medication guide and the unit-of-use packaging. The new core visual aid has the information regarding the unit-of-use packaging on the back cover so you can continue to remind physicians about the two new bottle sizes. This flashcard can be utilized on your pharmacy calls, as both the Unit-of-Use bottles and Patient Medication Guide are important for the pharmacists to understand.

Wallet Cards: New Wallet Cards will be available this cycle. These cards should be placed in your sample booklet in order to help you reinforce the PROPULSID message. The cards should help to stimulate questions from your physicians as you hand them the booklet and they sign for samples.

Revised File Card: This cycle you will also be receiving an updated file card. This version will have the Patient Medication Guide and Unit-of-Use packaging information included. By incorporating this information, you can leave it with healthcare providers and they will be able to use the file card as a reference in the future regarding the use of PROPULSID.

Revised Gastro Wellness Material: Both the Gastro Wellness Take-Ones and Tear-Off Pads are again available for re-order. You should continue to distribute these in your physician offices, pharmacies, and hospitals. A revised welcome packet as well as a new Motility Newsletter will be mailed to all enrollees during the months of January and February. These will be the first newly revised materials produced since the most recent labeling change. The goal of the fulfillment materials is to either help convert consumers to PROPULSID therapy or improve the compliance of current PROPULSID users. Finally, we will also be mailing out the PROPULSID 1999 calendars to all consumers in the database. These calendars are great daily reminders about motility, lifestyle modifications, and PROPULSID. More details will follow as new fulfillment materials are introduced.

Unit-Of-Use Stickers: Stickers announcing the Unit-of-Use sizes are now available. The stickers should be placed on the sample boxes when appropriate. They are available for re-order.

INTRODUCTION

The momentum continues with the new PROPULSID® (cisapride) visual aid

This cycle, Janssen is pleased to introduce the "make the link" approach to promoting PROPULSID. Linking the symptoms of GERD to a motility problem is critical to you, to Janssen, to the physician, and most importantly, to the patient. If physicians fail to make the link between a motility disorder, GERD, and patients' symptoms, they will not prescribe PROPULSID, and their patients will continue to suffer.

Strong quotes support the motility message

Quotes from two respected physicians will help you "make the link" between a motility disorder, GERD, and patient symptoms. The quotes are from an article by Kenneth R. DeVault, MD and Donald O. Castell, MD, which was published in the *Archives of Internal Medicine*. Castell, president of the American Gastroenterological Association, is a Kimbel professor and chairman of the Department of Medicine at The Graduate Hospital in Philadelphia, PA. He is internationally recognized as a leading authority on diseases of the esophagus and esophageal function, and has authored or coauthored more than 400 scientific publications.

DeVault and Castell state that the pathogenesis of GERD relates to defects in motility, and that symptom control is important.

A testimonial from a real patient adds credibility to the motility message

This visual aid includes an actual patient testimonial about PROPULSID. The letter was sent to Janssen's "Gastro Wellness" program and describes how PROPULSID helped relieve the patient's symptoms—after "acid blockers," antacids, and a proton pump inhibitor had failed. This is a great example of the PROPULSID positioning: relieving motility-related symptoms that acid-suppressant therapy can't. Use the letter to begin the PROPULSID efficacy story, which is further supported by the PACT data. These data prove that PROPULSID is highly effective in patients with varying degrees of adult nocturnal heartburn due to GERD.

The brand team sends its thanks and appreciation to the GI Advisory Panel members who field tested this visual aid, and the sales training classes that provided feedback. Their suggestions helped make this a great sales tool for you to kick off the new year.

COMMUNICATION POINT/RATIONALE:

The quotes state that the underlying cause of GERD is a motility disorder and that controlling symptoms is critical. Use the quotes to support the link between a motility disorder, GERD, and patients' symptoms.

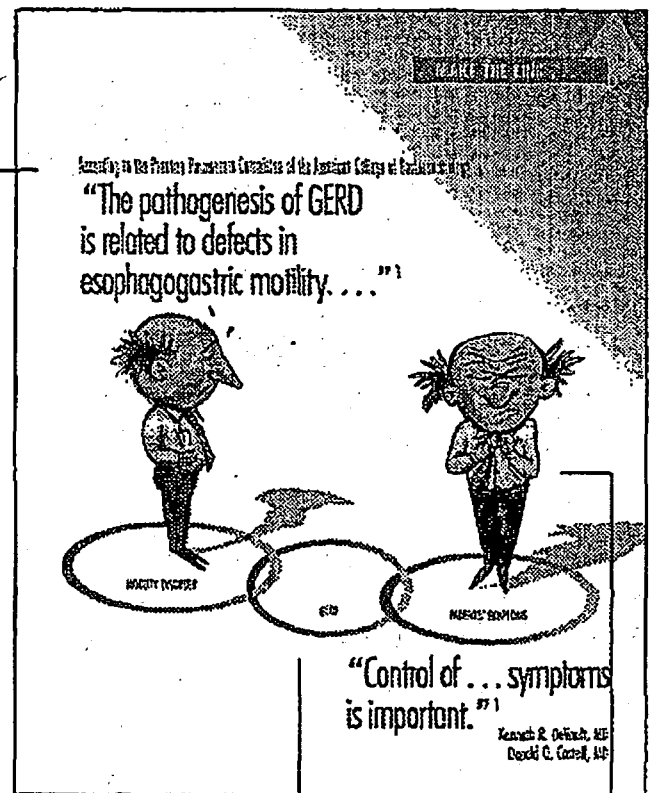
Please note: In the quote, "Control of . . . symptoms is important," the missing word is "these"; we could not include this word because the quotes came from different parts of the published paper and, as a result, the word "these" would be taken out of context. During field testing of this visual aid, members of the GI Advisory Panel reported that the ellipses in the quote gave them an opportunity to ask the physicians what symptoms they saw most often.

In their article, DeVault and Castell reported on the recommendations made by the Practice Parameters Committee of the American College of Gastroenterology on guidelines for the diagnosis and treatment of GERD. The committee arrived at their recommendations by reviewing worldwide literature and abstracts from national and international gastroenterology meetings. They also solicited consensus from experts in the field.

The committee's recommendations were developed under the auspices of the American College of Gastroenterology and approved by other gastroenterology societies. The recommendations were published in the *Archives of Internal Medicine*, a respected peer-reviewed journal.

Use these links to ask the physician what symptoms patients complain about when they present with GERD. Based on their reply, you may want to say the following:

"[Mentioned symptom] is a common patient complaint. I would now like to share with you a letter from a real patient and how his problem was relieved."



As you can see, Sid is back and ably demonstrates the motility-related symptoms most often experienced by GERD patients.

COMMUNICATION POINT/RATIONALE:

This actual patient letter adds credibility to how effective PROPULSID® (cisapride) is in relieving the symptoms of adult nocturnal heartburn due to GERD. It is very rare for a patient to write about how well any product works for them. Reinforce this rarity and that it demonstrates the satisfaction PROPULSID provides.

Ask physicians what types of symptoms their patients usually present with, and then direct their attention to this patient whose primary complaint was upper GI pains. Be sure to point out that PROPULSID was the only therapy that provided effective relief.

Point out that this person has a motility problem, and that acid-suppressant therapy could not relieve his symptoms. Importantly, we do not know if the proton pump inhibitor was stopped or if PROPULSID therapy was added.

Note: We also do not know what strength or dose was prescribed for this patient. If a physician asks about this, explain that we do not have this information and then ask the physician what strength or dosage he or she would have prescribed.

Remind physicians of Janssen's "Gastro Wellness" program to help their patients implement lifestyle changes. Look at the impact the program had on this patient.

ACTUAL PATIENT LETTER



Call 1-800-421-7111 for Janssen's "Gastro Wellness" program to help patients implement lifestyle changes.

The information presented above is representative of a patient with nocturnal heartburn. Patient responses to therapy may vary. This is not a qualified letter from the actual patient. The accompanying photograph, however, is not the actual patient.
© Janssen Pharmaceutica, Inc. 1993

Be sure that physicians understand that this letter was unsolicited, and that it was sent to the Janssen "Gastro Wellness" program.

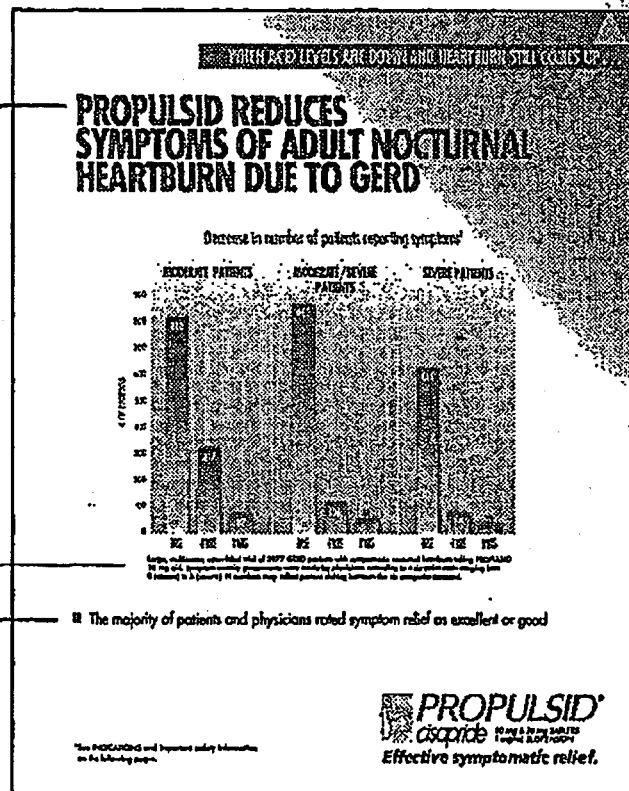
COMMUNICATION POINT/RATIONALE:

The PACT data further demonstrate the effectiveness of PROPULSID® (cisapride) in reducing the symptoms of adult nocturnal heartburn due to GERD.

Use the PACT data to demonstrate how, in adult patients, PROPULSID reduced nocturnal heartburn due to GERD. Note the dramatic decrease in symptoms from baseline to 4 weeks—especially in moderate/severe patients.

Mention that the PACT study was practice-based and included a large patient base.

Point out that both patients and physicians rated symptom relief with PROPULSID as excellent or good.



COMMUNICATION POINT/RATIONALE:

To ensure that physicians prescribe PROPULSID® (cisapride) for the appropriate patients, review the safety information on these pages.

Remind physicians that PROPULSID has the potential for cardiac complications in certain patients, particularly those who are taking drugs that inhibit P450 3A4 enzymes (see listing), patients who are predisposed to arrhythmias, and patients who are taking drugs that prolong the QT interval.

Based on a patient's cardiac condition and history, physicians may want to consider an ECG prior to starting PROPULSID therapy.

IMPORTANT SAFETY INFORMATION

PROPULSID has the potential for cardiac complications that can include serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation. Some of these events have been fatal. These complications are of particular concern and PROPULSID is contraindicated in the following patient groups:

Patients taking drugs that inhibit P450 3A4 enzymes

- ketoconazole ■ fluconazole ■ clarithromycin ■ indinavir ■ nefazodone
- itraconazole ■ erythromycin ■ telithromycin ■ zalcitabine

Patients with disorders that predispose them to arrhythmias

- history of prolonged electrocardiographic QT intervals
- history of ischemic heart disease and congestive heart failure
- renal failure
- uncorrected electrolyte disorders (hypokalemia, hypomagnesemia)
- history of ventricular arrhythmias
- respiratory failure

Please note: Based on the patient's cardiac condition and history, an ECG should be considered prior to initiating PROPULSID therapy.

Patients taking drugs known to prolong the QT interval

- certain antiarrhythmics, including those of Class IA (such as quinidine and procainamide) and Class II (such as sotalol)
- certain antipsychotic medications (such as certain phenothiazines and serindole)
- tricyclic antidepressants (such as amitriptyline)
- certain tetracycline antidepressants (such as maprotiline)
- astemizole
- bepridil
- sparfloxacin
- terfenadine

(The preceding list of drugs are not comprehensive.)

Before prescribing PROPULSID, please see prescribing information for CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and DRUG INTERACTIONS.

PROPULSID® (cisapride) is well tolerated. The most common side effects are headache and diarrhea.

PROPULSID is indicated for adult nocturnal heartburn due to GERD and can be used with patients who are not taking the drugs listed and have not responded to lifestyle modifications and antacid therapy.

Point out the simple dosing schedule and the special dosing recommendations for patients with hepatic insufficiency

In US clinical trials, the following adverse events were most commonly reported:

	PROPULSID	Placebo
Headache	19.3%	17.1%
Diarrhea	16.2%	10.2%

INDICATIONS

PROPULSID is indicated for the symptomatic treatment of adult patients with nocturnal heartburn due to gastroesophageal reflux disease. Because of the risk of serious, sometimes fatal, ventricular arrhythmias (see Box Warning), PROPULSID should generally be reserved for patients who do not respond adequately to lifestyle modifications (see Medication Guide), antacids, and gastric acid reducing agents.

SIMPLE DOSING SCHEDULE

- Initiate therapy with 10 mg to 150 mg of PROPULSID 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.
- Recommended doses of PROPULSID should not be exceeded.
- It is recommended that the daily dose be halved in patients with hepatic insufficiency.

References:
1. Schindler H, Lind H. Guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Arch Intern Med. 1990;150:1457-1570.
2a. Johnson L, Martin A, Lindor K, et al. (eds). American Gastroenterology Association. AGA Study Group. Management of acid dyspepsia in patients with symptoms of gastroesophageal reflux. (Printed) Digestive Diseases Week, May 1992.



PROPULSID®
cisapride 15 mg tablets
Effective symptomatic relief.

	PROFUSED	Accepted
Headache	19.3%	17.1%
Diarrhea	14.2%	10.3%

INDICATIONS

PROPULSID is indicated for the symptomatic treatment of adult patients with nocturnal heartburn due to gastroesophageal reflux disease. Because of the risk of serious, sometimes fatal, ventricular arrhythmias (see Box Warning), PROPULSID should generally be reserved for patients who do not respond adequately to lifestyle modifications (see Medication Guide), antacids, and gastric acid reducing agents.

SIMPLE DOSING SCHEDULE

- Initiate therapy with 10 mg tablets of PROPULSID 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.
- Recommended doses of PROPULSID should not be exceeded.
- It is recommended that the daily dose be halved in patients with hepatic insufficiency.

1. Datta R, Kundu D. Evidence for the diagnosis and treatment of postmenopausal osteoporosis. *Arch Intern Med*. 1995;155:2145-2152.

PROPULSID
cisapride 15 mg & 30 mg tablets
Effective symptomatic relief.

COMMUNICATION POINT/RATIONALE:

The back cover reinforces the PROPULSID® (cisapride) message: relief for patients with adult nocturnal heartburn due to GERD. Sid demonstrates the elation patients feel after taking PROPULSID, and the fact that he has broken free from the links further demonstrates the efficacy of PROPULSID.

More than 11 years of worldwide clinical experience and over 30 million prescriptions written in the United States should make physicians confident about the safety of PROPULSID.

It is important to remind physicians that PROPULSID is now offered only in new unit-of-use sizes for patient convenience: 10 mg tablets in bottles of 120 and 20 mg tablets in bottles of 60. Suspension is still available in the 16 oz bottle.

The PROPULSID Patient Medication Guide, which provides important product safety information, is attached to each unit-of-use bottle to ensure that patients receive this important information.

**PROPULSID
MEANS RELIEF**

EXTENSIVE WORLDWIDE EXPERIENCE

- More than 11 years of clinical experience worldwide
- 30 million prescriptions dispensed in the United States

SIMPLE DOSING SCHEDULE

- One 10 mg tablet or 10 mL of the suspension, 4 times daily at least 15 minutes before meals and at bedtime

NEW UNIT-OF-USE PACKAGING

- PROPULSID is available only in unit-of-use sizes
 - 10 mg tablets in bottles of 120
 - 20 mg tablets in bottles of 60
 - Suspension remains available in the 16 oz bottle
- Patient Medication Guide is attached to each bottle

FOR SALE REPRESENTATIVE USE ONLY. NOT TO BE SET WITH PHYSICIAN. FOR HIGH PHYSICIAN WITH FULL PRESCRIPTION INFORMATION, INCLUDING BOX WARNING, FOR MORE INFORMATION, CALL JANSSEN'S ORAL TO ORAL CUSTOMER ACTION CENTER AT 1-800-JANSSEN (1-800-773-6146) OR TO YOUR SALES REPRESENTATIVE, MEDWAT THROUGH FIELD.

Please see product pages for important safety information.

PROPULSID®
cisapride 10 mg & 20 mg tablets
Effective symptomatic relief.

Manufactured by Janssen Pharmaceutica, Inc., Division of Janssen Pharmaceutica, Inc., 1110 North Zeeb Road, Titusville, FL 32781

Patented in U.S.A.

Product of Janssen Pharmaceutica, Inc.

The sample prescriptions suggest how to write PROPULSID. The "as directed" dosing allows you to answer physician questions about dosing.

INTRODUCTION

This cycle's ElderCare visual aid is targeted at treating GERD in the elderly. Its design will allow you to uncover specific physician issues and generate discussions about motility-related symptoms.

Elderly patients with GERD present a different set of problems for physicians. They are often on multiple medications and they often do not tell their doctors about GERD symptoms. Many believe these symptoms are part of the aging process. Therefore, it is important to remind physicians that while a majority of patients aged 65 years or older experience symptoms of GERD every day, they rarely report them.

Once you have established the frequency of GERD symptoms in the elderly population, linking them to motility is important to Janssen, to the physician, and to the patient.

For Janssen, PROPULSID® (cisapride) is most effective in relieving motility-related symptoms, and this activity is what differentiates PROPULSID from acid-suppressant therapy.

For the physician, resolving motility-related symptoms may result in a healthier patient.

For the patient, improved motility means more complete symptom relief and better quality of life.

Link motility disorders to GERD to symptoms

Most physicians are aware that motility is the underlying problem in GERD, but they need to be reminded of motility-related symptoms. Once you have linked the symptoms experienced by the elderly to a motility problem it should be easy to convince physicians that it makes sense to prescribe the best pro-motility agent (PROPULSID) rather than increase the use of acid suppressants.

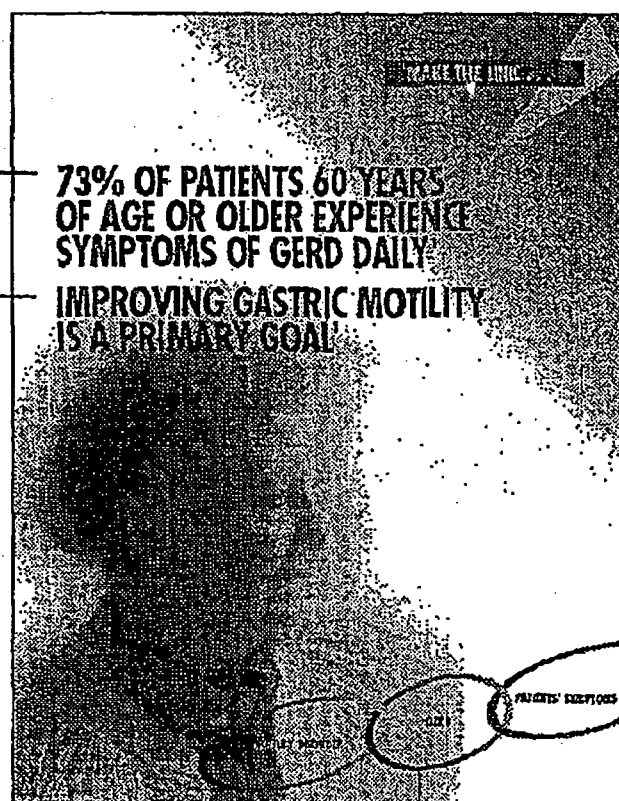
A typical case is used in this visual aid to illustrate the tendency of the elderly to underreport their symptoms. It is a way to get physicians thinking about the importance of motility-related symptoms in these patients.

COMMUNICATION POINT/RATIONALE:

The cover is designed to alert physicians to the incidence of symptoms of GERD in the elderly, and to make the link between these symptoms and a motility problem. In this regard, the visual aid highlights the fact that improving gastric motility is a primary goal of treatment.

73% of elderly patients suffer from motility-related symptoms of GERD every day.

Improving gastric motility is critical in relieving these patients of their symptoms.



Use the link graphic to ask your physicians what motility-related symptoms they see most often in their elderly patients. You need to get your physician to comment on these symptoms before progressing through the visual aid.

COMMUNICATION POINT/RATIONALE:

Motility-related symptoms increase with age, however, the elderly often attribute these symptoms to normal aging or coexisting illnesses. For this reason it is important for physicians to ask about such symptoms. The case of an actual nursing home patient is typical of an elderly patient's response to motility-related symptoms. Present it to the physician as an example of how PROPULSID® (cisapride) provides effective relief of motility-related symptoms after acid-suppressant therapy has failed to provide complete relief.

It is a well-known fact that motility-related symptoms increase with age. However, elderly patients often learn to tolerate their symptoms and usually don't complain about them.

Take this actual case. A 78-year-old Parkinson's patient had severe symptoms of nocturnal heartburn, but she rationalized that she ate too much.

She was given antacids that provided her with some relief but caused significant constipation. After receiving cimetidine 300 mg tid and at bedtime, her heartburn improved slightly. However, the drug was discontinued because she had difficulty sleeping.

Her symptoms were caused by delayed gastric emptying, which worsened when she reclined at night.

SYMPTOMS INCREASE WITH AGE

"THERE IS A TENDENCY FOR OLDER PEOPLE TO UNDERREPORT AND TOLERATE SYMPTOMS . . ."

The American Journal of Gastroenterology

- Their pain perception may be altered and symptoms are often attributed to coexisting illnesses.
- It is important to ask elderly patients about GI symptoms.

A typical case:

A 78-year-old female nursing home resident with Parkinson's disease presented with severe symptoms of nocturnal heartburn. The patient attributed symptoms to her hearty appetite, but did not complain to the nursing staff. Lifestyle modifications were not successful.

Medication History:

Antacid therapy proved somewhat effective, but resulted in significant constipation. Antacids were discontinued and the patient was placed on cimetidine 300 mg tid and at bedtime with slight improvement. Cimetidine was discontinued because the patient had difficulty sleeping.

Diagnosis:

Symptoms reflected delayed gastric emptying, aggravated at night when the patient reclined.

Rx:

Patient given PROPULSID® (cisapride) suspension (10 mL, 15 minutes before meals and at bedtime).

Follow-up:

Nocturnal heartburn symptoms improved within 2 days.

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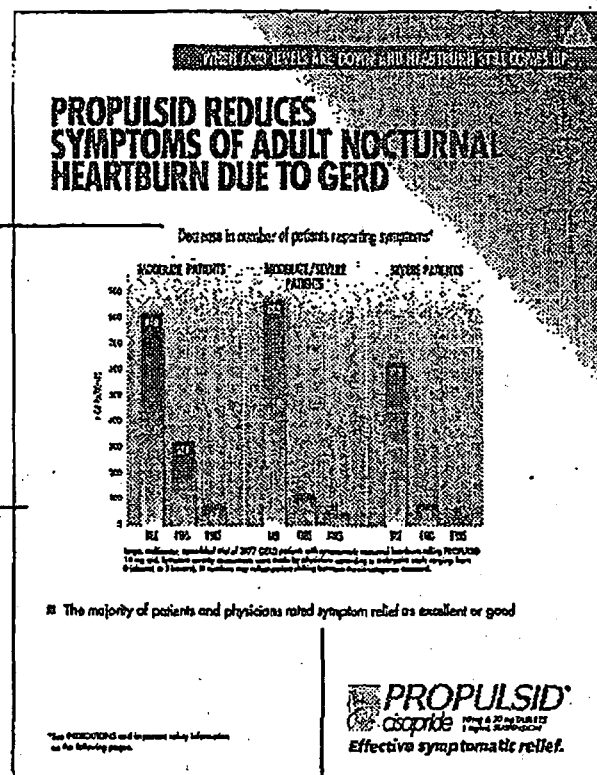
After the patient received PROPULSID suspension (10 mL, 15 minutes before meals and at bedtime), adult nocturnal heartburn symptoms improved within 2 days.

COMMUNICATION POINT/RATIONALE:

Now that you've established the prevalence of motility-related symptoms in the elderly, present the PACT study as evidence that PROPULSID® (cisapride) reduces the motility-related symptoms of adult nocturnal heartburn due to GERD in elderly patients.

Point out the total decrease in the number of patients reporting symptoms and the reduction in symptom severity.

Of the 2977 patients in this office-based study 1088 were aged 65 years or older.



Tell your physicians that the majority of patients and physicians who participated in this study rated the symptom relief as excellent or good.

COMMUNICATION POINT/RATIONALE:

To ensure that physicians prescribe PROPULSID® (cisapride) for the proper elderly patients, review the safety information on these pages. With appropriate use, physicians can be assured of the safety and effectiveness of PROPULSID in patients such as the one you have just presented.

Remind physicians that PROPULSID has the potential for cardiac complications in certain patients, particularly those who are taking drugs that inhibit P450 3A4 enzymes (see listing), patients who are predisposed to arrhythmias, and patients who are taking drugs that prolong the QT interval. This is particularly important in elderly patients who may be on multiple drugs.

IMPORTANT SAFETY INFORMATION

PROPULSID has the potential for cardiac complications that can include serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation. Some of these events have been fatal. These complications are of particular concern and PROPULSID is contraindicated in the following patient groups:

Patients taking drugs that inhibit P450 3A4 enzymes

■ ketoconazole ■ fluconazole ■ clarithromycin ■ itraconazole ■ erythromycin ■ telavandamycin ■ ritonavir

Patients with disorders that predispose them to arrhythmias

■ history of prolonged electrocardiographic QT intervals ■ history of ischemic heart disease and congestive heart failure
■ renal failure ■ uncorrected electrolyte disorders [hypokalemia, hypomagnesemia]
■ history of ventricular arrhythmias ■ respiratory failure

Please note: Based on the patient's cardiac condition and history, an ECG should be considered prior to initiating PROPULSID therapy.

Patients taking drugs known to prolong the QT interval

■ certain antiarrhythmics, including those of Class IA (such as quinidine and procainamide) and Class II (such as sotalol) ■ certain antipsychotic medications (such as certain phenothiazines and terfenadine)
■ tricyclic antidepressants (such as amitriptyline) ■ cimetidine
■ certain tetracycline antidepressants (such as maprotiline) ■ terfenadine

(The preceding lists of drugs are not comprehensive.)

Before prescribing PROPULSID, please see prescribing information for CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and DRUG INTERACTIONS.

PROPULSID® (cisapride) is well tolerated. Again, this is important in elderly patients. Frequency of the most common side effects, headache and diarrhea, were not much different from placebo. (Approximately 2% more for headache and 4% more for diarrhea.)

PROPULSID can be used effectively for elderly patients with adult nocturnal heartburn due to GERD, who are not taking the drugs listed and have not responded to lifestyle modifications and antacid therapy.

Point out the simple dosing schedule and special dosing recommendations for patients with hepatic insufficiency.

In US clinical trials, the following adverse events were most commonly reported:

	PROPULSID	Placebo
Headache	12.5%	17.1%
Diarrhea	14.2%	10.7%

INDICATIONS

PROPULSID is indicated for the symptomatic treatment of adult patients with nocturnal heartburn due to gastroesophageal reflux disease. Because of the risk of serious, sometimes fatal, ventricular arrhythmias (see Box Warning), PROPULSID should generally be reserved for patients who do not respond adequately to lifestyle modifications (see Medication Guide), antacids, and gastric acid reducing agents.

SIMPLE DOSING SCHEDULE

- Initiate therapy with 10 mg tablets of PROPULSID 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.
- Recommended doses of PROPULSID should not be exceeded.
- It is recommended that the daily dose be halved in patients with hepatic insufficiency.
- 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.

References

1. Kishioka H. Gastroesophageal reflux disease: a common condition in the elderly. *Postgrad Med J* 1997;73:629-33.
2. Smith JH, Gao S. Dosing strategy in the elderly. *Pharmacol Ther* 1995;59:217-34.
3. Smith JH, Gao S, Gao S, et al. Pharmacokinetics of gastroesophageal reflux in elderly patients: a primary care study. *Am J Geriatr* 1997;45:100-105.
4. Smith JH, Gao S, Gao S, et al. Pharmacokinetics of gastroesophageal reflux in elderly patients: a primary care study. *Am J Geriatr* 1997;45:100-105.

PROPULSID®
cisapride
Effective symptomatic relief.

COMMUNICATION POINT/RATIONALE:

For elderly patients, PROPULSID® (cisapride) can add measurable relief. The fact that PROPULSID is well tolerated and easy to take is also important when treating elderly patients. And the new unit-of-use packaging can provide considerable convenience. Finally, Sid continues to demonstrate the relief that PROPULSID provides as he breaks free of the symptoms link.

More than 11 years of worldwide clinical experience and over 30 million prescriptions written in the United States should make physicians confident about the safety of PROPULSID.

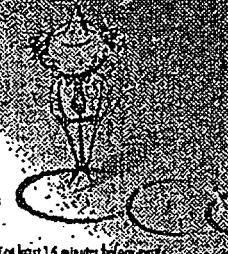
The easy dosing regimen is welcomed by both patients and nursing staffs, and helps ensure patient compliance.

It is important to point out that PROPULSID is now offered only in new unit-of-use sizes for convenience: 10 mg tablets in bottles of 120 and 20 mg tablets in bottles of 60. Suspension is still available in the 16 oz bottle.

Finally, remind physicians that they can get more information from Janssen's One To One™ Customer Action Center at 1-800-JANSSEN (526-7736) 8 AM to 8 PM Eastern time, Monday through Friday.

FOR ELDERLY PATIENTS WITH GASTROGASTRIC HEARTBURN DUE TO GERD

PROPULSID MEANS RELIEF



WELL TOLERATED

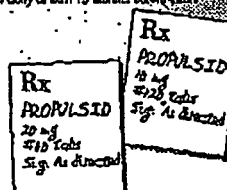
- More than 11 years of clinical experience worldwide
- Over 30 million prescriptions dispensed in the United States

EASY DOSING SCHEDULE

- One 10 mg tablet or 10 mL of the suspension, 4 times daily at least 15 minutes before each meal and at bedtime

NEW UNIT-OF-USE PACKAGING

- PROPULSID is available only in unit-of-use sizes:
 - 10 mg tablets in bottles of 120
 - 20 mg tablets in bottles of 60
- Suspension remains available in the 16 oz bottle
- Patient/Medication Guide is attached to each bottle



FOR SALES REPRESENTATIVE USE ONLY. DO NOT RELY ON PHYSICAL. FURNISH PHYSICIAN WITH FULL PRESCRIBED INFORMATION, INCLUDING BOX WARNING.

FOR MORE INFORMATION, CALL JANSSEN'S ONE TO ONE™ CUSTOMER ACTION CENTER AT 1-800-JANSSEN (526-7736) 8 AM TO 8 PM EASTERN TIME, MONDAY THROUGH FRIDAY.

See our product page for important safety information.

PROPULSID®
cisapride
Effective symptomatic relief.

JANSSEN PHARMACEUTICALS, INC. KILMEAD, ILL. 60139

Order 1990 10 mg 20 mg 16 oz

WARNING: See package insert for important safety information.

RISPERDAL®

**RISPERDAL® (risperidone)
1st Cycle 1999**

The #1 Prescribed Antipsychotic

Congratulations to our field teams for your focus in driving **RISPERDAL** sales in excess of \$700 million in 1998. In addition, despite intense competition, **RISPERDAL** remains the #1 APS in the US! In 1999, the challenge is even greater – Continue to Grow the Leadership Position of **RISPERDAL** and exceed the annual forecast of \$853 million!

If \$853 million and continued market leadership aren't enough to get your attention, keep in mind the **RISPERDAL FOCUS CONTEST**. This contest is designed to reward the top performers in each sales force with a one week trip at the luxurious Four Seasons Resort Hualalai in scenic Hawaii.

Market Update/Key Communication Points

RISPERDAL continues to be the #1 most prescribed antipsychotic in the United States. October NRx share of 25.8% represents an all time high. While we should be very proud of our success, we cannot rest - - NRx share for olanzapine also continues to increase and is at an all time high of 21.8%. In order for us to accelerate the growth of **RISPERDAL** and stop olanzapine, our ability to differentiate **RISPERDAL** as the first choice agent will be critical to our success.

We will accomplish this goal by communicating the major competitive advantages of **RISPERDAL** over olanzapine. These advantages are reinforced by the results of the RIS-112 comparative trial where **RISPERDAL** showed statistically significant superiority over olanzapine on two key measures of efficacy - positive and affective symptoms. Weight gain was also significantly greater in patients taking olanzapine. So let's turn up the heat...about 112 degrees, by delivering the following key communication points on every call:

Emphasis on Efficacy - Efficacy is the most critical factor when selecting an antipsychotic medication. **RISPERDAL** is the only antipsychotic that has demonstrated superiority over Haldol in controlling positive, negative and affective symptoms. With the recent data, psychiatrists will quickly realize that **RISPERDAL** is also superior to other atypicals in these key efficacy measures. **RISPERDAL** also rarely requires the use of a concomitant antipsychotic and is co-prescribed with another antipsychotic 3x less often than olanzapine.

Stress Low Weight Gain - The significant weight gain associated with olanzapine and its impact on both patient health and compliance is a message that resonates well with psychiatrists. Recent data indicates that the average weight gain with olanzapine can be as much as 1lb a week, with the incidence of weight gain almost 2x as high for olanzapine than for **RISPERDAL**.

Ensure Appropriate Dosing - RISPERDAL provides optimal treatment response at low doses. Remind physicians that the average daily prescribed dose for schizophrenia is 4.6 mg/day. RISPERDAL also has convenient QD dosing and unlike olanzapine, is also available in an oral solution (now in 30ml bottles).

RESOURCES FOR CNS AND HOSPITAL SALES FORCES - Please reference the RISPERDAL section of the Resource Binder for selling materials. These materials are intended to support your efforts in growing our business.

1st Cycle Materials

"Quality Control" Sales Aid

This Sales Aid is designed so you can hit the key RISPERDAL selling points on every call: **Efficacy, Weight Gain and Dosing**. Only RISPERDAL offers outstanding symptom control combined with minimal weight gain and simple dosing. Use the first four sections of your Sales Aid to deliver this message on every call, and refer to the tabbed sections to answer physician questions on specific issues.

Efficacy Pocket Card (NEW)

In a simple, yet highly effective, piece you can reinforce the efficacy of RISPERDAL along with reminding the physician of our dosing message. Perfect for a "hallway" call and/or a great leave-behind, this card is one that we hope to find in the physician's jacket pocket for a quick RISPERDAL reference.

RISPERDAL Travel Mug (NEW)

For those car rides to the office, psychiatrists will really enjoy the convenience of the RISPERDAL travel mug. It's not just a mug, but a great way for you to reinforce the RISPERDAL core message. Each mug will come with tear-away wrap which has the core message printed on it so every mug can be delivered with a quick detail.

Weight Gain Tearpad & Scales

This tearpad provides important information on excessive weight so physicians can see just how serious weight gain can be. While the medical implications of excessive weight are always a concern, this piece also highlights predisposing factors, which put certain patients at additional risk for morbidities and mortalities. And patients' unhappiness with weight gain may influence medication compliance. Remind physicians of these treatment issues, and point out how the chart and accompanying scale can help them assess patients during treatment.

Receptor Binding Wall Chart/Calendar (REVISED!)

Back by popular demand, we're starting off the new year with a new Receptor Binding Wall Chart/Calendar. This one takes us all the way through 1999, from January to December. Per your request, this year's is laminated and conveniently sized (8 1/2" x 11"), so it can be posted in offices and clinics. Of course, it still shows the unique RISPERDAL receptor activity that distinguishes the best from all the rest!

Quality Control Dosing Slim Jim

In addition to the core message, this piece provides guidelines for various dosing scenarios. Leave it with your key customers for a detailed dosing reference.

Quality Control File Card

Useful as a handy reference, the File Card contains the RISPERDAL core message and full prescribing information.

Acute Care Flashcard

When patients present in acute settings, it's important to start them on a medication that provides quality control of symptoms. This piece will help you reinforce key RISPERDAL advantages for acute situations: rapid symptom control, low incidence of EPS at appropriate doses, a low incidence of drug interactions, and availability in an oral solution.

Prolactin/Weight Gain Flashcard

If you hear a prolactin objection, be sure to follow the appropriate protocol: probe for whether the physician has seen side effects, remind him/her that RISPERDAL is rarely associated with prolactin side effects, and that side effects are reversible and easily managed by slightly decreasing the dose. Remind physicians that weight gain is not easily reversible, and it may have serious health implications. This flashcard can help squash any lingering doubts, and it will help you put prolactin in the proper perspective while reinforcing key points on weight gain.

Dosing Slide Rule

No matter what the patient scenario, the RISPERDAL dosing regimen is simple and convenient. This piece reminds physicians to go "low and slow," and is consistent with your sales aid.

Premiums

Use these items to remind physicians that RISPERDAL is the #1 prescribed antipsychotic:

- Desk Caddies
- Clocks
- Mugs
- Popcorn
- Magnets
- Pens
- Post-it Pads

Thanks to your input and requests, new items are also coming. We'll keep you posted as they become available!

RISPERDAL is the #1 prescribed antipsychotic and will remain the #1 prescribed antipsychotic because of your diligence and focus on the core message. **Efficacy, Safety Low Weight Gain and Dosing** are the keys to our success. With these messages we are sure to stifle the competition and convince your customers that RISPERDAL should always be their first choice.

Please feel free to contact the RISPERDAL brand team with any questions or feedback.
GOOD SELLING!!!!

**RISPERDAL® (risperidone)
1st Cycle 1999**

The #1 Prescribed Antipsychotic in Long-Term Care

Market Update

Thanks to your selling efforts, RISPERDAL remains the market leader and continues to be the #1 prescribed antipsychotic in long-term care.

The geriatric market is critically important to the continued growth of RISPERDAL. The long-term care APS NRx market is growing at a modest 4% while RISPERDAL LTC NRx has increased 26% versus last year. Great Job! RISPERDAL LTC NRx market share through September is at an all time high of 30.9% vs. Zyprexa at 16.6%. As the conventional market continues to erode, let's keep those switches to RISPERDAL coming!

Congratulations on a job well done!

Positioning

The issue of most concern to professionals when treating the hostile/fragile geriatric patient is balancing efficacy and safety. The RISPERDAL profile is advantageous over other antipsychotics because it allows for the control of psychotic symptoms while minimizing side effects.

In the 1st cycle we will continue to remain focused on our key communication points:

- **When considering efficacy, RISPERDAL improves a broad range of psychotic symptoms:**
 - RISPERDAL controls the disturbing positive symptoms such as delusions, excitement, suspiciousness, hallucinations, and paranoia
 - RISPERDAL controls the less obvious negative symptoms that conventional antipsychotics *don't* treat (blunted affect, apathy, emotional withdrawal, poor rapport)
- **When considering safety, RISPERDAL has a low incidence of:**
 - Movement disorders (EPS) that may restrict daily living
 - Excessive sedation that can cloud daily living
 - Anticholinergic effects that often disrupt daily activities
- **RISPERDAL dosing fits patient and caregiver lifestyles**
 - BID and QD dosing options
 - Available in tablets and oral solution

1st Cycle Materials

To ensure our continued success and assist you in your 1999 selling efforts, we have developed a variety of new and exciting promotional and educational materials:

Dosing Flashcard (NEW!)

We are pleased to provide you with the new 30-mL Dosing/Conversion Flashcard. This flashcard will assist you in communicating proper dosing and help emphasize RISPERDAL dosing flexibility. Remember to communicate:

- RISPERDAL is effective at low doses, which makes it appropriate for geriatric patients
- Start low and go slow
- Oral Solution is available in new convenient 30 ml bottles
- Orthostatic hypotension is rare. Limiting the initial dose helps minimize it's occurrence

The Expert Consensus Guidelines (NEW!)

We are pleased to announce this resource is now available to you as an approved resource for distribution to your key physicians, nurses and pharmacists.

These Guidelines, published in a recent issue of Post Graduate Medicine, were developed by the leading experts in the field of dementia. We are confident that the Guidelines will support your efforts to emphasize the benefits of RISPERDAL:

- RISPERDAL is recommended as the first choice treatment for psychosis in dementia and agitation
- EPS and the long-term risk of tardive dyskinesia are concerns with conventional antipsychotics such as Haldol. Risks are much lower with RISPERDAL
- Low dose RISPERDAL is recommended:
 - Initial dose 0.25 - 0.5 mg/day
 - Target dose 0.5 - 1.5 mg/day

Caregiver Guidelines & Easel (NEW!)

We all know what an important role caregivers play in treatment decisions. When dealing with dementia, caregivers are often the main contact with their loved one's healthcare provider. Many times they are the first to notice medication side effects and they are often "self-educated" bringing information regarding new medication options directly into their loved one's doctor.

With this in mind, we are pleased to provide copies of "Agitation in Older Persons with Dementia: A Guide for Families and Caregivers," (previously published in Postgraduate Medicine), along with a convenient stand-up easel. These caregiver guidelines discuss, in lay terms, strategies for reducing agitation based on "The Expert Consensus Guidelines." You should distribute this important educational piece to your high volume psychiatry and primary care offices and key nursing homes.

Geriatrics At Your Fingertips (NEW!)

This valuable resource book, available to your key doctors, nurses and pharmacists, through you, is designed to be a ready reference which provides immediate access to specific information needed to care for older persons in a variety of long-term care healthcare settings. Key chapters on dementia, psychotic disorders and OBRA regulations should be of interest to your customers.

Antipsychotic Treatment Options/Considerations in the Geriatric Population Video (CME 1hr) (NEW!)

Featuring a leading expert in geriatric psychiatry, Dr. George Grossberg, this presentation discusses epidemiology of psychotic symptoms in later life, differential diagnosis, office evaluation, the nursing home setting, and treatment of psychosis/agitation. We are pleased to offer 1 hour of CME/ACPE/CNE credit to physicians, pharmacists and nurses who view this tape.

Medical Simulations in the Management of Dementia (CME 1hr) (NEW!)

Featuring Pierre Tariot, M.D., a leading geriatric psychiatrist. This challenging medical case study introduces your doctors to a typical patient, and sets the stage for a series of clinical decisions the doctor must make that include; evaluation, tests, diagnosis and management.

Nursing Challenges: Simulations in the Management of Patients with Psychotic Disorders (CE 1hr) (NEW!)

Featuring Mary Ann Boyd, Ph.D., DNS, RN, CS. This CE program guides your nurses through a patient case history and challenges them to make clinical decisions at critical points throughout the case. When you introduce the program to nurses, you'll want to be sure to inform them of the CE credit and challenge them to 'try their hand' at solving the case.

Management of Non-cognitive Symptoms in Dementia: Agitation and Psychosis
(CME 1 Hr)

Based on the positive feedback from you, the Teletopics program for nurses featuring Mary Ann Boyd, Ph.D., R.N. will continue. Dr. Boyd focuses her discussion on differentiating dementia from delirium, describing psychosis and agitation, and giving recommendations for psychosocial interventions and pharmacologic treatment.

Geriatric Core Sales Aid

The sales aid continues to emphasize our key communication points. It will help you sell the benefits of RISPERDAL in controlling symptoms while minimizing side effects.

Anticholinergic Fact Sheet

Continue to use this valuable piece with your key physician and nurses. Keep in mind this fact sheet provides a general overview of anticholinergic effects. Anticholinergic effects are detrimental to fragile geriatric patients. That's why it's critically important to choose an antipsychotic (RISPERDAL) that has minimal anticholinergic activity.

Make sure professionals do not take away the message that RISPERDAL causes anticholinergic effects. Remind your customers RISPERDAL has minimal anticholinergic activity because it has no affinity for cholinergic muscarinic receptor sites.

Premiums

To build on the messages you disseminate during sales calls, a number of leave-behind premiums are available. They'll help you remind your customers why RISPERDAL should continue to be their first choice.

Use these items to remind physicians that RISPERDAL is the #1 prescribed antipsychotic in Long-Term Care:

- Mugs
- Clocks
- Popcorn
- Magnets
- Pens
- 30 ml Post-it Pads (NEW)

Remember, RISPERDAL is the #1 antipsychotic in long-term care and it's up to you to ensure its continued success in 1999.

Thank you for your continued support and good selling!

SPORANOX®

CONFIDENTIAL

R. 3728

J-TXCID1673072

SPORANOX® (itraconazole) Capsules
1st Cycle 1999

The Mycology Brand Team would like to thank the entire sales force for your commitment to SPORANOX® in 1998. We surpassed 1997 sales, exceeded our 1998 forecast, began to narrow the gap between SPORANOX® and Lamisil, and your sales efforts have paid incredible dividends. Now we are in a solid position to regain market leadership in 1999. Novartis now realizes we are not going away. The challenge for the first cycle is to continue the momentum and grow SPORANOX® share at the expense of Lamisil.

The keys to SPORANOX® success remain simple:

- 1) Sell against Lamisil! It's a two-player game and SPORANOX® has better players, better equipment and better support. Differentiate SPORANOX® from Lamisil by embellishing on all benefits of *PulsePak*™ and pulse dosing.
- 2) Target your highest volume physicians.
 - Use your promotional items where they'll have the most impact
 - Sample them appropriately

PulsePak sales are strong! In fact, the SPORANOX *PulsePak* is the fastest growing product for onychomycosis in the oral antifungal market! Keep selling your customers on all the benefits associated with *PulsePak* and Pulse dosing. Remind your physicians that if they start their onychomycosis patients on SPORANOX now, they will have clear, beautiful nails in the summer.

Core Brochure

We've done extensive testing on the new visual aid for 1st cycle and have incorporated feedback from the field. The *PulsePak*™ and *PulsePak Promise*® are in the 1st spread and should help you drive home all the advantages of SPORANOX® vs. Lamisil. Please see the accompanying key communication points before you role-play to ensure a consistent message.

Market Definition

The market definition for 1999 has been realigned. In terms of your performance index, you will be evaluated on SPORANOX® market share and volume growth vs. Lamisil only. For targeting purposes, you will still be calling on high AFO physicians who may be prescribing other oral antifungals such as Diflucan or griseofulvin.

Starter Kits

The Starter Kits will continue to be available. Feedback from the field around this program has been extremely positive. Physicians appreciate that everything that must be relayed to the patient is all in one convenient card, making their job easier.

The Physician's Office

The Mycology Brand Team wants to assure that Janssen owns the physician's office. To assist you, we have created Exam Room Posters, new Kick brochures, new post-it pads, and have many marketing initiatives ready to roll out throughout 1999.

PulsePak™ Promise

Over 2000 patients have already enrolled in the Patient Support Program that is part of the PulsePak™ Promise. When explaining this program to physicians, highlight that they do not have to get involved at all. During market research testing, physicians viewed this as a great benefit.

Samples

Samples will be allocated according to the number of 9-94 physicians in each District. The District Managers will allocate the samples to the individual territories depending on the local market dynamics. Please use your samples wisely and judiciously. You will be receiving guidelines that will assist you in determining the amount to leave with each physician.

Good luck in making 1999 an even better year for SPORANOX!

SPORANOX® PulsePak™ 1st Cycle Visual Aid

KEY COMMUNICATION POINTS

INTRODUCTION

OBJECTIVES

To continue to position SPORANOX® *PulsePak*™ as the easiest way to kick onychomycosis and achieve patient success.

BACKGROUND

SPORANOX® *PulsePak*™ is continuing to gain market share. We have surpassed 1997 sales by 10% and exceeded our 1998 forecast. Sales are strong! In fact, SPORANOX® *PulsePak*™ is the fastest growing onychomycosis product on the market. Congratulations!

Thanks to your great selling efforts, physicians realize that SPORANOX® *PulsePak*™ is the easiest way to help their patients kick onychomycosis — and are prescribing SPORANOX® *PulsePak*™ over Lamisil®.

Let's keep up the momentum! Continue to position SPORANOX® *PulsePak*™ as the easy prescription for patient success.

SPORANOX® *PulsePak*™ IS THE COMPLETE SYSTEM FOR PATIENT SUCCESS

This cycle continues to highlight our unique selling feature: the SPORANOX® *PulsePak*™. SPORANOX® *PulsePak*™ makes it easy for patients to kick onychomycosis. No other oral antifungal delivers the confidence and support that SPORANOX® *PulsePak*™ provides to patients and physicians...it is a complete system for patient success!

With SPORANOX® *PulsePak*™, patients receive:

- One complete pulse (7 pouches each containing one day of therapy)
- A patient-friendly guide that includes pulse dosing instructions, photos to help manage patient expectations, important information on what drugs to avoid, and tips to prevent reinfection
- The SPORANOX® *PulsePak*™ Promise, a money-back guarantee with a patient support program

CONFIDENTIAL

Recent feedback has told us that physicians respond very favorably to the SPORANOX® *PulsePak™* Promise. Physicians like the idea of being able to offer patients a support program to help manage expectations and aid in compliance. Physicians also like the fact that Janssen provides a money-back guarantee. Physicians connect the guarantee with the fact that SPORANOX® works (which is good news)! During market research testing, physicians also viewed the "no physician documentation" aspect as a real benefit. So, make sure you mention it during your sales presentation.

When physicians prescribe SPORANOX® *PulsePak™*, their patients will also receive the great benefits of SPORANOX® Pulse Dosing, which include:

- Less drug
- Less cost
- Fewer treatment days
- Patient-preferred dosing

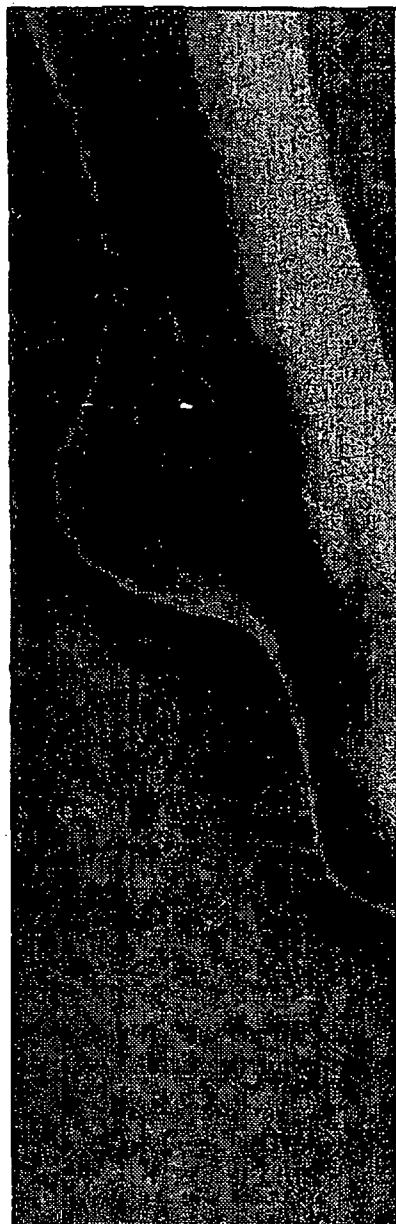
When closing your sales presentation, tell physicians to prescribe the easy prescription for patient success: SPORANOX® *PulsePak™*. Remind physicians that no other oral antifungal delivers the confidence and support that SPORANOX® *PulsePak™* provides for physicians and patients. This is the message we need to keep driving to regain our market-leader position in 1999. The key to positioning SPORANOX® against Lamisil® is through the SPORANOX® *PulsePak™*. Continue to highlight the SPORANOX® *PulsePak™* and its value-added benefits to physicians and we will gain market share in 1999!

Please note: This cycle, to make it easier for you to detail the SPORANOX® *PulsePak™*, we have numbered each key communication point on each page. You will see that this "flow" makes great sense and provides a most effective presentation of information. Additionally, we have supplied recommended bridges that will effectively lead you into each page of the visual aid. We hope these changes make it even easier for you to detail the great advantages of SPORANOX®. Good selling!

Janssen
sporanoX^{100mg}
(itraconazole) Capsules

Communication Point/Rationale

Tell physicians that SPORANOX® is the easiest way to KICK onychomycosis, and Janssen is so confident that patients will achieve success that they guarantee it!



The Easy Way To
KICK
ONYCHOMYCOSIS

...Guaranteed

Janssen ^{100mg}
sporanoX
(itraconazole) Capsules

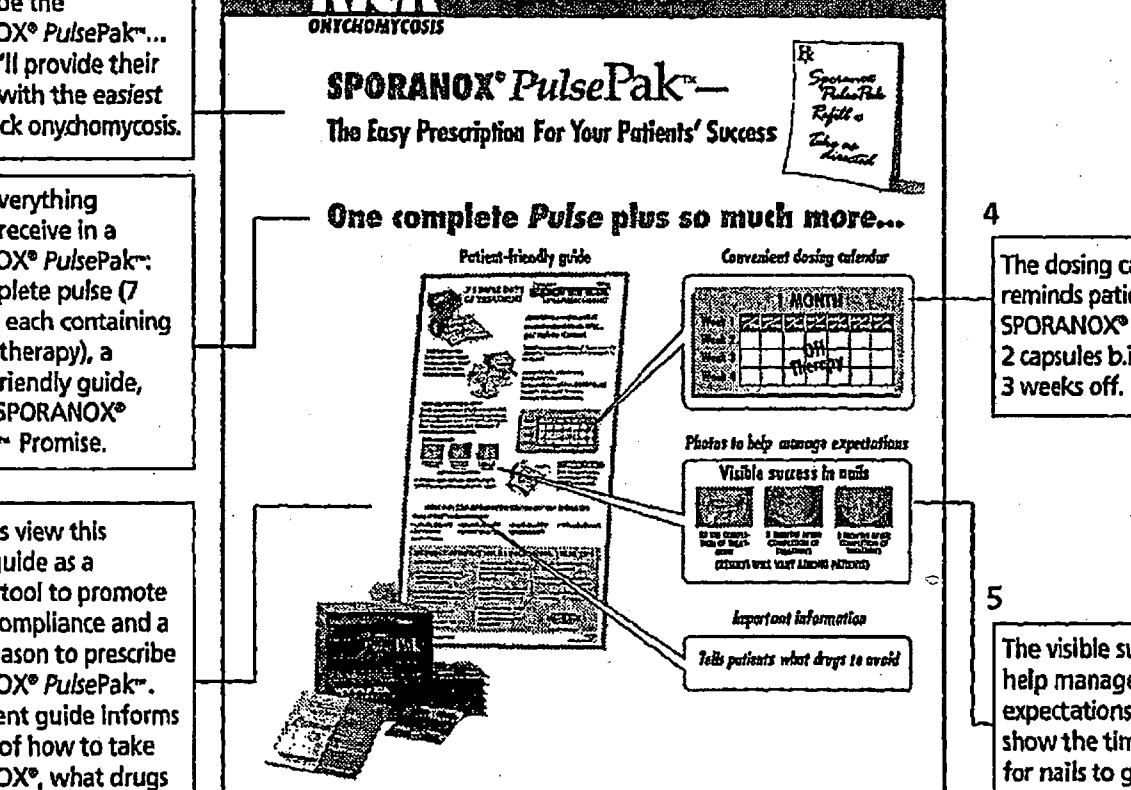
Communication Point/Rationale

The first page communicates the reason why physicians should prescribe SPORANOX®—the *PulsePak*™. No other oral antifungal can deliver the confidence and support that SPORANOX® *PulsePak*™ provides physicians and patients. It is a complete system to help ensure patient compliance and success.

- 1** Describe how easy it is! All physicians have to do is prescribe the SPORANOX® PulsePak™... and they'll provide their patients with the easiest way to kick onychomycosis.

2 Discuss everything patients receive in a SPORANOX® PulsePak™: one complete pulse (7 pouches, each containing 1 day of therapy), a patient-friendly guide, and the SPORANOX® PulsePak™ Promise.

3 Physicians view this patient guide as a valuable tool to promote patient compliance and a strong reason to prescribe SPORANOX® PulsePak™. The patient guide informs patients of how to take SPORANOX®, what drugs to avoid during therapy, and tips to prevent reinfection.



KICK Guaranteed!
ONYCHOMYCOSIS

SPORANOX® PulsePak™—
The Easy Prescription For Your Patients' Success

*SPORANOX® PulsePak™
Refill as
They are
Directed*

One complete Pulse plus so much more...

Patient-friendly guide

It's done! Day 1 of treatment!

SPORANOX® PulsePak™

7 Pouches of Therapy

1 MONTH

ON THERAPY

PHOTOS TO HELP MANAGE EXPECTATIONS

VISIBLE SUCCESS IN NAILS

3 MONTHS AFTER COMPLETION OF THERAPY

6 MONTHS AFTER COMPLETION OF THERAPY

1 YEAR AFTER COMPLETION OF THERAPY

PHOTOS WERE TAKEN ALONG PATIENT'S

Important information

Tells patients what drugs to avoid

4 The dosing calendar reminds patients that SPORANOX® Pulse Dosing is: 2 capsules b.i.d., 1 week on, 3 weeks off.

5 The visible success photos help manage patient expectations, since they show the time it takes for nails to grow out after treatment is completed. They also show how well SPORANOX® works!

4 The dosing calendar reminds patients that SPORANOX® Pulse Dosing is: 2 capsules b.i.d., 1 week on, 3 weeks off.

5 The visible success photos help manage patient expectations, since they show the time it takes for nails to grow out after treatment is completed. They also show how well SPORANOX® works!

Recommended bridge to next page:

"Also included in each SPORANOX® *PulsePak*™ is the SPORANOX® *PulsePak*™ Promise—a money-back guarantee with a patient support program..."

Communication Point/Rationale

Janssen is so confident that patients will achieve success—they guarantee it!

Be sure to discuss the SPORANOX® PulsePak™ Promise and how it works with physicians. Stress that there is no physician documentation necessary. Remember...research has shown physicians are impressed to hear this.

1 Stress that only SPORANOX® guarantees patient satisfaction with the SPORANOX® PulsePak™ Promise.

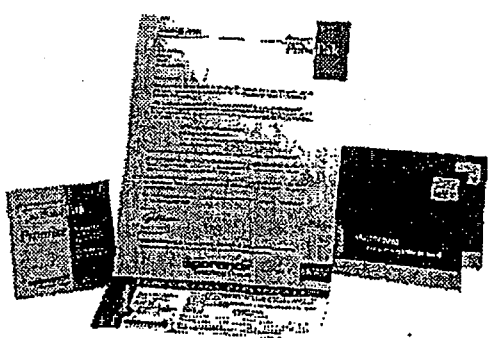
2 If patients are not completely satisfied with the results 1 year after therapy has started, Janssen will refund their out-of-pocket cost of the prescription. Remember, patients must enroll in the support program to be eligible for the money-back guarantee.

3 This insert is inside every SPORANOX® PulsePak™. It describes how patients enroll in the program and the money-back guarantee.

...with SPORANOX® PulsePak™

**SPORANOX® PulsePak™ Promise —
Guarantees Patient Satisfaction**

- Money-back guarantee
 - No physician documentation required
- Patient compliance program



Janssen
sporanoX^{100mg}
(itraconazole) Capsules

4 Make sure you tell physicians that there are no nail assessments or documentation required. They just have to prescribe the SPORANOX® PulsePak™—it's that easy! All the program details are inside the SPORANOX® PulsePak™. Patients simply call an 800# to enroll in the program. Unlike the Lamisil® money-back guarantee, which requires documentation and physician involvement.

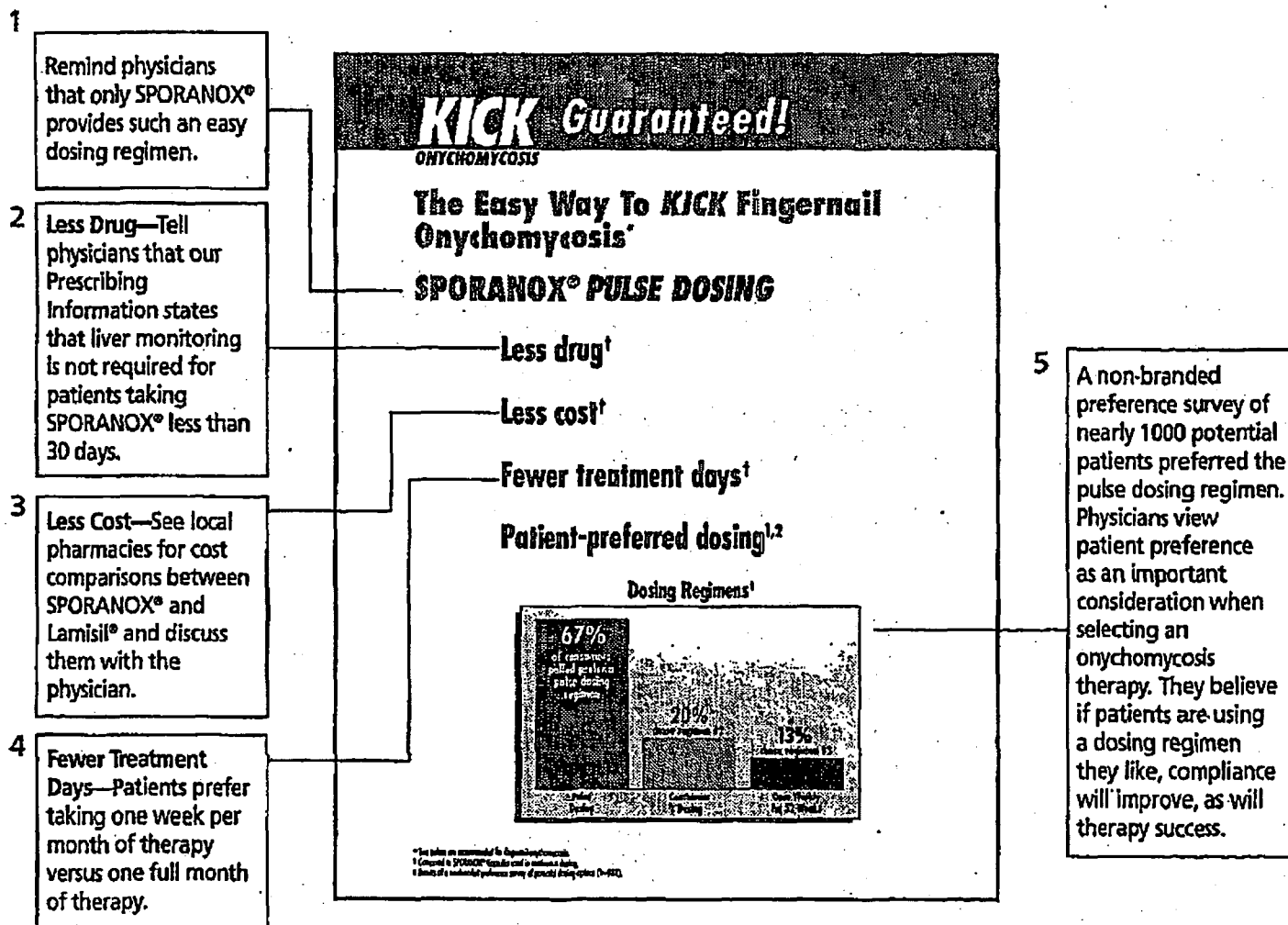
5 The compliance program really motivates patients and helps reduce physician call-backs regarding therapy. A series of mailings remind patients of the time it takes for nails to grow out fully and discusses the importance of adhering to the prescribed regimen. It also encourages patients to refill with a \$5 savings certificate.

Recommended bridge to next page:

"And best of all, when you prescribe the SPORANOX® PulsePak™, your patients are receiving the benefits of pulse dosing..."

Communication Point/Rationale

This page communicates the additional benefits of the SPORANOX® PulsePak™: the pulse dosing regimen.



Recommended bridge to next page:

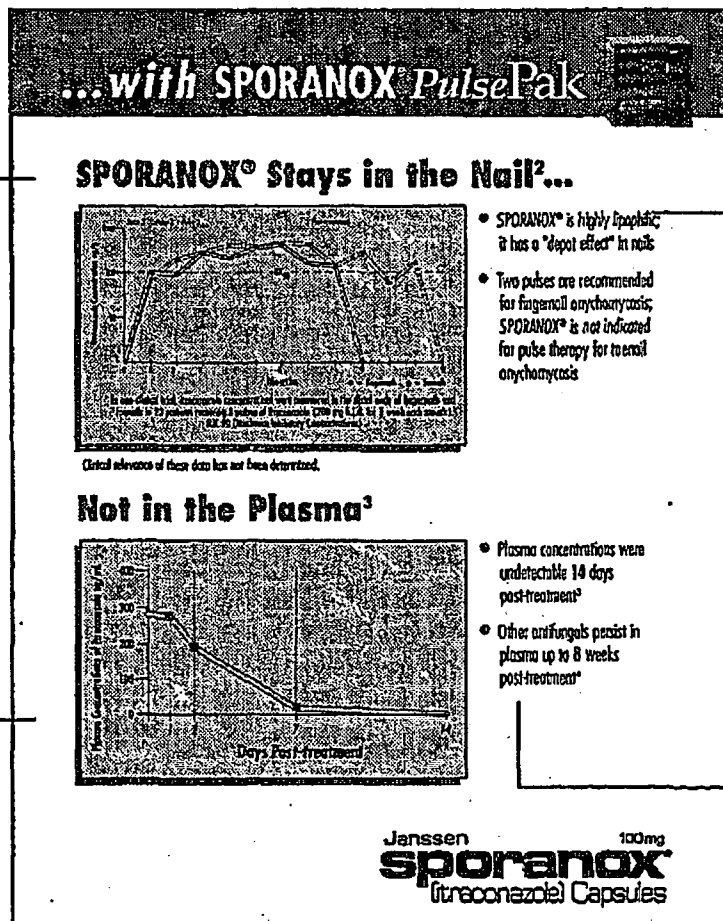
"SPORANOX® is the only oral antifungal on the market that can be pulse dosed due to its unique pharmacokinetics..."

Communication Point/Rationale

The reason why Janssen can guarantee the efficacy of SPORANOX® is because of its unique and favorable pharmacokinetics. The "depot effect" enables the drug to work long after therapy has ended and the nail grows out. Importantly, while SPORANOX® stays in the nail, it quickly clears plasma, which helps improve safety.

1

This chart shows post-treatment concentrations of SPORANOX® in fingernails and toenails. Note that these levels stay well above the minimum inhibitory concentrations (MICs) for up to 9 months in fingernails and 12 months in toenails.



2

Because SPORANOX® is lipophilic, it has a "depot effect" in nails. The "depot effect" enables the drug to work long after therapy has stopped and the nail grows out.

Note: The MIC represents the minimum level of drug necessary to clear the infection. SPORANOX® maintains necessary levels even after patients stop taking the drug. This is why SPORANOX® can be pulse dosed.

3

Point out that while SPORANOX® stays in the nail, it quickly clears plasma. The faster the drug clears plasma, the safer it is for the patient.

4

Lamisil® can linger in plasma for up to 8 weeks post-treatment. Drugs that remain in plasma a long time can prolong the effect of adverse events, or interfere with other therapeutic regimens. It can also make patient management more complex and difficult.

Recommended bridge to next page:

"SPORANOX® is a very safe drug. SPORANOX® quickly clears the plasma, unlike Lamisil®, which remains in the plasma for up to 8 weeks and can prolong adverse events. These events have been documented with Lamisil®..."

Communication Point/Rationale

It's easy for physicians to be confident when they prescribe SPORANOX®. It has vast clinical experience and is a safe and well-tolerated drug.

1 Physicians don't have to worry about these side effects with SPORANOX®. However, all of these side effects have been identified with Lamisil®—and potentially could persist up to 8 weeks post therapy, raising safety concerns.

2 In the Lamisil® Prescribing Information, liver monitoring is recommended in patients for therapy greater than 6 weeks.

KICK Guaranteed!
ONYCHOMYCOSIS

It's Easy To Be Confident with SPORANOX®

Over 65 Million Patient Days* of Experience...
Safe and Well Tolerated

	SPORANOX®
Causes hepatotoxicity as a listed potential and adverse event	No
Causes disturbances as a frequently reported adverse event	No
Causes /rashes changes	No
Decreases in absolute lymphocyte counts (ALC)	No
Requires monitoring in recommended for continuous therapy >30 days	No
Can be prescribed for 6 weeks	

*US Studies, National Prescribing Centre (NPC), October 1992 to September 1993.

Contraindicated Drugs	Alternative Approaches*
Terfenadine (Serevent®), disastemine (Lazax®)	Flavonoids (Lazax®) or propanolol (Procardia®) short-term discontinuation of disastemine (Lazax®) upon
Allopurinol (Probenecid®)	Allopurinol (Probenecid®), allopurinol, or allopurinol
Terfenadine (Serevent®), disastemine (Lazax®)	Terfenadine (Serevent®), disastemine (Lazax®), or OTC antihistamines
Terfenadine (Serevent®)	Terfenadine (Serevent®)
oral contraceptives (Oral contraceptives)	oral contraceptives is indicated for use in postmenopausal women with this SPORANOX® is not indicated for postmenopausal use

*SPORANOX® is a potent inhibitor of the cytochrome P-450 3A4 enzyme system and increases plasma concentrations of drugs metabolized by this pathway. The potential for interaction of SPORANOX® with these drugs is therefore increased. When prescribing any drug, there is no substitute for good clinical judgment, including the monitoring of individual patient needs.

3 Physicians can be confident that SPORANOX® works and that it is extremely safe for patients. Point out that SPORANOX® has been available since 1992 and has over 65 million patient days of experience in the U.S. alone. It is well known and predictable, which is a key safety advantage.

4 Be sure to know the brand name of each contraindicated drug and its alternative, because sometimes physicians are unfamiliar with the generic names of drugs.

Communication Point/Rationale

This page discusses important safety information, including contraindicated drugs.

...with SPORANOX PulsePak



More Facts About SPORANOX®

1 SPORANOX® is contraindicated with specified drugs.

SPORANOX® is contraindicated with terfenadine, astemizole, and cisapride due to potentially serious cardiovascular events. SPORANOX® is also contraindicated with triazolam, oral midazolam, lovastatin, or simvastatin. PLEASE SEE BOX WARNING AND PRECAUTIONS.

2 SPORANOX® should be discontinued if signs and symptoms of liver disease develop. SPORANOX® should not be given to pregnant women or women contemplating pregnancy.

Postmarketing experience across indications has included reports of elevated liver enzymes and rare hepatitis. If clinical signs and symptoms consistent with liver disease develop, SPORANOX® should be discontinued. SPORANOX® should not be administered for the treatment of onychomycosis to pregnant patients or to women contemplating pregnancy.

SPORANOX® is well tolerated. In fingernail clinical trial experience, the following adverse events led to either a temporary or permanent discontinuation of treatment: rash/pruritus (3%) and hypertriglyceridemia (3%).

3 SPORANOX® is well tolerated compared to other therapies. Minor adverse events such as rash have been reported.

Janssen
sporanoX[®]
(itraconazole) Capsules

SUMMARY

Reinforce the reasons why SPORANOX® PulsePak™ is the easiest way to KICK onychomycosis—guaranteed!

- Less drug
- Less cost
- Fewer treatment days
- Patient-preferred dosing

Plus, we support patients and guarantee their success with the SPORANOX® PulsePak™ Promise—a money-back guarantee with a patient support program that requires no physician documentation.

Point out that as a result of all the benefits of SPORANOX® PulsePak™, SPORANOX® has now become the fastest growing oral antifungal on the market!

Before you close your presentation, ask the physician if he or she has any questions you did not answer.

Then close your presentation by reminding the physician that SPORANOX® PulsePak™ is the easy way to kick onychomycosis...guaranteed! It is a complete system for patient success. No other oral antifungal delivers the confidence and support that SPORANOX® PulsePak™ provides physicians and patients. Now, ask the physician to make his or her next prescription for onychomycosis, a SPORANOX® PulsePak™ prescription.

KICK Guaranteed!

ONYCHOMYCOSIS

SPORANOX® PulsePak™

Less drug*

Less cost*

Fewer treatment days*

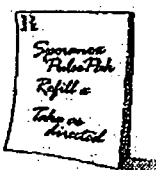
Patient-preferred dosing^{1,2}

PLUS...

The PulsePak™ Promise



The Fastest Growing Oral Antifungal*



*US Agency, National Prescription Audit Plus, October 1998.
*Compared to SPORANOX® Capsules (itraconazole tablets).

REFERENCES:
1. In: Buehler W, eds. The Art & Science of Medicine. New York: McGraw-Hill, 1998:110-112.
2. In: Buehler W, eds. The Art & Science of Medicine. New York: McGraw-Hill, 1998:110-112.
3. In: Buehler W, eds. The Art & Science of Medicine. New York: McGraw-Hill, 1998:110-112.
4. In: Buehler W, eds. The Art & Science of Medicine. New York: McGraw-Hill, 1998:110-112.
5. In: Buehler W, eds. The Art & Science of Medicine. New York: McGraw-Hill, 1998:110-112.
6. In: Buehler W, eds. The Art & Science of Medicine. New York: McGraw-Hill, 1998:110-112.
7. In: Buehler W, eds. The Art & Science of Medicine. New York: McGraw-Hill, 1998:110-112.
8. In: Buehler W, eds. The Art & Science of Medicine. New York: McGraw-Hill, 1998:110-112.
9. In: Buehler W, eds. The Art & Science of Medicine. New York: McGraw-Hill, 1998:110-112.
10. In: Buehler W, eds. The Art & Science of Medicine. New York: McGraw-Hill, 1998:110-112.

FOR SALES REPRESENTATIVE USE ONLY. NOT TO BE LEFT WITH PHYSICIAN.
FURNISH PHYSICIAN WITH FULL PRESCRIBING INFORMATION, INCLUDING BOX WARNING.

Janssen ^{100 mg}
sporanoX
(itraconazole) Capsules

World's largest oral antifungal market

JANSSEN

10 months, 10 years, 100 years

© J.P. 89-238 January 2000 Printed in U.S.A.



10 months, 10 years, 100 years

BULK SHIPMENT

CONFIDENTIAL

TO: All Janssen 425 Sales Representatives

SUBJECT: 1ST Cycle 1999 Bulk Shipment

The following materials will be shipped from our Distribution Center beginning January 29th:

		QUANTITY	
JPI #	DESCRIPTION	O.B. REPS	HOSP REPS
<u>DURAGESIC®</u>			
DR-347	CASE STUDY: Chronic Back Pain	-	3
DR-402	25mcg Conversion Chart	-	100
DR-403	Sample Sign in Book	-	2
DURAGESIC MATERIALS ARE FOR REPS WITH DURAGESIC SELLING RESPONSIBILITY - APPROX. 107			
<u>PROPULSID®</u>			
PR-622	Rep Reference Guide	1	1
PR-659R	Revised Effective Relief File Card	150	150
PR-679	Unit-of-Use Stickers	1 Roll	1 Roll
PR-680	Core Vis Aid	2	2
PR-681	Efficacy Wallet Card	2	2
PR-682	MRS Wallet Card	2	2
PR-683	ElderCare Link Vis Aid	-	2
PR-684V	CME: Non-ulcer Dyspepsia Video	1	1
PR-684B	CME: Non-ulcer Dyspepsia Booklet	10	10
PR-685	CME: GI series CD Rom	1	1
<u>SPORANOX®</u>			
SP-338	SPORANOX Waiting Room (Kick) Brochure	100	100
SP-385	SPORANOX Exam Room Poster	100	100
SP-389	1 st Cycle Visual Aid	2	2
SP-390	Wide Body PulsePak Pen	100	100
SP-392	SPORANOX PulsePak Post-It Notes	100	100

CONFIDENTIAL

R. 3742

J-TXCID1673086

CONFIDENTIAL

TO: All Janssen 500 Sales Representatives

SUBJECT: 1st Cycle 1999 Bulk Shipment

The following materials will be shipped from our Distribution Center beginning January 29th:

		QUANTITY
DESCRIPTION		QTY REPS
<u>DURAGESIC®</u>		
DR-347	CASE STUDY: Chronic Back Pain	3
DR-402	25mcg Conversion Chart	100
DR-403	Sample Sign in Book	2
DURAGESIS MATERIALS ARE FOR REPS WITH DURAGESIC SELLING RESPONSIBILITY – APPROX 319		
<u>PROPULSID®</u>		
PR-622	Rep Reference Guide	1
PR-659R	Revised Effective Relief File Card	150
PR-679	Unit-of-Use Stickers	1 Roll
PR-680	Core Vis Aid	2
PR-681	Efficacy Wallet Card	2
PR-682	MRS Wallet Card	2
PR-684V	CME: Non-ulcer Dyspepsia Video	1
PR-684B	CME: Non-ulcer Dyspepsia Booklet	10
PR-685	CME: GI series CD Rom	1
<u>SPORANOX®</u>		
SP-338	SPORANOX Waiting Room (Kick) Brochure	100
SP-385	SPORANOX Exam Room Poster	100
SP-389	1 st Cycle Visual Aid	2
SP-390	Wide Body PulsePak Pen	100
SP-392	SPORANOX PulsePak Post-It Notes	100

CONFIDENTIAL

R. 3743

J-TXCID1673087

CONFIDENTIAL

TO: All Janssen ElderCare Sales Representatives

SUBJECT: 1st Cycle 1999 Bulk Shipment

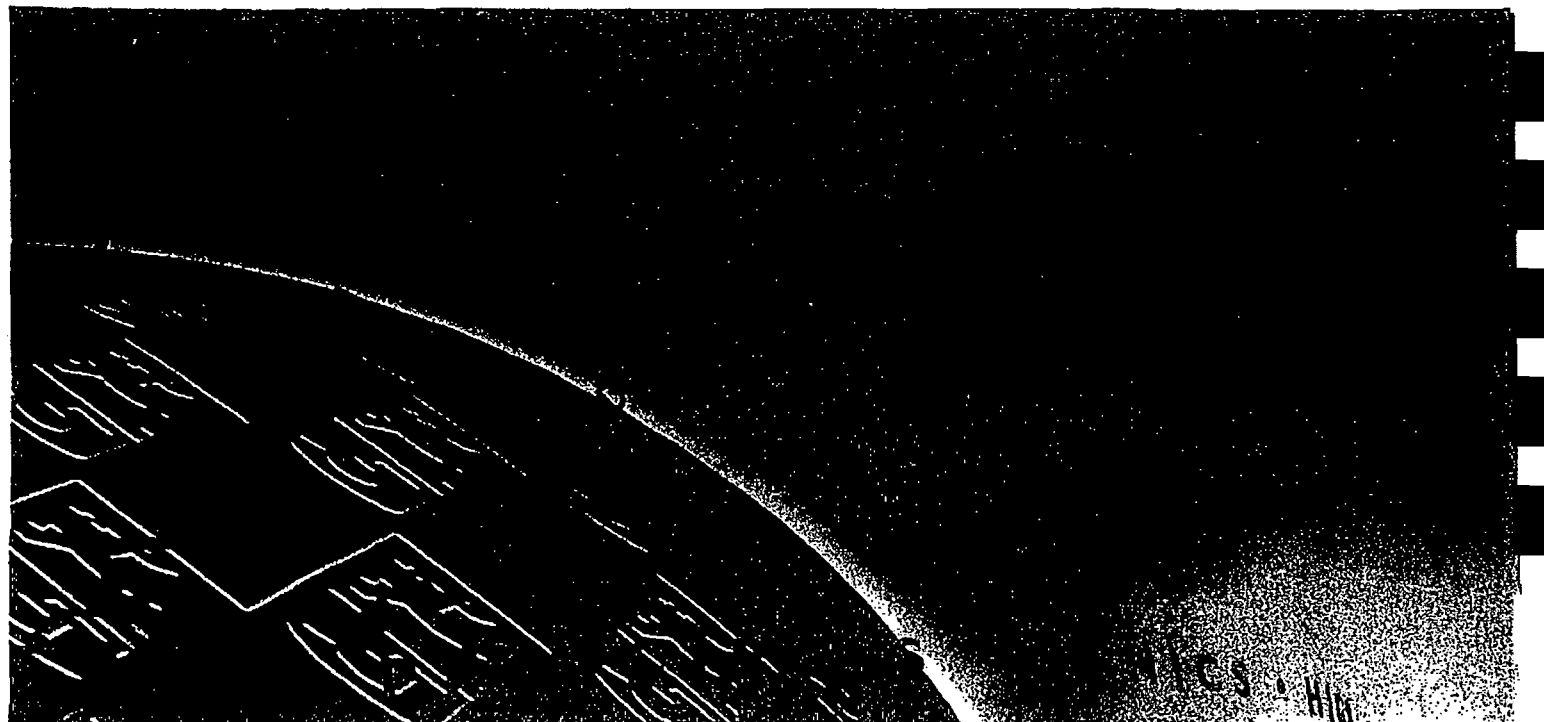
The following materials will be shipped from our Distribution Center beginning January 29th:

JPI	DESCRIPTION	QTY REPS
<u>DURAGESIC®</u> DR-367 DR-397 DR-402 DR-403 DR-404	AGS Guidelines CASE STUDY: Geriatric # 1 25mcg Conversion Chart Sample Sign in Book CASE STUDY: Geriatric # 2	100 5 100 2 5
<u>PROPULSID®</u> PR-622 PR-659R PR-679 PR-680 PR-681 PR-682 PR-683 PR-684V PR-684B PR-685	Rep Reference Guide Revised Effective Relief File Card Unit-of-Use Stickers Core Vis Aid Efficacy Wallet Card MRS Wallet Card ElderCare Link Vis Aid CME: Non-ulcer Dyspepsia Video CME: Non-ulcer Dyspepsia Booklet CME: GI series CD Rom	1 150 1 Roll 2 2 2 2 1 10 1

CONFIDENTIAL

R. 3744

J-TXCID1673088



CONFIDENTIAL

R. 3745

J-TXCID1673089

JANSSEN



• PHARMACEUTICA •
• RESEARCH FOUNDATION •

RISPERDAL Q&A
(For use with financial analysts and media)

The #1 Claim

- Q. How can Risperdal be #1 when Haldol is generally acknowledged to be #1?**

Risperdal is currently the #1 prescribed antipsychotic by psychiatrists, and the #1 antipsychotic used in the treatment of schizophrenia, based on the National Prescription Audit of the market research firm IMS America. With the growth we're experiencing -- 73% in the first half of this year -- we anticipate overtaking Haldol to become #1 in new antipsychotic prescriptions in the next several months.

- Q. What about overall prescriptions?**

Overtaking Haldol in overall Rx's may take a little longer, but as you know, the better indicator of current prescribing habits is in new Rx's.

REDACTED

- Q. Why the discrepancy between total Rx growth and new Rx growth for Risperdal?**

Risperdal is still a relatively new drug, so most of last year's Rx's were new Rx's, which skews the numbers somewhat. (??? yes?)

- Q. What's your current market share in new and total Rx's compared to Haldol?**

As of May 1996, Risperdal had a 16.0% new Rx share to Haldol's 21.4% share, compared to a 10.0% share and 22.0% share, respectively, a year earlier. Regarding total Rx's as of May 1996, Risperdal had a 14.5% share to Haldol's 21.1% share, compared to a 8.8% share and 22.2% share, respectively, a year earlier.

REDACTED

- Q. What's your market share within the schizophrenia segment compared to Haldol?**

As of May, Risperdal has a market share of 19% within the schizophrenia segment compared to Haldol's market share of 16%.

- Q. What's your market share with psychiatrists compared to Haldol?**

As of May, Risperdal has an antipsychotic market share of 17.8% with psychiatrists compared to Haldol's market share of 14.6%.

- Q. How much do psychiatrists account for Risperdal Rx's?**

Psychiatrists account for approximately 70% of Risperdal prescriptions, which is to be expected since psychiatrists treat the majority of severe mental illnesses.

Superiority Claims

- Q. You've been claiming superiority over Haldol, and yet there's nothing in your labeling to suggest that. Why not?**

The preponderance of data and experience with Risperdal show superiority over Haldol in both positive and negative symptoms. We believe FDA has some very specific category issues regarding comparative claims, and doesn't want companies making such claims in their labeling. We doubt any of the newer products will be able to get comparative claims, either.

- Q. Lack of EPS was supposed to be one of Risperdal's hallmarks, yet that doesn't seem to be the case.**

Unlike conventional antipsychotics, Risperdal has a low potential for EPS. Some physicians who initially tried using the drug at unnecessarily high doses found a higher incidence of EPS, but at the recommended lower doses of 4-6 mg the incidence of placebo is comparable to placebo.

- Q. Independent reports suggest that the physician community is disappointed in Risperdal and that it's being viewed as an expensive Haldol. Is it?**

No. Our experience suggests that initially some physicians weren't dosing Risperdal optimally because of lack of experience with the drug, and we've learned that one tends to get better results by titrating slowly and using smaller doses. Our market research data (SMC) shows that as physicians have become more familiar about how to use Risperdal, their satisfaction with it has gone up substantially, from 65% somewhat or very positive in 1994 to 90% somewhat or very positive by the end of 1995.

- Q. When are you going to have data to support long-term safety/efficacy in your labeling for Risperdal?**

The preponderance of data and experience in over one million patients supports the long-term safety and efficacy of Risperdal. Physicians know that, so our seeking a label change on that score isn't a top priority at the moment.

- Q. At the FDA advisory committee meeting for Risperdal, Janssen said there was a major comparative trial underway. What happened to that trial?**

Based on FDA's reluctance to allow comparative claims in labeling, we decided to devote our energies elsewhere. The preponderance of data and experience in over one million patients demonstrates the superiority of Risperdal over conventional antipsychotics.

- Q. Aren't elevated prolactin levels a weakness for Risperdal?**

Like all antipsychotics, Risperdal may elevate prolactin levels in some patients. In clinical trials, no patients discontinued Risperdal due to prolactin-related issues; also, the clinical significance of elevated prolactin levels is unknown.

Sales/growth

- Q. What are Risperdal's current sales?**

It is against company policy to release specific product sales figures, but we can cite IMS audited figures, which were \$363 million in 1995, and \$155 million from January to April 1996, which translates to an annualized figure of \$465 million without any further growth — although we expect sales to continue increasing.

- Q. Can you make a projection of 1996 sales? 1997?**

We don't make official projections, but you can pretty much guess based on the IMS audited numbers and our growth rate, which was 73% in the first half of this year, compared to overall market growth of 5%.

- Q. The 5% overall market growth doesn't suggest you've grown the market much, compared to other categories, like the SSRI's where the market grew in the 20s after Prozac's introduction.**

The depression market has vast numbers of untreated patients. That's not the case with severe mental illness. We've grown the market, and we've taken market share from conventional therapies such as Haldol and Mellaril. The antipsychotic market was virtually stagnant when Risperdal was introduced.

- Q. Where do you expect your future growth to come from?**

We expect it to come from many places: Higher volume with psychiatrists, some of whom are slow adopters or niche users with new drugs; greater use among elderly patients as more safety data in that population are published and incorporated in to our labeling (hopefully in 1997); broader use in a variety of disorders; and through line extensions and new indications. Remember, Risperdal is only 2 1/2 years old.

- Q. Aren't psychiatrists generally early adopters, particularly in an unsatisfied market?**

Generally, yes; however, we're aware of opportunities among high prescribing psychiatrists who are either late adopters, niche users or non-users at this point.

- Q. Why haven't you garnered an even larger share of such an unsatisfied market?**

We've done very well considering some of the market dynamics. Most patients who are being treated chronically are not going to be switched from standard antipsychotics if the physician is getting adequate results. This is especially true for patients who are part of the public sector/Medicaid market, where reimbursement costs are an issue. We're making progress in demonstrating the cost-effectiveness of Risperdal and hope to make increasing inroads in this area.

- Q. If certain psychiatrists aren't using Risperdal as first-line therapy now, what's going to make them change?**

Increasing familiarity with the drug will help. Our own market research data (SMC) has shown increasing physician satisfaction with Risperdal since its introduction. In 1994, 81% of physicians were somewhat or very positive about Risperdal, and that number has since increased to 90% in the first half of 1996. In addition, we've made a lot of headway on formulary approvals over the last two years.

- Q. How broadly is Risperdal being used?**

A rough breakout of Risperdal's usage is as follows: 32% schizophrenia, 28% bipolar disorders, 12% schizoaffective disorders, 8% dementia, and the balance in other miscellaneous psychoses (IMS NDTI data for 12 mos. ending 1st Q 1996).

- Q. Why are you getting so much use in bipolar disorders? Are you seeking an official indication for that use?**

We've seen that Risperdal has benefits in bipolar disorders. Abstracts for a new investigator-initiated study have been submitted to APA, and separately Janssen is investigating the use of Risperdal as adjunctive therapy in acute mania.

- Q. What about other indications?**

We're looking at a number of expanded uses for Risperdal, including behavioral disturbances dementia; relapse prevention; treatment resistance (which compares Risperdal to Haldol and Clozaril); early psychosis (first break); elderly psychosis; Alzheimer-type dementia; and behavioral disturbances in mental retardation. In addition, a number of investigator-initiated studies are underway, evaluating uses from schizotypal personality disorder, to childhood conduct disorders, autism and stuttering.

- Q. Which ones are likeliest to be added to the labeling, or at least see widespread use?**

We're optimistic that the bipolar and psychosis-related studies will contribute to expanded use of the drug, especially in elderly patients, because Risperdal is known to be a very safe, well-tolerated drug with minimal hepatic and anticholinergic effects.

- Q. How much do you think these expanded uses are worth, and when do you see them coming on-stream?**

That's hard to say. We'd be happy to see Risperdal continue to grow at the rate that it currently is enjoying.

- Q. What about line extensions?**

Risperdal oral solution was introduced in July, and we expect that to expand sales by up to about 10% because of its benefits to a wider range of patients, particularly the elderly, for whom liquid formulations are frequently prescribed, and for patients treated in an acute care setting. In addition, we're working on a Quick-Solv tablet that offers the benefits of oral solution without pipetting and mixing of the drug with flavored drinks; Depot IM injection, which offers advantages in the in the long-term management of chronically psychotic patients; acute IM Injection, for use in emergency settings to gain rapid control of agitated patients; and additional tablet strengths (0.25, 0.5, 6, 8 mg) to increase dosing flexibility, particularly in new patient populations.

- Q. What's the potential for changing your BID dosing to once-daily dosing?**

Approximately 35% of Risperdal use is already once a day, in part because its 20-hour half-life is suitable for such dosing. We're seeking a label change and hope to have that approved by FDA sometime next year.

Cost-Effectiveness

- Q. Wouldn't you be seeing a higher acceptance rate if Risperdal were less expensive?**

Newer medications are going to be more expensive than older ones; the question is which are more cost-effective in helping to reduce overall healthcare costs. We've done some retrospective work and have found considerable cost-effectiveness with Risperdal concerning reductions in hospital stays, physician visits and use of mental health services. We have a published study from May of this year that we can share with you (Saskatchewan study). We're also doing prospective studies that will further validate Risperdal's cost-effectiveness.

- Q. When are your prospective studies going to be made public?**

We plan to have data on our prospective studies later this year.

New Competition

Q: Analysts are predicting that olanzapine is going to have a major impact on the antipsychotic market. How do you think Risperdal will stand up to it?

We're confident that Risperdal will stand up very well and further entrench itself as the leading antipsychotic. Risperdal has demonstrated superior efficacy in both positive and negative symptoms when compared to Haldol; Risperdal also has a strong safety record in over one million patients. We see olanzapine as offering no advantages over Haldol, except in the highest doses for negative symptoms; olanzapine also has some safety issues and side effects which we think will inhibit its prospects.

Q. What kind of safety issues and side effects does olanzapine have?

We think olanzapine has safety issues with regard to liver enzyme elevations (3% discontinuation rate in pivotal N.A. trials), seizures (___% in N.A. trials), and reported weight gain of up to 27 lbs. in long term trials, which can be a significant health risk. In addition to affecting liver function, seizure threshold and weight, olanzapine has sedative effects and anticholinergic effects such as blurred vision, urinary retention and constipation.

Q. The word on the street is that olanzapine is like clozapine -- only safer.

Olanzapine appears to differ from clozapine in three major areas: receptor activity, efficacy and safety. Regarding receptor activity, the two drugs differ significantly in the potency of their action on dopamine-D2 receptors, the receptor subtype that has been most closely associated with antipsychotic effects. Regarding efficacy, whereas clozapine has shown superiority over conventional antipsychotics in treating both positive and negative symptoms, the very large study with olanzapine presented in Puerto Rico at the ACNP failed to show superiority of olanzapine over Haldol in treating positive symptoms, and showed only a minimal advantage for negative symptoms. Regarding safety, olanzapine is known to affect liver function, seizure threshold and weight, and – unlike clozapine – has been associated with EPS and TD in its clinical studies.

Q: How will Janssen maintain Risperdal's market leadership in the face of stiff competition from Lilly and Abbott?

We see Abbott's product, sertindole, as being second-line therapy because of the safety issues that were brought up at the July 15 FDA advisory committee meeting. Although Lilly has been very effective in touting olanzapine, we believe that it will find tough-sledding when it's actually marketed because of its limitations.

JANSSEN



• PHARMACEUTICA •
• RESEARCH FOUNDATION •

August 10, 2000

Russell G. Katz, MD, Director
Division of Neuropharmacological Drug Products/HFD-120
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Attention Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-272, Risperdal® (risperidone) Tablets
NDA 20-588, Risperdal® (risperidone) Oral Solution

**Response to FDA Request for Information: Evaluation of the Effect of Risperidone
on Glucose Metabolism**

Dear Dr. Katz:

Please reference our new drug applications (NDA) for Risperdal (risperidone), and your letter of May 1, 2000, copy enclosed. Your letter requested that Janssen conduct a comprehensive review of all preclinical, clinical and pharmacovigilance data pertaining to the effect of risperidone on disturbances in glucose metabolism. Additionally, we were requested to provide an estimate of patient exposure to Risperdal, copies of correspondence with foreign regulatory agencies regarding this subject, and to possibly collaborate with organizations having large databases for evidence of hyperglycemia or new-onset diabetes mellitus associated with risperidone.

The enclosed submission responds to each of the six items mentioned in your letter. Individual reports have been prepared to address the nonclinical, clinical, pharmacovigilance and epidemiology items identified in your letter. A brief description of the scope of each of these is provided below.

- **Nonclinical:** This report presents tabulations of serum and urine glucose data, and effects on the pancreas from nonclinical toxicity studies in dogs, mice and rats of up to 12, 18, and 25 months durations in dogs, mice and rats, respectively.
- **Clinical:** The report summarizes data from over 11,000 patients in 56 Phase 2 and 3, and 10 Phase 1 worldwide clinical trials encompassing three age groups (pediatric adolescent, adult and geriatric) performed over the last 15 years. A total of 26 Phase 1 trials have been conducted during the clinical development of risperidone. Only trials with multiple dose designs (10) have been included in this evaluation. For some uncontrolled Phase 2-3 trials included in the original NDA, the data were not available in an appropriate database format for inclusion in the combined database.

JANSSEN AT WASHINGTON CROSSING
1125 TRENTON-HARBORLTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200

EXHIBIT	2
WT:	BRANN
DATE:	4.28.98
TERRI SAPP	

Plaintiff Ex. 1728

CONTAINS CONFIDENTIAL COMMERCIAL INFORMATION

C-RISP00000251

- Pharmacovigilance: This report provides an overview of all postmarketing spontaneous adverse event reports on disturbances in glucose metabolism in association with use of risperidone. A total of 202 case reports have been retrieved from the database.
- Epidemiology study: This document, which summarizes data in a combined database from two large health plans, evaluated the risk of new onset diabetes among patients with psychosis who are treated with antipsychotics, while controlling for numerous potential confounding factors.

Information on the final two items in your letter is indicated below.

- Estimate of patient exposure: Worldwide use information indicates that approximately 9.7 million patients have been treated with Risperdal. Total patient exposure to Risperdal is approximately 3.5 million patient-years (see Pharmacovigilance report).
- Correspondence with foreign regulatory agencies: Copies of correspondence with the Swedish Medical Products Agency and the United Kingdom's Medicines Control Agency concerning glucose metabolism are included under the appropriate tab.

Janssen is also including the following documents, which we believe will facilitate your assessment of the impact of Risperdal on disturbances in glucose metabolism.

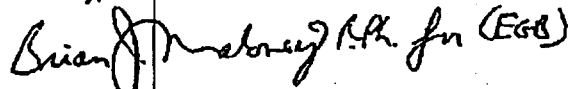
- Integrated summary report: This report provides a brief summary of the findings presented in the nonclinical, clinical, pharmacovigilance, and epidemiology reports.
- Literature review: The review provides a brief summary of the published literature on this topic.

The nonclinical data in dogs, mice and rats do not indicate any risperidone-induced changes in glucose metabolism. Clinical data indicate that there is no evidence that abnormalities of glucose metabolism occurred at a higher rate in patients treated with risperidone compared with those patients treated with placebo. Pharmacovigilance data support the low incidence of abnormalities of glucose metabolism seen in the clinical trial data. The epidemiology report concludes that risperidone, in contrast to olanzapine, clozapine, and high and low potency neuroleptics, has little or no effect on the incidence of type II diabetes. We believe this substantial body of evidence indicates that risperidone is not associated with alterations in glycemic control. Clinical data show that clinically significant weight gain in patients treated with risperidone occurred at rate higher than that for patients treated with placebo, and lower than that observed for patients treated with olanzapine.

Please refer to the comprehensive index for the location of all documents in this submission. In addition, the Clinical Data section includes a list of all Phase 1, 2, and 3 trials included in the review and a reference to the original NDA or supplemental applications to which these reports may have been submitted.

If you have any questions regarding the contents of this submission, please contact me at 609-730-3486.

Sincerely,

A handwritten signature in dark ink, appearing to read "Edward G. Brann" followed by "A.P. for (EGB)".

Edward G. Brann
Assistant Director, Regulatory Affairs
Janssen Research Foundation

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE (Title 21, Code of Federal Regulations, 314 & 601)		Form Approved: OMB No 0910-0138 Expiration Date: April 30, 2000 See OMB Statement on last page
		FOR FDA USE ONLY
		APPLICATION NUMBER
APPLICANT INFORMATION		
NAME OF APPLICANT Janssen Research Foundation		DATE OF SUBMISSION August 10, 2000
TELEPHONE NO. (Include Area Code) (609) 738-3436		FACSIMILE (FAX) Number (Include Area Code) (609) 738-3691
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued) 1125 Trenton-Harbourton Road P.O. Box 200 Titusville, NJ 08560-0200		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE
PRODUCT DESCRIPTION		
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)		20-272
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) risperidone		PROPRIETARY NAME (trade name) IF ANY RISPERDAL®
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one		CODE NAME (if any) R064766
DOSAGE FORM: Tablets	STRENGTHS: 0.25, 0.5, 1, 2, 3, 4 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: Management of the manifestations of psychotic disorders		
APPLICATION INFORMATION		
APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507		
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: _____ Holder of Approved Application: _____		
TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION		
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER		
REASON FOR SUBMISSION Response to FDA Request for Information: Evaluation of the Effect of Risperdal on Glucose Metabolism		
PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED: 2		THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC
ESTABLISHMENT INFORMATION		
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, county, telephone number, registration number (CFR), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.		
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application) NDA 20-588, IND 31.931		

FORM FDA 356b (4/97)

This application contains the following items: (Check all that apply)		
X	1. Index	
	2. Labeling (check one)	Draft Labeling Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))	
	4. Chemistry section	
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)	
X	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)	
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)	
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))	
X	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)	
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)	
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)	
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)	
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)	
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))	
	15. Establishment description (21 CFR Part 600, if applicable)	
	16. Debarment certification (FD&C Act 306 (k)(1))	
	17. Field copy certification (21 CFR 314.5 (k) (3))	
	18. User Fee Cover Sheet (Form FDA 3397)	
	19. OTHER (Specify):	
CERTIFICATION I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following: 1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809. 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202. 5. Regulations on making changes in applications in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12. 6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81. 7. Local, state and Federal environmental impact laws. If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision. The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate. Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT		DATE
 Edward G. Brann, Asst. Dir., Regulatory Affairs		August 10, 2000
ADDRESS (Street, City, State, and ZIP Code)		Telephone Number
1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560-0200		(609) 730-3486
Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:		
DHHS, Reports Clearance Officer Paperwork Reduction Project (0910-0338) Hubert H. Humphrey Building, Room 331-11 200 Independence Avenue, S.W. Washington, DC 20201		An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Please DO NOT RETURN this form to this address		

FORM FDA 356b (4/97)

Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

920 U.S. Highway 202, P.O. Box 300
Raritan NJ 08869

TRANSMITTED VIA FACSIMILE AND FEDEX

April 28, 2004

Thomas W. Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising and Communications
HFD-42, Rm. 8B-45
5600 Fishers Lane
Rockville, MD 20857

**RE: NDA 20-272 and 20-588
RISPERDAL® (risperidone) Tablets and Oral Solution
MACMIS # 12195**

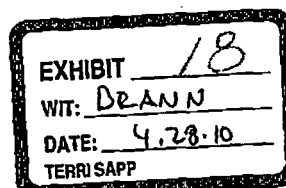
Dear Mr. Abrams:

On behalf of Janssen Pharmaceutica Products L.P. (Janssen), please refer to our approved New Drug Applications, NDA 20-272 and 20-588 for RISPERDAL® (risperidone) Tablets and Oral Solution, and MACMIS # 12195. Reference is also made to the Division of Drug Marketing, Advertising & Communication's (DDMAC) correspondence to Janssen dated April 19, 2004, sent in response to a "Dear Healthcare Provider Letter (DHCP)" disseminated by Janssen on November 10, 2003. We have carefully reviewed your letter of April 19, 2004, and provide our response below.

Janssen and Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) share FDA's interest in accurate and timely communication of labeling changes to the healthcare community. Janssen and J&JPRD received the Division of Neuropharmacological Drug Products' (DNDP) letter of September 11, 2003 to all manufacturers of atypical antipsychotics requesting that labeling for all atypical antipsychotics, including RISPERDAL, be updated to include information about diabetes mellitus adverse events. Within three days, Janssen and J&JPRD contacted DNDP to request an opportunity to discuss the proposed class labeling.

On November 6, 2003, after several correspondences between J&JPRD and DNDP regarding the proposed class labeling, which led to agreement on modified class labeling, J&JPRD submitted a "Special Supplement - Changes Being Effected" ("Special Supplement") to provide for changes in the WARNINGS section of the RISPERDAL® labeling. Immediately thereafter, with the goal of informing health care professionals in a timely manner regarding these labeling changes, Janssen voluntarily issued, to healthcare providers, the November 10, 2003 DHCP communication.

On November 21, 2003, DNDP approved our Special Supplement and at that time requested that Janssen issue a "Dear Health Care Professional" letter regarding the addition of language relative to hyperglycemia and diabetes mellitus to the WARNING section of the prescribing information for RISPERDAL®. On November 26, 2003, J&JPRD informed DNDP that a medical communication with this purpose was previously sent on November 10 and provided a copy of the letter to DNDP at that time.



PRD-18

NDA #20-272, 20-588
MACMIS # 12195

Regarding your assertions of omission of material information and minimization of risks/misleading comparative claims, it is important to note that the November 10, 2003 communication contained a copy of the complete prescribing information for RISPERDAL containing the updated, FDA approved, WARNING language on hyperglycemia related events, with a prominent reference to the full prescribing information in the body of the DHCP letter.

Based upon Janssen's comprehensive review of the data pertaining to risperidone¹, we have a differing view of the data on Risperdal and diabetes mellitus. However, we acknowledge the Agency's position.

Notwithstanding our differing views, in order to address your concerns, we agree to do the following. With your agreement, we will send the attached proposed DHCP letter (Attachment A) pursuant to 21 CFR 200.5 (c)(1) to the same audience that received the November 10, 2003 communication. Please be aware that the November 10, 2003 letter is no longer being disseminated. In addition, we are providing as attachment B, pursuant to your request, a list of current RISPERDAL promotional materials containing same or similar claims to those addressed in your April 19, 2004 letter, all of which are discontinued.

With regard to submission pursuant to post marketing requirements, we considered the November 10, 2003, letter a medical communication informing healthcare providers of an important change to labeling, and therefore did not consider it subject to 21 CFR 314.81(b)(3)(i). However, we acknowledge your position and will modify future submissions accordingly.

We trust that this letter adequately responds to your April 19 letter and we look forward to resolving this matter in a timely fashion. Should you have any questions, please contact James Burrus at 609-730-3617.

Sincerely,



Donna Ohye
Senior Director, Advertising and Promotion
Global Regulatory Affairs and Quality Assurance
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Attachments

¹ Including the eight published studies cited in the November 10 DHCP letter and other epidemiology, physiology, clinical trial and pharmacovigilance data (data submitted to DNDP 3/29/04)

Attachment A

[insert date]

Dear Health Care Provider,

Janssen Pharmaceutica Products L.P., makers of RISPERDAL®(risperidone), distributed a "Dear Healthcare Provider" letter dated November 10, 2003, notifying you that the product labeling for RISPERDAL had been updated to include a WARNING regarding hyperglycemia and diabetes mellitus. FDA has informed us of their view that this letter was misleading, in part due to omission in the letter of certain information, and the inclusion of certain other information. FDA has requested us to further clarify the new WARNING information, which is provided below:

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 to the FDA MedWatch program by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), or by email (www.fda.gov/medwatch).

Sincerely,

Ramy A. Mahmoud, MD, MPH
Vice President, CNS
Janssen Medical Affairs, LLC

Attachment B

The following promotional items have been discontinued in accordance with the requested action.

Bipolar Mania Promotion aides:

- 01-RS-1374-PCP/CNS, 01-RS-1404, 01-RS-1377, 01-RS-1440,

Managed Care Promotional aide template: (Note: These are identical excluding the managed care plan name)

- 01-RS-MAN- (338, 349, 229, 252, 272, 278, 279, & 281)

Reprint Carriers & Reprint & Speaker Slide Kit:

- 01-RS-1433, 01-RS-1200R1, 01-RS-146101-RS-1126, 01-RS-1385

Exhibit Panels

- 01-RS-1290E, 01-RS-1299A

JANSSEN



PHARMACEUTICA INC.

November 10, 2003

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 research¹⁻³ 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.

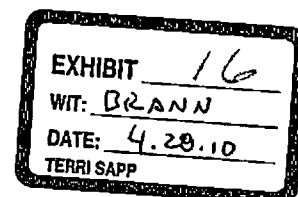
For additional information about RISPERDAL or any other Janssen product, please call 1-800-JANSSEN (526-7736) from 9AM to 5PM EST, Monday through Friday.

Sincerely,

Ramy Mahmoud, MD
Vice President CNS Medical Affairs
Janssen Pharmaceutica, Inc.

1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200
(609) 730-2000

US.JANSSEN.COM



References:

1. Buse JB, Cavazonni P, Hombuckle 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. *Glin 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, Alarcón RD et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry* 2002;159:561-566.

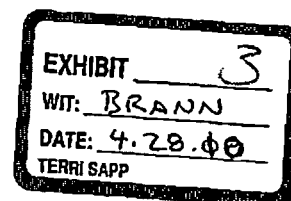
Janssen Research Foundation

NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

JANSSEN RESEARCH FOUNDATION
a division of Janssen Pharmaceutica N.V.

INTEGRATED SUMMARY REPORT	
R - number:	R064766
Report No.	EDMS-BEBE-1788252
Title:	Integrated Summary of the effects of risperidone on glucose metabolism and weight.
Authors:	G. De Smedt ¹ , M.D., R. Mahmoud ² , M.D., A. Grogg ² , PharmD., and A. Derivan ¹ , M.D.
Department:	¹ Global Clinical Research and Development and Regulatory Affairs, Worldwide; ² CNS US Medical Affairs



CONFIDENTIALITY STATEMENT

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Volume 1/Page 15

Plaintiff Ex. 1741

CONTAINS CONFIDENTIAL COMMERCIAL INFORMATION

C-RISP00000243

Janssen Research Foundation

NDA 20-272 and 20-388

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

Integrated Summary

2

TABLE OF CONTENTS

1.	INTRODUCTION.....	3
2.	NONCLINICAL STUDIES.....	3
3.	CLINICAL STUDIES.....	4
	3.1. Glucose metabolism.....	4
	3.2. Body weight.....	5
4.	PHARMACOVIGILANCE DATA.....	8
5.	EPIDEMIOLOGICAL RESEARCH.....	8
6.	EVALUATION OF PUBLISHED LITERATURE.....	9
7.	OVERALL CONCLUSIONS.....	10
8.	REFERENCES.....	11

Volume 1/Page 16

Integrated Summary

3

1. INTRODUCTION

A growing number of publications report an increased frequency of diabetes or glucose intolerance in patients treated with some atypical antipsychotics¹⁻³. Indications that antipsychotic drug treatment may cause or contribute to glucose intolerance have been reported for conventional neuroleptics, including chlorpromazine⁴, loxapine⁵ and amoxapine⁵. Recently, clozapine⁶⁻¹⁶ and olanzapine¹⁷⁻²¹, have been linked to glucose intolerance and reports of an association between quetiapine²¹ and diabetes have also emerged. Even more recently, the FDA's Division of Neuropharmacologic Drug Products, in response to an apparent increase in spontaneous reports of glucose intolerance during treatment with atypical antipsychotic agents, has asked sponsors for a summary of their relevant data.

It has been suggested that the increase in diabetes risk in clozapine- and olanzapine-treated patients with schizophrenia is not adequately explained by weight gain alone, and that suppression of insulin release, insulin resistance or impairment of glucose utilization are implicated as potential factors.

In contrast, the risperidone nonclinical, clinical, and pharmacovigilance databases reveal no suggestion of an increased risk related to diabetes or other disturbances in glucose metabolism.

The following sections summarize the nonclinical, clinical and pharmacovigilance data available for risperidone regarding the occurrence of diabetes and other disturbances in glucose metabolism as well as the clinical data regarding changes in body weight. An evaluation of published literature and data from an epidemiological study investigating the incidence of Type II diabetes and association with antipsychotic exposure among patients from large health plans in two states in the US, have been added for completeness.

2. NONCLINICAL STUDIES

A number of repeated-dose toxicity trials²² have been performed in mice, rats and dogs. Serum and urine levels of glucose were determined and a macroscopic and histological examination of the pancreas was performed.

Mice were dosed with risperidone (up to 10 mg/100g food), orally through the diet, in a 3-month toxicity study and in an 18-month carcinogenicity study. Rats were dosed with risperidone (up to 10 mg/kg/day or up to 10 mg/100g food), orally by gavage or through the diet, in 1-month, 3-month, 3-month with 1-month recovery period and 12-month repeated-dose toxicity studies and in a 25-month carcinogenicity study. In both species, no changes in urine glucose levels, and decreases instead of increases in serum glucose levels, were seen. Minor histological changes in the rat and mouse pancreas were considered prolactin-mediated, rodent-specific effects.

Dogs were dosed with risperidone (up to 5 mg/kg/day) orally during 1-month, 3-month, 3-month with 2-month recovery period and 12-month toxicity studies. Neither

Integrated Summary

4

changes in serum and urine glucose levels nor any effect on the pancreas were observed.

Therefore, it can be concluded that the current nonclinical data in dogs, mice and rats do not indicate any risperidone-induced glucose metabolism-related changes nor any related effects on the endocrine pancreas.

3. CLINICAL STUDIES

3.1. Glucose metabolism

Analysis of the risperidone database²³ through March 31, 2000, showed no excess in glucose-related adverse events compared with placebo.

A total of 11727 subjects, including 8415 nonelderly adults, 1797 elderly and 417 pediatric subjects, were enrolled in different clinical programs. Of these subjects, 8907 were treated with risperidone.

In the short-term trials (12 weeks or less), the incidence of glucose-related adverse events was very low with risperidone treatment (0.62% of 5330 subjects) and comparable to, if not lower than, with placebo (0.81% of 868 subjects). Compared with risperidone and placebo, olanzapine showed a somewhat higher (0.89% of 448 patients) incidence of adverse events, whereas haloperidol and other neuroleptics (0.28% of 712 patients and 0.34% of 293, respectively) were associated with fewer events (Table 1).

Table 1: Incidence (number of patients and %) of adverse events related to abnormalities in glucose metabolism in short-term Phase 2-3 trials

	Placebo ^a N=868	Risperidone ^a N=5330	Haloperidol ^b N=712	Olanzapine ^c N=448	Other Neuroleptics ^{cd} N=293
Any glucose-related adverse event	7 (0.81%)	33 (0.62%)	2 (0.28%)	4 (0.89%)	1 (0.34%)
Blood sugar increased	0	2 (0.04%)	0	0	0
Coma, diabetic ^e	0	1 (0.02%)	0	0	0
Diabetes mellitus	1 (0.12%)	4 (0.08%)	0	1 (0.22%)	1 (0.34%)
Diabetes mellitus aggravated	0	2 (0.04%)	0	0	0
Glycosuria	0	0	0	1 (0.22%)	0
Hyperglycaemia	5 (0.58%)	20 (0.38%)	2 (0.28%)	3 (0.67%)	0
Hypoglycaemia	1 (0.12%)	7 (0.13%)	0	0	0
Ketosis	0	1 (0.02%)	0	0	0
Plasma osmolality increased	0	1 (0.02%)	0	0	0

^a Trials included 3 populations: adults (18-65 years), elderly (>65 years) and pediatric subjects (<18 years); ^b Trials included 2 populations: adults (18-65 years) and elderly (>65 years); ^c Trials included 1 population: adults (18-65 years).

^d Other neuroleptics included zuclopentixol, perphenazine, remoxipride, clozapine, methotimprazine.

^e Although originally coded as "coma diabetic", this elderly patient (#1204) experienced hyperglycaemia with a hyperosmolar non-ketotic state as a complication of urinary sepsis and acute renal failure.

In long-term trials (6 months or longer), there was a lower incidence of glucose-related adverse events with risperidone treatment (1.30% of 3072 subjects) than with

Integrated Summary

5

haloperidol treatment (2.98% of 302 subjects) (Table 2). Among 234 patients treated with other neuroleptics, there were no glucose-related adverse events. There were no long-term, double-blind trials with placebo or olanzapine.

Table 2: Incidence (number of patients and %) of adverse events related to abnormalities in glucose metabolism in long-term Phase 2-3 trials

	Risperidone ^a N=3072	Haloperidol ^b N=302	Other Neuroleptics ^{b,c} N=234
Any glucose-related adverse event	40 (1.30%)	9 (2.98%)	0
Acidosis	1 (0.03%)	0	0
Diabetes mellitus	11 (0.36%)	5 (1.66%)	0
Glycosuria	2 (0.07%)	0	0
Hyperglycaemia	23 (0.75%)	5 (1.66%)	0
Hypoglycaemia	5 (0.16%)	1 (0.33%)	0
Ketosis	1 (0.03%)	0	0

^a Trials included 3 populations: adults (18-65 years), elderly (>65 years) and pediatric subjects (<18 years);

^b Trials included 1 population: adults (18-65 years);

^c Other neuroleptics included zuclopenthixol, perphenazine, remoxipride, clozapine, methotimprazine

This information derived from 11727 subjects (8907 subjects who received risperidone), supports the conclusion that risperidone is indistinguishable from placebo in terms of the percentage of individuals with abnormalities in glucose metabolism. Specifically, there is no evidence of an excess of serious or nonserious reports of any type of glucose metabolism abnormality, including new-onset diabetes, hyperosmolar coma, diabetic ketoacidosis or hyperglycemia.

3.2. Body weight

Body weight changes were analyzed as adverse events, mean changes from baseline, and the incidence of body weight increases $\geq 7\%$ of baseline weight²³.

Analysis of the adverse events in the risperidone database through March 31, 2000, showed little difference between risperidone and placebo treatment regarding subjects spontaneously reporting weight gain.

In the short-term trials, 1.39% of 5330 patients treated with risperidone reported weight gain as an adverse event compared to 0.92% of the 868 placebo patients. The incidence with haloperidol was 1.26% (of 712 patients), and with other neuroleptics it was 0.34% (of 293 patients). The highest incidence of weight gain adverse events was seen in the olanzapine-treated patients (9.38% of 448 patients) (Table 3).

Table 3: Weight increase reported as an adverse event in Phase 2-3 trials

	Placebo n/N (%)	Risperidone n/N (%)	Haloperidol n/N (%)	Olanzapine n/N (%)	Other Neuroleptics ^a n/N (%)
Short-term trials	8/868 (0.92)	74/5330 (1.39)	9/712 (1.26)	42/448 (9.38)	1/293 (0.34)
Long-term trials	-	95/3072 (3.09)	5/302 (1.66)	-	1/234 (0.43)

^a Other neuroleptics included zuclopenthixol, perphenazine, remoxipride, clozapine, methotimprazine

Integrated Summary

6

In long-term trials, the incidence with risperidone treatment was 3.09 % (of 3072 patients) relative to 1.66% (of 302 patients) with haloperidol and 0.43% with other neuroleptic treatment. There were no long-term trials with placebo or olanzapine.

Body weight changes were also analyzed in terms of the incidence of body weight increases $\geq 7\%$ of baseline weight. A 7% weight gain is the equivalent to a gain of approximately 5 kg in a 70 kg individual, and is a commonly quoted standard for clinically meaningful weight gain in adults. Since growth and weight gain would be expected in patients younger than 18 years, any discussion of this age group should take into account the natural weight gain. According to the National Center for Health Statistics (NCHS) percentiles²⁴, the annual expected weight gain for an 8-year-old male of 34.6 kg (the average age and baseline weight for risperidone-treated pediatric/adolescent patients in the long-term trial) is 5.1 kg. This corresponds with a weight gain of 14.7%. The standard of 7% as the definition for clinically meaningful weight gain is therefore not appropriate for children.

Table 4 summarizes the clinically relevant weight changes ($\geq 7\%$ of baseline weight) in short- and long-term trials in the risperidone adult and elderly programs. The incidence of clinically significant weight gain in the short-term trials in adults was greater in the risperidone group (12.5%) than in the placebo group (7.2%). Table 4 also illustrates the incidence of clinically significant weight gain for haloperidol (7.9%), olanzapine (26.7%) and other neuroleptics (12.9%). In long-term trials, the incidence of clinically significant weight gain with risperidone treatment was 19.9 % relative to 3.2% with haloperidol treatment. It should be recognized that individual patients treated with haloperidol were treated for a shorter duration than were most patients treated with risperidone. Weight data was not available for long-term trials with other neuroleptics.

Table 4: Incidence of body weight increase $\geq 7\%$ in subjects >18 years

Treatment	% patients gaining $\geq 7\%$ of baseline weight	
	18-65 years	>65 years
Short-term trials		
Placebo	7.2%	6.2%
Risperidone	12.5%	10.6%
Haloperidol	7.9%	4.6%
Olanzapine	26.7%	-
Other neuroleptics ^a	12.9%	-
Long-term trials		
Risperidone	19.9%	14.8%
Haloperidol	3.2%	-

^a Other neuroleptics included zuclopentixol, perphenazine, remoxipride, clozapine, methotimprazine

Among elderly patients, the incidence of clinically significant weight gain in the short-term trials was greater in the risperidone group (10.6%) than in the placebo group (6.2%) or the haloperidol group (4.6%) (Table 4). No comparisons between treatment groups can be made for the long-term trials.

Integrated Summary

7

Finally, body weight changes were analyzed in terms of mean changes from baseline. Table 5 summarizes the mean weight changes in short- and long-term trials in the risperidone adult, elderly and pediatric/adolescent programs. The mean weight gain in the short-term trials in adults was greater in the risperidone group (1.3 kg) than in the placebo group (0.2 kg). Table 5 also illustrates the weight gain for haloperidol (0.1 kg), olanzapine (3.2 kg) and other neuroleptics (1.0 kg). In long-term trials, the mean weight gain with risperidone treatment was 1.8 kg relative to 0.1 kg with haloperidol treatment.

Table 5: Mean $\pm$ SD weight change from baseline at endpoint

	Mean $\pm$ SD weight change (kg) from baseline to endpoint		
	<18 years	18-65 years	>65 years
Short-term trials			
Placebo	0.57 $\pm$ 1.67	0.17 $\pm$ 3.76	-0.31 $\pm$ 3.35
Risperidone	2.13 $\pm$ 1.87	1.32 $\pm$ 3.66	0.37 $\pm$ 3.08
Haloperidol	-	0.07 $\pm$ 3.34	-1.17 $\pm$ 3.52
Olanzapine	-	3.21 $\pm$ 4.45	-
Other neuroleptics*	-	0.96 $\pm$ 3.28	-
Long-term trials			
Risperidone	5.48 $\pm$ 4.51	1.76 $\pm$ 5.66	0.25 $\pm$ 4.34
Haloperidol	-	0.06 $\pm$ 2.41	-

* Other neuroleptics included zuclopenthixol, perphenazine, remoxipride, clozapine, methotrimeprazine.

In the short-term trials in elderly, the mean increase in weight was 0.4 kg for risperidone-treated patients; in the same trials, the mean weight change in placebo-treated patients was a loss of 0.3 kg, compared to a loss of 1.2 kg for haloperidol patients (Table 5). No comparisons between treatment groups can be made for the long-term trials.

Evaluation of drug-related weight change over time in a pediatric/adolescent population needs to take into account the natural growth of subjects. Since there were no long-term trials in this population using placebo, comparisons with placebo are restricted to the short-term trials. In the short-term trials, the mean increase in body weight from baseline was 2.1 kg for risperidone-treated pediatric/adolescent patients; in the same trials, the mean weight increase in placebo-treated pediatric/adolescent patients was 0.6 kg.

During long-term trials in pediatric subjects, a weight increase of 5.5 kg was seen for risperidone. According to the National Center for Health Statistics (NCHS) percentiles²⁴, the annual expected weight gain for an 8-year-old male of 34.6 kg (the average age and baseline weight for risperidone-treated pediatric/adolescent patients in the long-term trial) is 5.1 kg. With respect to long-term treatment, only observed annual gains greater than that amount could be attributed to treatment.

In summary, results regarding weight gain from 11727 subjects showed that risperidone-treated patients demonstrated a higher incidence of clinically significant weight gain than patients receiving placebo, but a lower incidence of clinically significant weight gain than olanzapine-treated patients.

Integrated Summary

8

4. PHARMACOVIGILANCE DATA

The currently available cumulative spontaneously reported safety data in the international safety database²⁵ (through 31 March, 2000) do not point to a relationship between the use of risperidone and disturbances of glucose homeostasis.

Spontaneous case reports have been retrieved, that include WHO-ART dictionary codes indicative of disturbances in the glucose homeostasis of 202 patients (1.26% of a total of 16,062 spontaneous adverse event reports). Of these 202 patients, 41 had newly recognized diabetes, 60 had pre-existing diabetes, 26 had no information on the onset of their diabetes, and 75 had no concise diagnosis of the underlying cause of the glucose homeostasis disturbance.

Given the extensive cumulative exposure to risperidone -estimated at 3,541,514 patient-years (through 31 March, 2000) and with reference to data in the literature, the total of 41 cases of possible newly recognized diabetes cases can be considered to be low. Even if the worst-case scenario is adopted, meaning that all 202 patients with reported disturbed glucose homeostasis are considered to have newly recognized diabetes, the reported incidence of diabetes with risperidone-exposure remains low.

It can be concluded that the currently available cumulative spontaneous safety data do not point to a relationship between the use of risperidone and disturbances in glucose metabolism.

5. EPIDEMIOLOGICAL RESEARCH

An analysis was performed of the data from two large third-party mixed indemnity and managed care databases in the US²⁶ encompassing greater than 2,000,000 covered lives. A total of 7933 subjects with psychosis were identified for analysis of Type II diabetes incidence, controlling for a number of important potential confounding factors. Results showed risperidone to have little or no diabetic effect in contrast with other antipsychotics including olanzapine, clozapine and high- and low-potency conventional neuroleptics.

Comparisons among five antipsychotic categories suggest that the association with Type II diabetes varies considerably depending on the specific antipsychotic therapy. Odds ratios for risperidone, while higher than those for untreated psychotics, are invariably much lower than those for olanzapine. Comparison with clozapine is limited by the small number of psychotics treated with this medication. Logistic regression was used to determine the odds ratios for each antipsychotic versus untreated psychotic subjects per month of observation period. These have been adjusted to demonstrate odds ratios per 12 months of exposure (Table 6). Confounding factors included in the logistic model are: age, sex, observation period (months), dosage (standardized mg/day), other psychotropic drugs, concurrent antipsychotics, type of insurance coverage, and diagnosis. The odds ratios for risperidone versus untreated patients are close to or less than '1' depending on the patient population included, while those for the other antipsychotics are statistically significantly higher

Table 6: Odds of diabetes among treated psychotic patients for 12 months of exposure versus untreated patients

	Excluding patients with pre-existing diabetes prior to observation at:		
	4 months	6 months	8 months
Risperidone	1.256	1.235	0.791
Olanzapine	2.427*	2.544*	2.448*
High potency neuroleptics	1.704*	1.647**	1.987*
Low potency neuroleptics	1.946*	2.596*	3.214*
Clozapine	2.422**	4.018*	6.699*

**p < 0.05; *p < 0.1

Logistic regression was also used to determine the odds ratios for each of the other antipsychotics versus risperidone at 6.8 months of treatment, the average treatment duration across all antipsychotics (Table 7). All antipsychotics demonstrated higher odds ratios for diabetes than risperidone.

Table 7: Odds of diabetes among treated psychotic patients at 6.8 months of exposure versus risperidone

	Excluding patients with pre-existing diabetes prior to observation at:		
	4 months	6 months	8 months
Risperidone	1	1	1
Olanzapine	1.457	1.460	1.767
High potency neuroleptics	1.187	1.158	1.595
Low potency neuroleptics	1.283	1.477	2.033
Clozapine	1.457	1.856	2.960

Epidemiological data suggest that some antipsychotic drugs including olanzapine, clozapine and some conventional antipsychotics are more associated with (Type II) diabetes risk than risperidone

6. EVALUATION OF PUBLISHED LITERATURE

A critical, worldwide review of the published literature concerning diabetes as it pertains to psychosis and antipsychotic treatment was prepared for Janssen Research Foundation by an external expert on diabetes¹. A copy of this report is provided in this submission, and the review is summarized below.

The limited body of evidence available tends to suggest that diabetes or ketoacidosis may be a possible consequence of antipsychotic drug treatment. Publications to date are predominantly concerned with two chemically related drugs: clozapine and olanzapine. There are few published reports of diabetes problems in association with risperidone^{25,27}, despite its substantially larger patient-time exposure compared with some other antipsychotic drugs.

An effect of antipsychotic drugs on diabetes independent of their effect on body weight may exist¹. There appears to be qualitative (ie, severity of effect) and quantitative (ie, risk of effect) variability among antipsychotic treatments and

Integrated Summary

10

patients. This may relate to specific patient or drug factors. Some patients may develop impaired insulin release while others may develop peripheral tissue insulin resistance.

It is clear that further research is required, including careful metabolic studies in subjects with an appropriate range of baseline conditions. We are aware of two researchers who have publicly presented interim data from metabolic studies, but no study reports have been published^{28, 29}.

7. OVERALL CONCLUSIONS

- There is a substantial body of evidence from nonclinical, clinical and pharmacovigilance data that risperidone treatment is not associated with induction of glucose intolerance/diabetes.
- Epidemiological data suggest that the risk for Type II diabetes is different for different antipsychotics and that it is lower with risperidone than with other antipsychotics including olanzapine, clozapine and some high- and low-potency conventional neuroleptics.
- Clinical data show that clinically significant weight gain in patients treated with risperidone occurred at a rate higher than that for patients treated with placebo, and lower than that observed for patients treated with olanzapine.

8. REFERENCES

1. Ipp E. Atypical antipsychotics and diabetes: a review. Summary report, August 2000.
2. Goldstein LE, Henderson DC. Atypical Antipsychotic Agents and Diabetes Mellitus. *Primary Psychiatry* 2000; 7 (5) : 65-68.
3. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel Antipsychotics and New Onset Diabetes. *Biol Psychiatry* 1998; 44 : 778-783.
4. Eric G, Basso M, Federspil G, et al. Effect of Chlorpromazine on Blood Glucose and Plasma Insulin in Man. *Europ J Clin Pharmacol* 1977; 11 : 15-18.
5. Tollefson G, Lesar T. Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. *J Clin Psychiatry* 1983; 44: 347-348.
6. Henderson DC, Caglicio E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities : a five-year naturalistic study. *Am J Psychiatry* 2000; 157 : 975-981
7. Maule S, Giannella R, Lanzio M, et al. Diabetic ketoacidosis with clozapine treatment. *Diabetes Nutr Metab* 1999; 12 : 187-8.
8. Colli A, Cocciolo M, Francobandiera F, et al. Diabetic ketoacidosis associated with clozapine treatment. *Diabetes Care* 1999; 22 : 176-177.
9. Yazici KM, Erbas T, Yazici AH, et al. The effect of clozapine on glucose metabolism. *Exp Clin Endocrinol Diabetes* 1998; 106 : 475-477.
10. Al D, et al. Diabetic ketoacidosis and clozapine. *Postgrad Med J* 1998; 74 : 493-494.
11. Thompson J, Chengappa KN, Good CB, et al. Hepatitis, hyperglycemia, pleural effusion, eosinophilia, hematuria and proteinuria occurring early in clozapine treatment. *Int Clin Psychopharmacol* 1998; 13 : 95-98
12. Melkersson KI, Hulting AL, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. *J Clin Psychiatry* 1999; 60 : 783-791.
13. Kostakoglu AE, Yazici KM, Erbas T, et al. Ketoacidosis as a side-effect of clozapine : a case report. *Acta Psychiatr Scand* 1996; 93 : 217-218
14. Koval MS, Rames LJ, Christie S. Diabetic ketoacidosis associated with clozapine treatment. *Am J Psychiatry* 1994; 151 : 1520-1521
15. Peterson GA and Byrd SL. Diabetic ketoacidosis from clozapine and lithium cotreatment. *Am J Psychiatry* 1996; 153 : 737-738.
16. Popli AP, Konicki PE, Jurjus GJ, et al. Clozapine and associated diabetes mellitus. *J Clin Psychiatry* 1997; 58 : 108-111
17. Von Hayek D, Huul V, Reiss J, et al. Hyperglycemia and ketoacidosis associated with olanzapine. *Nervenarzt* 1999; 70 : 836-837
18. Gatta B, Rigalleau V, Gin H. DKA with olanzapine treatment. *Diabetes Care* 1999; 22 : 1002-1003

Integrated Summary

12

19. Goldstein LE, Sporn J, Brown S, et al. New onset diabetes mellitus and DKA associated with olanzapine treatment. *Psychosomatics* 1999; 40 : 438-442.
20. Fertig MK, Brooks VG, Shelton PS, et al. Hyperglycemia associated with olanzapine. *J Clin Psychiatry* 1998; 59 : 687-689.
21. Sobel M, Jagger ED, Franz MA. New-onset diabetes mellitus associated with the initiation of quetiapine treatment. *J Clin Psychiatry* 1999; 60 (8) : 556-557.
22. Verstynen B, Lampo A, Coussemant W. Risperidone: Preclinical observation of glucose metabolism-related changes. Non-clinical Summary Report, July 2000.
23. De Smedt G, Ding D, Meyvisch P, Hoffman K, Masukawa L, Rosenberg J, Derivan A, Caers L. Evaluation of the effects of risperidone on glucose metabolism and weight in Phase 1-3 trials. Clinical Summary Report, August 2000.
24. Hamill PV, Drizd TA, Johnson CL, Reed RB, Rock AF, Moore WM. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr* 1979; 32: 607-629.
25. De Deene A, Van Tittelboom T. Reported disturbances in the glucose metabolism with risperidone: a post-marketing review. International Pharmacovigilance Report, June 2000.
26. Gianfrancesco F, Markowitz J, Grogg A. Antipsychotic and Type II diabetes. Janssen Research Report, July 2000.
27. Croarkin PE, Jacobs KM, Bain BK. Diabetic ketoacidosis associated with risperidone treatment? *Psychosomatics* 2000; 41(4):369-370.
28. Henderson DC, Cagliero E, Borba CP, Hayden DL, Schoenfeld DA, Goff DC. Atypical antipsychotic agents and glucose metabolism: Bergman's MINMOD analysis. NCDEU 40th Annual Meeting, May 30 - June 2, 2000, Boca Raton, Florida. Poster Abstracts: No 128.
29. Newcomer JW, Melson AK, Selke G, Fucciola R, Schweiger JA. Antipsychotic-related change in glucose metabolism. American Psychiatric Association, 200th Annual Meeting, May 13-18, 2000, Chicago. New Research Abstracts: NR660.

Janssen Research Foundation

NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

SIGNATURE OF JRF RESPONSIBLE MEDICAL OFFICER

JRF Integrated Summary Report	
Title	Integrated Summary of the effects of risperidone on glucose metabolism and weight.
Authors	G. De Smedt, M.D., R. Mahmoud, M.D., A. Grogg, PharmD., and A. Derivan, M.D.

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of this investigation.



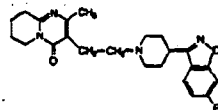
G. De Smedt, M.D.
Clinical Project Scientist
Global Clinical R&D and Regulatory Affairs, Worldwide, CNS

8 August 2000



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-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{26}H_{28}FNO$, 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 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 (K_i 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 H₁ histaminergic receptors. RISPERDAL® antagonizes other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (K_i of 47 to 253 nM) for the serotonin $5HT_{1A}$, $5HT_{1B}$, and $5HT_{1C}$ receptors, weak affinity (K_i of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-6}$ 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 P₄₅₀ 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 cytochrome P₄₅₀ 2D₆, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. Cytochrome P₄₅₀ 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 low 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 P₄₅₀ 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 cytochrome P₄₅₀ 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 -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 μ g/mL), warfarin (10 μ g/mL) and carbamazepine (10 μ g/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 -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 (6- 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.

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 hyperreflexia, 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 α -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 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 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 premarketing 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 Medications: 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 P₂ and Other P₂ Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome P₂, 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 P₂ isozymes, including 1A1, 1A2, 1C9, 1P, and 1A4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome P₂: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome P₂. 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 (16 mg/day) 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/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)
	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland neoplasms, Total				

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 or 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 mutagenicity 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. Sprague-Dawley and Wistar rats and in one Segment I 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. 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 orgasmic 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. Patient 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: Treatment-Emergent Adverse Experience Incidence in 6- to 8-Week Controlled Clinical Trials*

Body System/ Preferred Term	RISPERDAL®		Placebo (N=142)
	≤10 mg/day (N=324)	16 mg/day (N=77)	
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†	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 System/ Preferred Term	RISPERDAL®		Placebo (N=142)
	≤10 mg/day (N=324)	16 mg/day (N=77)	
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%

* 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, 4, 8, 16, and 32 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, organic dysfunction, asthenia/asthene/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: 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 listings that follow); 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, enucation, 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, photophobia, 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, hyperglycemia, 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*, 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, 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 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.

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® overdose 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 hypernatremia, 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® overdose, with estimated doses of up to 350 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 overdose, 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. 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 5048-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 5048-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 5048-330-50.

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 100 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.

US Patent 4,804,663

7503213

July 1996, September 1996



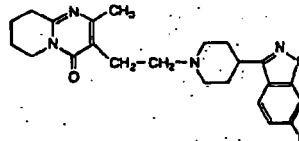
RISPERDAL®

(RISPERIDONE) TABLETS

7503205

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-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® 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 (K_i 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 (K_i of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (K_i of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-6}$ 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 $P_{450}1D_6$ 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 $P_{450}1D_6$, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. Cytochrome $P_{450}1D_6$ 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 $P_{450}1D_6$ 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 $P_{450}1D_6$. 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 μ g/mL), warfarin (10 μ g/mL) and carbamazepine (10 μ g/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 (6- 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.

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 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 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 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. 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 clobazepam with risperidone may decrease the clearance of risperidone.

Drugs that Inhibit Cytochrome P₄₅₀1D₂ and Other P₄₅₀ Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome P₄₅₀1D₂, 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 P₄₅₀ isozymes, including 1A1, 1A2, 1C3, MP, and 11A4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome P₄₅₀1D₂: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome P₄₅₀1D₂. 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/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/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. 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 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 orgasmic 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 Trials¹

Body System/ Preferred Term	≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric Disorders			
Insomnia	26%	23%	18%
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	2.8
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, orgasmic dysfunction, asthenia/fatigue/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: 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, hyposensitivity, tongue paralysis, leg cramps, tonic-clonus, 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*, 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, leukopenia, 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, atrial fibrillation, cerebrovascular disease, diabetes mellitus aggravated, hypothermia, intestinal obstruction, jaundice, mania, Parkinson's disease aggravated, pulmonary embolism, sudden death.

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 beryllium 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. 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.

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
December 1994, April 1995



JANSSEN
PHARMACEUTICA
Titusville, NJ 08560

JANSSEN**PHARMACEUTICA INC.**

XX-November-2003

Dear Healthcare Provider,

Janssen Pharmaceutica Products, L.P., has been notified by the U.S. Food and Drug Administration (FDA) that they have requested updated product labeling for all atypical antipsychotics to include a warning regarding hyperglycemia and diabetes. This requested update applies to RISPERDAL® (risperidone) as well as ABILIFY™ (aripiprazole, Bristol-Myers Squibb), CLOZARIL® (clozapine, Novartis), GEODON® (ziprasidone, Pfizer), SEROQUEL® (quetiapine, AstraZeneca), and ZYPREXA® (olanzapine, Eli Lilly and Company).

As a result of the FDA's request, the RISPERDAL prescribing information has been updated with the addition of the following information:

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.

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.

1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200
(609) 730-2000

us.janssen.com

EXHIBIT

Palumbo-13
12-13-10 370

JANSSEN



PHARMACEUTICA INC.

Janssen Pharmaceutica Products, L.P., remains committed to providing you with the most current product information available for the management of your patients. Please refer to the enclosed package insert for full prescribing information. As always, we request that serious adverse events be reported to Janssen at 1-800-JANSSEN (525-7736) or to the FDA MedWatch Program by phone 1-800-FDA-1088, by fax (1-800-FDA-0178), or by email (www.fda.gov/medwatch). For additional medical information about RISPERDAL or any other Janssen product, please call 1-800-JANSSEN (525-7736) from 9AM to 5PM EST, Monday through Friday.

Sincerely,

Christine Cote, MD
Vice President Medical Affairs
Janssen Pharmaceutica Inc.

1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200
(609) 730-2000

us.janssen.com

JJRE 08978941

Confidential/Produced in Litigation Pursuant to Protective Order

R. 3789

JANSSEN**PHARMACEUTICA INC.**

XX-November-2003

Dear Healthcare Provider,

Janssen Pharmaceutica Products, L.P., has been notified by the U.S. Food and Drug Administration (FDA) that they have requested updated product labeling for all atypical antipsychotics to include a warning regarding hyperglycemia and diabetes. This requested update applies to ABILIFY™ (aripiprazole, Bristol-Myers Squibb), CLOZARIL® (clozapine, Novartis), GEODON® (ziprasidone, Pfizer), SEROQUEL® (quetiapine, AstraZeneca), and ZYPREXA® (olanzapine, Eli Lilly and Company), as well as RISPERDAL® (risperidone).

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.

For additional medical information about RISPERDAL or any other Janssen product, please call 1-800-JANSSEN (526-7736) from 9AM to 5PM EST, Monday through Friday.

Sincerely,

Christine Cote, MD
Vice President Medical Affairs
Janssen Pharmaceutica Inc.

1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200
(609) 730-2000

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EXHIBIT

Palumbo-14
12-13-10 JPO

JANSSEN**PHARMACEUTICA INC.**

XX-November-2003

Dear Healthcare Provider,

Janssen Pharmaceutica Products, L.P., has been notified by the U.S. Food and Drug Administration (FDA) that they have requested updated product labeling for all atypical antipsychotics to include a warning regarding hyperglycemia and diabetes. This requested update applies to RISPERDAL® (risperidone) as well as ABILIFY™ (aripiprazole, Bristol-Myers Squibb), CLOZARIL® (clozapine, Novartis), GEODON® (ziprasidone, Pfizer), SEROQUEL® (quetiapine, AstraZeneca), and ZYPREXA® (olanzapine, Eli Lilly and Company).

The FDA's request is based on reports of hyperglycemia-related adverse events and epidemiological studies suggesting an increased risk of glucose abnormalities in patients treated with atypical antipsychotics. However, the relationship between atypical antipsychotic use and these events is not completely understood due to an increasing incidence of diabetes mellitus in the general population and an established elevated risk for diabetes in patients with schizophrenia.

All patients receiving atypical antipsychotics should be monitored for symptoms of hyperglycemia; those patients who develop symptoms of hyperglycemia and those at risk for diabetes should undergo blood glucose testing. Patients with an established diagnosis of diabetes mellitus should be monitored regularly for worsening of glycemic control. For additional details please refer to the enclosed package insert for full prescribing information.

Janssen Pharmaceutica Products, L.P., remains committed to providing you with the most current product information available for the management of your patients. As always, we request that serious adverse events be reported to Janssen at 1-800-JANSSEN (525-7736) or to the FDA MedWatch Program by phone 1-800-FDA-1088, by fax (1-800-FDA-0178), or by email (www.fda.gov/medwatch). For additional medical information about RISPERDAL or any other Janssen product, please call 1-800-JANSSEN (525-7736) from 9AM to 5PM EST, Monday through Friday.

Sincerely,

Christine Cote, MD
Vice President Medical Affairs
Janssen Pharmaceutica Inc.

1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200
(609) 730-2000

us.janssen.com**EXHIBIT**

Palumbo - 15
12-13-10 *SP*

JJRE 08978940

Plaintiff Ex. 2354

Confidential/Produced in Litigation Pursuant to Protective Order

R. 3791

From: Reines, Scott [PRDUS] [/o=JNJ/ou=JANUSTI/cn=Recipients/cn=SRelines] on behalf of Reines, Scott [PRDUS]
Sent: Wednesday, April 28, 2004 1:12 PM
To: Waldstretcher, Joanne [PRDUS]
Subject: RE: Project Alpha....BMS and Merck

Joanne,

I'm glad that you and I spoke in advance, too. I don't think they realize all the issues of trying to maintain internal blinding when investigators are receiving unblinded reports, or that these rare events don't compromise us.

The warning letter is ugly. As soon as I saw the JPI letter last November I called Garry and asked how it could have gone out, but it was too late. They never consulted the team or anyone in PRD except some unnamed regulatory and legal people whom they say reviewed it. But no competent person would have let it go out. If you're interested I can send it. It's really a black mark for J&J. The Wall St Journal and other media slammed us yesterday.

Regards.

Scott

-----Original Message-----

From: Waldstretcher, Joanne [PRDUS]
Sent: Wednesday, April 28, 2004 9:02 AM
To: Reines, Scott [PRDUS]
Subject: RE: Project Alpha....BMS and Merck

I actually didn't see the letter but I heard about it.

I had a big discussion with shif and peter before the meeting - they were NOT in favor of the clinical team being unblinded to sua's before I spoke to them. I talked to them for quite a while, and as a result of that, the meeting this morning was scheduled. Thank goodness you were there!

-----Original Message-----

From: Reines, Scott [PRDUS]
Sent: Wednesday, April 28, 2004 8:26 AM
To: Waldstretcher, Joanne [PRDUS]
Subject: RE: Project Alpha....BMS and Merck

Good point. I hope they succeed with Zetia - it's the only hope left for my stock options!!

That teleconf could have lasted 5 minutes, since the only issue is whether we're talking about SUAs or all SAEs. Also, I think it's ironic that Christine is so purist about the database, after JPI wrote such a flagrant letter about Risperdal that the whole management team almost got canned. I'm sure you've seen the DDMAC Warning Letter.

Scott

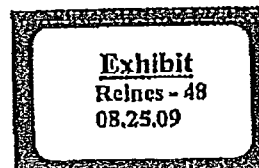
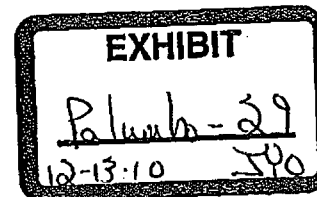
-----Original Message-----

From: Waldstretcher, Joanne [PRDUS]
Sent: Wednesday, April 28, 2004 8:12 AM
To: Reines, Scott [PRDUS]
Subject: RE: Project Alpha....BMS and Merck

Yes... we'll see. I think for alpha, merck has the entire zocor sales force with nothing to do soon (except zocor/zetia) so I think they made a very compelling case.

-----Original Message-----

From: Reines, Scott [PRDUS]
Sent: Wednesday, April 28, 2004 8:11 AM



JJRE 02112214
Confidential/Produced in Litigation Pursuant to Protective Order

To: Waldstreicher, Joanne [PRDUS]
Subject: RE: Project Alpha....BMS and Merck

I had lunch with David Norton last Friday and he said that BMS was leaning heavily toward Merck. He said they were in there first. I keep wondering whether we should have been more enthusiastic about gaboxadol, but I guess time will tell...

Scott

-----Original Message-----

From: Waldstreicher, Joanne [PRDUS]
Sent: Wednesday, April 28, 2004 8:03 AM
To: Nell, Gary [PRDUS]; Reines, Scott [PRDUS]
Subject: FW: Project Alpha....BMS and Merck
Importance: High

So.... the lundbeck compound and alpha have both gone to merck....

-----Original Message-----

From: Sellhar, Len [PGSMUS]
Sent: Wednesday, April 28, 2004 7:08 AM
To: Grissinger, Michael [OMPUS]; Crane, Rosemary [PGSMUS]; Poon, Christine [JJCUS]; Heyman, Tom [JJCUS]; Norton, David [JJCUS]; Fischer, Seth [OMP]; Bondi, Joseph [OMPUS]; DeOrefice, Christopher [OMP]; Jom, Deborah [PGSMUS]; Brantley, Susan [OMP]; Suehnholz, Raymond [OMP]; Frangakis, Crist [JJCUS]; Waldstreicher, Joanne [PRDUS]; Fitchet, Martin [PRDUS]; Ross, Hamish [PRDUS]; Sheffield, David [Corp.] [JJCUS]; Gorsky, Alex [JACGB]; Sartarelli, Jose V. [JJCUS]; Reyn, Dirk [JanBe]; Laurijssen, Jos [JanBe]; Palo, Ralph [JJCUS]; Harbour, John W. [JJCUS]; Jung, Eric [JJCUS]; Wills, Robert J. [JJCUS]
Subject: Project Alpha....BMS and Merck
Importance: High

Bristol-Myers Squibb and Merck Announce Global Development and Commercialization Alliance For Muraglitazar, a Novel Compound for Diabetes

Wednesday April 28, 7:00 am ET

NEW YORK & WHITEHOUSE STATION, N.J.--(BUSINESS WIRE)--April 28, 2004--Bristol-Myers Squibb Company and Merck & Co., Inc. today announced that they have entered into a global collaborative agreement for muraglitazar, Bristol-Myers Squibb's dual PPAR (peroxisome proliferator-activated receptor) agonist, currently in Phase III clinical development for use in treating both blood glucose and lipid abnormalities in patients with type 2 diabetes.

Under the terms of the agreement, Bristol-Myers Squibb will receive a \$100 million upfront payment and \$275 million in additional payments based upon the achievement of certain regulatory milestones. Bristol-Myers Squibb and Merck will jointly develop the clinical and marketing strategy for muraglitazar and share equally in future development and commercialization costs. Both companies will co-promote the product to physicians on a global basis, and Merck will receive payments based on net sales levels. In addition, Merck received rights to development and commercialization for a back-up compound to muraglitazar, which is entering Phase II clinical trials for the treatment of diabetes. Further details of the agreement were not disclosed.

"This collaboration with Merck reflects our new corporate strategy, which will build long-term growth by focusing on critical disease areas such as diabetes and will optimize the value of all of our assets," said Peter R. Dolan, chairman and chief executive officer, Bristol-Myers Squibb. "As we move forward in implementing this new strategy, Bristol-Myers Squibb will center our efforts on reaching specialists and high prescribing primary care physicians. The company will also selectively develop strategic partnerships, such as this one, that enable us to realize the full potential of our promising pipeline."

Muraglitazar was discovered and developed by Bristol-Myers Squibb as part of an intensive internal research program to deliver innovative medicines for patients with type 2 diabetes. The dual PPAR agonist works by targeting both alpha and gamma PPAR receptors and, as a result of this dual agonist activity, muraglitazar is being tested to potentially provide both blood sugar control and improved lipid management in patients with type 2 diabetes. As announced previously, muraglitazar is expected to be submitted within the next nine to 12 months for U.S. regulatory approval. If approved, muraglitazar has the potential to be the first of the novel class of drugs known as dual PPAR agonists to be approved for marketing in the United States.

"We are very proud to be working with Bristol-Myers Squibb as their partner for the development and commercialization of muraglitazar, which has the potential to represent a true advance in the treatment of type 2 diabetes," said Raymond V. Gilman, chairman, president and chief executive officer, Merck. "We believe that the combined scientific and marketing talents of our two companies will help advance this potential new medicine."

"Through the discussions that have already taken place between our two teams, we believe that this will be a productive

relationship. This partnership is consistent with Merck's strategy to develop external alliances that complement our substantial internal research effort," Gilmartin added.

Type 2 diabetes, often known as adult-onset diabetes, occurs when the body does not produce enough insulin to normally regulate blood sugar levels or when the body develops resistance to the effects of insulin. Type 2 diabetes is a growing public health problem that today affects 17 million adult Americans and is now the sixth leading cause of death in this country, according to the U.S. Centers for Disease Control (CDC). The condition is associated with older age, obesity, a family history of diabetes and physical inactivity. Worldwide, type 2 diabetes affects an estimated 40 million people in major pharmaceutical markets today, a number that is expected to more than double to 90 million people by 2015. "Bristol-Myers Squibb and Merck are well established as leaders in the fields of type 2 diabetes and cardiovascular medicine," Dolan said. "This collaboration will enable Bristol-Myers Squibb and Merck to leverage the breadth of R&D and commercial capabilities and resources in both type 2 diabetes and cardiology to realize the full potential of muraglitazar. We are excited about this partnership and we are dedicated to combining our extensive resources to advance the development and commercialization of muraglitazar as a potential new treatment option for the millions of patients around the world with type 2 diabetes."

-----Original Message-----

From: Grissinger, Michael [OMPUS]

Sent: Tuesday, April 27, 2004 5:11 PM

To: Poon, Christine [JJCUS]; Heyman, Tom [JJCUS]; Norton, David [JJCUS]; Fischer, Seth [OMP]; Bondi, Joseph [OMPUS]; DeOrefice, Christopher [OMP]; Jom, Deborah [PGSMUS]; Sellhar, Len [PGSMUS]; Brantley, Susan [OMP]; Suehnholz, Raymond [OMP]; Frangakis, Crist [JJCUS]; Waldstrolcher, Joanne [PRDUS]; Fitchel, Martin [PRDUS]; Ross, Hamish [PRDUS]; Sheffield, David [Corp.] [JJCUS]; Gorsky, Alex [JACGB]; Sartarelli, Jose V. [JJCUS]; Reyn, Dirk [JanBe]; Laurijssen, Jos [JanBe]; Palo, Ralph [JJCUS]; Harbour, John W. [JJCUS]; Jung, Eric [JJCUS]; Wills, Robert J. [JJCUS]

Subject: Project Alpha

I was told this afternoon that Alpha will announce a partnership deal tomorrow morning on Muraglitazar. In two separate conversations that Tom Heyman and I had today with Alpha, the feedback received on why the other partner was selected over us was the following:

1. Financial Terms- the overall financial deal offered by the other party was better
2. Back Up compound- The deal terms around the backup compound were cleaner and financially more attractive with the other partner. I would take from this that the other partner was not looking to peg milestones and launch decisions to a specific product profile for the backup, and was probably not looking for an opt in/ opt out right during development
3. Governance- Although this one ranks third among the issues listed, we were told that the governance negotiations went "more smoothly" with the other party; no additional clarification was provided.

I will convene a small team to do a post mortem/ lessons learned exercise on this deal, but wanted to take this opportunity to thank the team for your commitment to objectively evaluating this opportunity and for your untiring efforts to land this deal for J&J. I look forward to working with you on the next deal, hopefully with a more satisfying result.

Mike

JANSSEN**PHARMACEUTICA INC.**

IMPORTANT DRUG INFORMATION

16-April-2003

Dear Healthcare Provider,

Janssen Pharmaceutica Products, L.P., would like to inform you of important changes regarding RISPERDAL® (risperidone). The RISPERDAL prescribing information has been updated with the addition of the following information:

WARNINGS**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 has not been shown to be safe or effective in the treatment of patients with dementia-related psychosis.

This update is based on data from 4 placebo-controlled trials conducted in elderly patients with dementia (N=1230). Additional information on these and other clinical trials conducted in elderly patients can be obtained by calling 1-800-JANSSEN (800-526-7736). We remind you that, like all other antipsychotics, RISPERDAL is not indicated for the treatment of dementia.

Janssen Pharmaceutica Products, L.P., remains committed to providing you with the most current product information available for the management of your patients. Please refer to the enclosed package insert for full prescribing information. As always, we request that serious adverse events be reported to Janssen at 1-800-JANSSEN (526-7736) or to the FDA MedWatch program by phone 1-800-FDA-1088, by fax (1-800-FDA-0178), or by email (www.fda.gov/medwatch). For additional medical information about RISPERDAL or any other Janssen product, please call 1-800-JANSSEN (526-7736) from 9AM to 5PM EST, Monday through Friday.

Sincerely,

Christine Cote, MD
Vice President, Medical Affairs
Janssen Pharmaceutica Inc.

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TITUSVILLE, NEW JERSEY 08560-0200
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**IMPORTANT
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WARNING**

R. 3796

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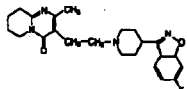
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RISPERDAL®

(RISPERIDONE)
TABLETS/ORAL SOLUTION

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to a new chemical class, the benzoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{26}H_{26}F_2N_4O_2$ 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, polyethylene 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 (K_i 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 H₁ histaminergic receptors. RISPERDAL® antagonizes other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (K_i of 47 to 253 nM) for the serotonin $5HT_{1A}$, $5HT_{1B}$, and $5HT_{1C}$ receptors, weak affinity (K_i of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-6}$ 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 major 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 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 hyperreflexia, 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

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 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 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/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/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

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

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 ($\geq 0.3\%$) 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 8 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 organic 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 8 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 8 to 8-Week Controlled Clinical Trials¹

Body System/ Preferred Term	RISPERDAL®		Placebo (N=142)
	≤ 10 mg/day (N=324)	16 mg/day (N=77)	
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	2.8
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, organic dysfunction, asthenia/fatigue/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 8 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 8 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 tenebrosa, 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, 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*, 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, leukopenia, 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 temporary (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* overdosage, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdosage.

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 overdosage 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 "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 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.

7503222

US Patent 4,804,663

Revised March 2003

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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



(From: Reines, Scott [PRDUS] [/o=JNJ/ou=JANUSTI/cn=Recipients/cn=SReines] on behalf of Reines, Scott [PRDUS]
Sent: Wednesday, March 10, 2004 3:14 PM
To: Grossman, Fred [PRDUS]
Subject: RE: CVAE in Europe

Thanks Fred, will do.

Scott

-----Original Message-----

From: Grossman, Fred [PRDUS]
Sent: Wednesday, March 10, 2004 9:51 AM
To: Reines, Scott [PRDUS]
Subject: RE: CVAE in Europe

Yes - I agree. Also - thank you for ccing me and feel free to send documents to me in real time for additional review - I am not sure why Ramy didn't add my name but I have my "psychodynamic" suspicions.

Regards,
Fred

-----Original Message-----

(From: Reines, Scott [PRDUS]
Sent: Wednesday, March 10, 2004 9:29 AM
To: Grossman, Fred [PRDUS]
Subject: RE: CVAE in Europe

Fred -

I'm going to have to learn not to trust their communications. When I reviewed this one last night, without the data or the benefit of Marielle's comments, it looked ok to me.

Scott

-----Original Message-----

From: Grossman, Fred [PRDUS]
Sent: Wednesday, March 10, 2004 8:30 AM
To: Reines, Scott [PRDUS]
Subject: RE: CVAE in Europe

They just never stop spinning !

Regards,
Fred

-----Original Message-----

(From: Reines, Scott [PRDUS]
Sent: Wednesday, March 10, 2004 7:30 AM
To: Eerdeken, Marielle [PRDBE]
Cc: Fred Grossman [PRDUS] (E-mail)
Subject: RE: CVAE in Europe

Thanks Marielle, these are excellent points.

Scott

-----Original Message-----

From: Eerdeken, Marielle [PRDBE]
Sent: Wednesday, March 10, 2004 3:08 AM
To: Mahmoud, Ramy [JANUS]; Caers, Ivo [PRDBE]; Reines, Scott [PRDUS]
Cc: Greenspan, Andrew [JANUS]
Subject: RE: CVAE in Europe

Hi Ramy,

Thanks for providing the opportunity to give input.

The text is not fully in line with the MHRA agreed upon text and should be reworked.

Also I do not fully understand where some of the numbers come from especially the ones cited for stroke incidence and odds ratio's. Based on our analysis, although not statistically significantly different, in both placebo and risperidone the odds are 3 fold for getting a stroke on risperidone.

See additional suggestions in text.

Kind regards, Mariëlle

-----Original Message-----

From: Mahmoud, Ramy [JANUS]
Sent: Wednesday, 10 March 2004 12:37 AM
To: Eerdeken, Marielle [PRDBE]; Caers, Ivo [PRDBE]; Reines, Scott [PRDUS]
Cc: Greenspan, Andrew [JANUS]
Subject: FW: CVAE in Europe

Just want to share a courtesy draft of an internal communication that Andrew is preparing that is intended to go to our field medical personnel in the U.S. on Wednesday to prepare and educate them around the MHRA label change. It is possible some of this may be of value to your team, that you may have comments, or that it may be of use in preparation of the FDA file. Please let me or Andrew know if you have comments.

-Ramy

-----Original Message-----

From: Mahmoud, Ramy [JANUS]
Sent: Tuesday, March 09, 2004 6:32 PM
To: Greenspan, Andrew [JANUS]
Subject: RE: CVAE in Europe

Label Change in the United Kingdom

At the request of the U.K. Medicines and Healthcare products Regulatory Agency (MHRA), Janssen-Cilag has updated the Risperdal label.

[Eerdeken, Marielle [PRDBE]] I think there is a mixing up in the below on what applies to patients with dementia and what does apply to all patients treated with risperidone. It is important to make that distinction!

Among other things, the label will advise physicians to consider carefully the risk of CAE with Risperdal before treating any patient with a previous history of stroke, hypertension, diabetes, smoking, and atrial fibrillation. [Eerdeken, Marielle [PRDBE]] the following is the label text agreed upon with MHRA Physicians should consider carefully the risk of cerebrovascular adverse events with Risperdal (given the observations in elderly patients with dementia detailed above) before treating any patient with a previous history of CVA/TIA. Consideration should also be given to other risk factors for cerebrovascular disease including hypertension, diabetes, current smoking, atrial fibrillation, etc. It will also strongly advise any use be limited to a short period of time (see full label for details). [Eerdeken, Marielle [PRDBE]] This is not correct either as this only applies to patients with dementia! Treatment of acute psychoses in patients with a history of dementia should be limited to short term only and should be under specialist advice.

The MHRA bases such decisions on clinical trial databases and their own pharmacovigilance, though all information included in the RISPERDAL labeling and communication is derived only from clinical trials. (attachment)

Eli Lilly has also been requested to update the Zyprexa label with very similar wording [Eerdeken, Marielle [PRDBE]]

for CVAE's. One important difference is that an increased mortality in dementia patients exposed to Zyprexa is reported (with RISPERDAL there is notation that mortality is not increased). (attachment)

[Eerdeken, Marielle [PRDBE]] At this moment Seroquel will not have any changes to its label in the UK. The authorities have stated that there is insufficient evidence available to take action on more recently introduced atypical antipsychotics, such as Seroquel.

These change have already been reported by several international newswires. In nearly all these reports, the word "stroke" is used, rather than CAE. (attachment)

New data analyses cited in the UK MHRA Webpage

Through its webpage, the MHRA provides a significant amount of data and analysis on the incidence and risk of CAE in Risperdal clinical trials, including:

- 1) CAE and death rates for RIS-AUS-5, RIS-USA-63, RIS-USA-232, RIS-INT-24
- 2) Odds ratios for CAE for the above trials and overall [AUS-5: 5.49 (95% CI 1.56, 19.35); USA-63: 0.88 (.17, 4.58); USA-232: 4.10 (.46, 36.99); INT-24: 4.75 (0.95, 45.95); Overall: 3.32 (1.44, 7.68)]
- 3) Number Needed to Harm (NNH)
 - a) Exposure Adjusted: 6.3, ie if 6 patients are treated for one year, then one CAE will be attributable to Risperdal exposure
 - b) Absolute Rates: 37.
- 4) All-Cause Mortality: No significant difference between Risperdal and placebo with meta-analysis odds ratio 1.2 (95% CI 0.7, 2.4)

Issues

- 1) CAE?Stroke. There is a misperception that the event rates, the odds ratios, and the NNH figures refer to stroke risk; whereas the majority of CAEs were not strokes, but rather transient, non-specific events.
- 2) NNH calculations. This information is misleading due to questionable assumptions by MHRA.
- 3) Non-dementia populations. Recommendation to take precautions in treating non-dementia population is not supported by data in our clinical trials.

Discussion

- 1) Serious CAEs represented 46% of the Total CAEs. The other 54% were non-serious CAEs, which consisted of a variety of non-specific symptoms. Therefore, it is important to clarify that although the MHRA and the media use CAE and stroke interchangeably, they should not be confused.
- 2) The distinction between CAE and stroke is crucial, because the stroke risk has not shown to be increased with Risperdal. While the Odds Ratio for stroke is 1.937, the Confidence Interval is 0.733 to 5.119 with a p value=0.182. [Eerdeken, Marielle [PRDBE]] Where does this data come from? It is not consistent with our analysis. Although also our figures do not show statistical differences between ris and pla, I think this statement is misleading (our data show odds ratio for stroke (defined as any CAE excluding TIA) : 2.83 (0.91,11.69) in the dementia population. If RIS-GER-16 (a large study of elderly patients with "organic psychosis syndrome", in which over 50% have dementia) is included in the analysis, the odds ratio is 1.425 (CI .611, 3.325; p=0.412). [Eerdeken, Marielle [PRDBE]] This is mixing the dementia population with a non dementia population. This should not be done in my opinion.
- 3) To calculate the Number Needed to Harm (NNH), the MHRA has used the pooled rate of CAEs in the placebo groups as their measure of baseline risk. However, NNH derived from pooled placebo rates can be misleading for a variety of reasons. The below reference states that it is preferable to calculate NNH by using the risk difference from the clinical trials and an external, population-based incidence from cohort studies, rather than the incidence from the placebo groups of the actual trials (Smeeth L, Haines A, Ebrahim S. "Numbers needed to treat derived from meta-analyses-sometimes informative, usually mis-leading". BMJ 1999). (attached) Calculating the NNH using the external epidemiological data yields a much different risk estimate. For example, the NNH for strokes using the odds ratio from above and the annual incidence of stroke for 80-84 year olds (mean age in Risperdal dementia trials = 82 year old) from the Rotterdam study, the NNH is 164.5. It is impossible to calculate the NNH for all CAEs appropriately in this manner, since there is no available data on the annual incidence of CAE. This can be interpreted to mean that for every 164 patients treated with risperidone, one will have a stroke attributed to the drug. Such an interpretation assumes an unproven causal relationship between stroke and Risperdal.
- 4) Analysis of our non-dementia clinical trial database does not reveal an increased risk of stroke, regardless of the presence of stroke risk factors. In placebo controlled or active comparator schizophrenia, bipolar and adolescent/pediatric disruptive behavior disorder trials, there was 1 patient with a CAE out of 4461 patients exposed to Risperdal versus 0 CAEs in patients exposed to placebo or active comparator. [Eerdeken, Marielle [PRDBE]] Again I do not understand where these figures come from we have much lower figures for total population. Furthermore, in an

analysis of open schizophrenia label trials with a combined total of 3 CAEs, the absence/presence of stroke risk factors did not predict the CAE. (attached)

Conclusions

- 1) The odds ratio for CAE with Risperdal versus placebo in patients with BPSD is approximately 3.
- 2) CAE?Stroke. Risperdal has not been shown to increase the risk of stroke per se (the odds ratio for stroke is not significantly increased) [Eerdekens, Marielle [PRDBE]] I think we should stay away from this type of statements (lower limit of the CI in our analysis is 0.91) .
- 3) According to a widely accepted methodology, the Number Needed to Harm (stroke) is 164.5. It is important to note that the odds ratio used to calculate the NNH is not statistically significantly different from 1.0 (i.e., risk may not be elevated). It is not possible to calculate a NNH for CVAE because there is no reported population incidence of "CVAE", which is clinical trial terminology rather than language used in clinical practice.
- 4) There is no evidence that Risperdal increases the risk of CAE in non-dementia patients. Additionally, the presence or absence of stroke risk factors do not predict CAE in non-dementia patients.

Andrew Greenspan, MD
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CNS Medical Affairs
Janssen Pharmaceutica Products, LP
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Phone: 609 730 7736
Fax: 609 730 3125
e-mail: agreensp@janus.jnj.com

From: Reines, Scott [PRDUS] [/o=JNJ/ou=JANUSTI/cn=Recipients/cn=SReines] on behalf of Reines, Scott [PRDUS]
Sent: Thursday, June 10, 2004 1:34 AM
To: Fred Grossman [PRDUS] (E-mail)
Subject: FW: DDMAC Response

Importance: High

Fred -

FYI only. There's a lesson in this unfortunate mess - I just hope Ramy and JPI learned it well.

Scot

-----Original Message-----

From: Burrus, James [PRDUS]
Sent: Wednesday, June 09, 2004 3:08 PM
To: Singer, Jack M [PRDUS]; Chester, Michael [JANUS]; Ohye, Donna [PRDUS]; Acker, Tracy [PRDUS]; Burrus, James [PRDUS]; Miller, Peter [JANUS]; Fabbri, David [JANUS]; Mahmoud, Ramy [JANUS]; Katz, Melissa [GPCUS]; Brann, Edward [PRDUS]; Adusumalli, Vidyasagar [PRDUS]; Reines, Scott [PRDUS]; Goldmann, Bonnie [PRDUS]; Deloria, Carmen [JANUS]; Smith, Jeff [JANUS]
Cc: Donnelly, Valerie A [PRDUS]; Drucker, Lisa [PRDUS]; Reagan, Shelley [PRDUS]; McGregor-Beck, Roxanne O [PRDUS]; Weiser, Brenda [PRDUS]; Brana, Ana [PRDUS]; McArthur, Philomena [PRDUS]
Subject: DDMAC Response
Importance: High

Team:

Attached is a pdf of the Janssen/J&PRD response to DDMAC's May 27, 2004 communication. It was sent yesterday via fax and FedEx. I also contacted Michael Brony, via voice mail, prior to the arrival of the faxed response to outline what was in the response and offer any additional clarification or assistance.

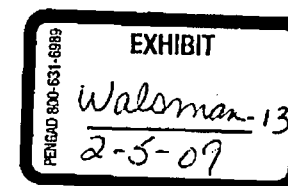
I will follow-up with DDMAC June 17 again to offer any assistance or clarification.

If anyone has any questions please do not hesitate to call.

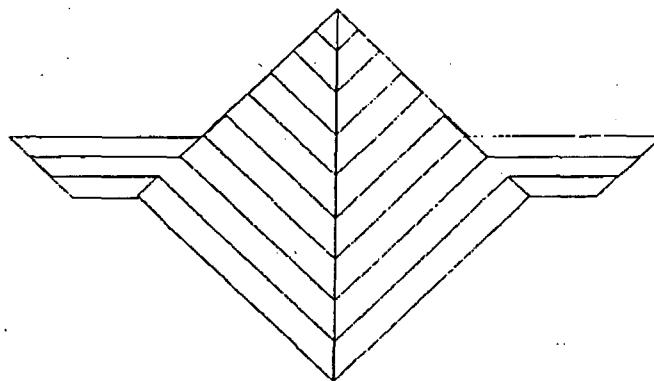
James Burrus
(609)-730-3617

RISPERDAL TRAINING MEETING

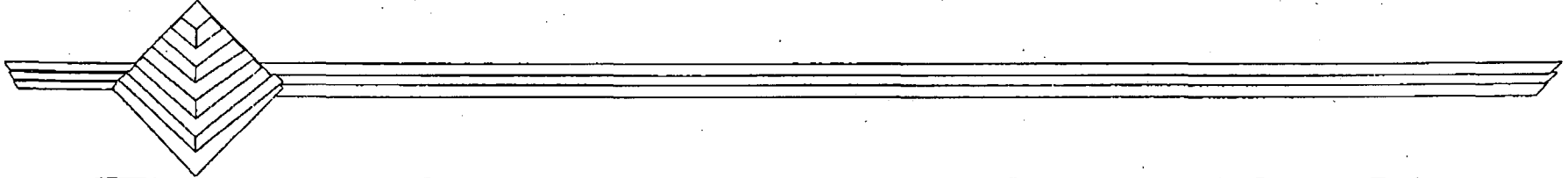
TUESDAY AM
GENERAL SESSION



MIKE WALSMAN
CNS National Sales Director



WELCOME TO SAN DIEGO!



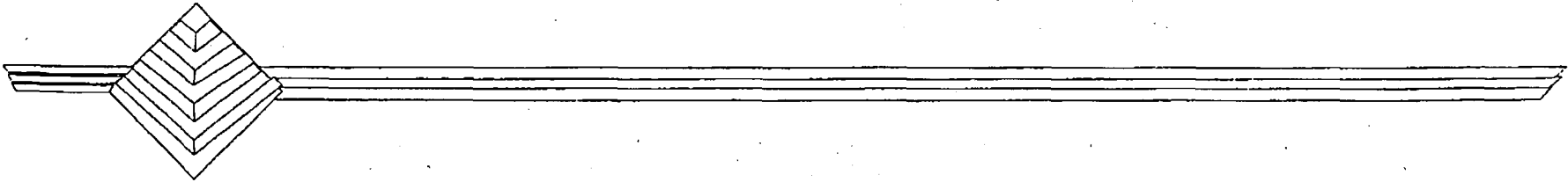
'THE BEST OF THE BEST IN CNS'

CNS SALES FORCE!

ELDERCARE SALES FORCE!

SCIOS SALES FORCE!

'THE BEST OF THE BEST IN CNS'



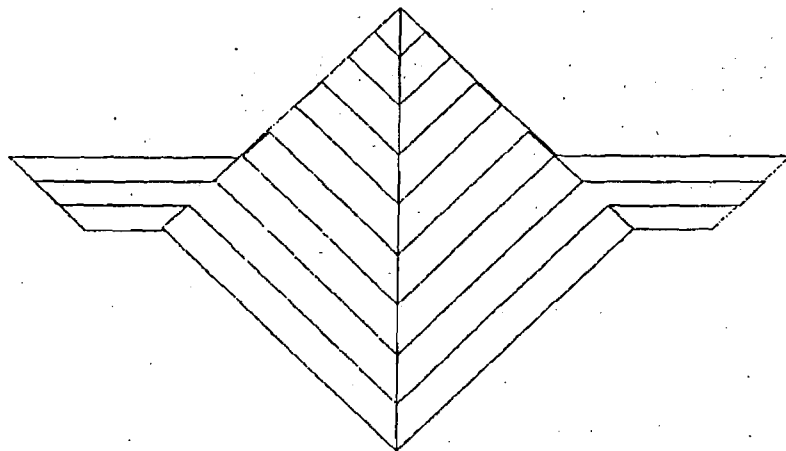
RISPERDAL IS #1!

RISPERDAL IS THE MARKET LEADER!!

**RISPERDAL WILL STAY THE
MARKET LEADER!!!**

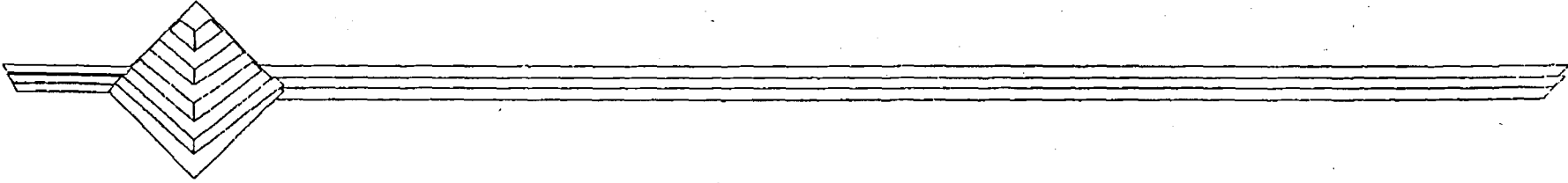
RISPERDAL

National Sales Meeting



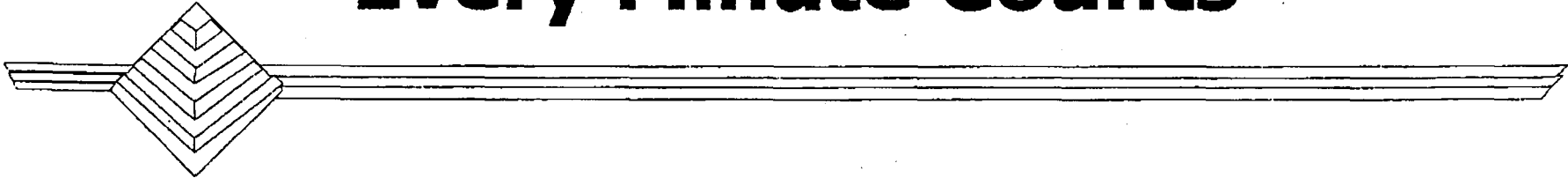
"Every Minute Counts"

1999 Sales Objective



\$874 MM

\$874 Million: "Every Minute Counts"



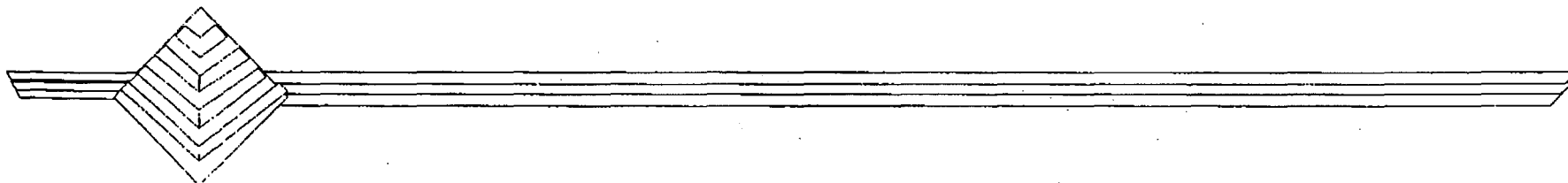
\$874 Million

\$3.5 Million / Day

\$350,000 / Hour

\$6,000 / Minute

1998 RISPERDAL Sales Meeting: Goals

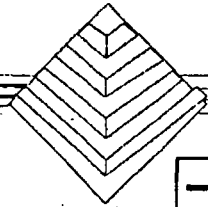


Grow RISPERDAL Share!

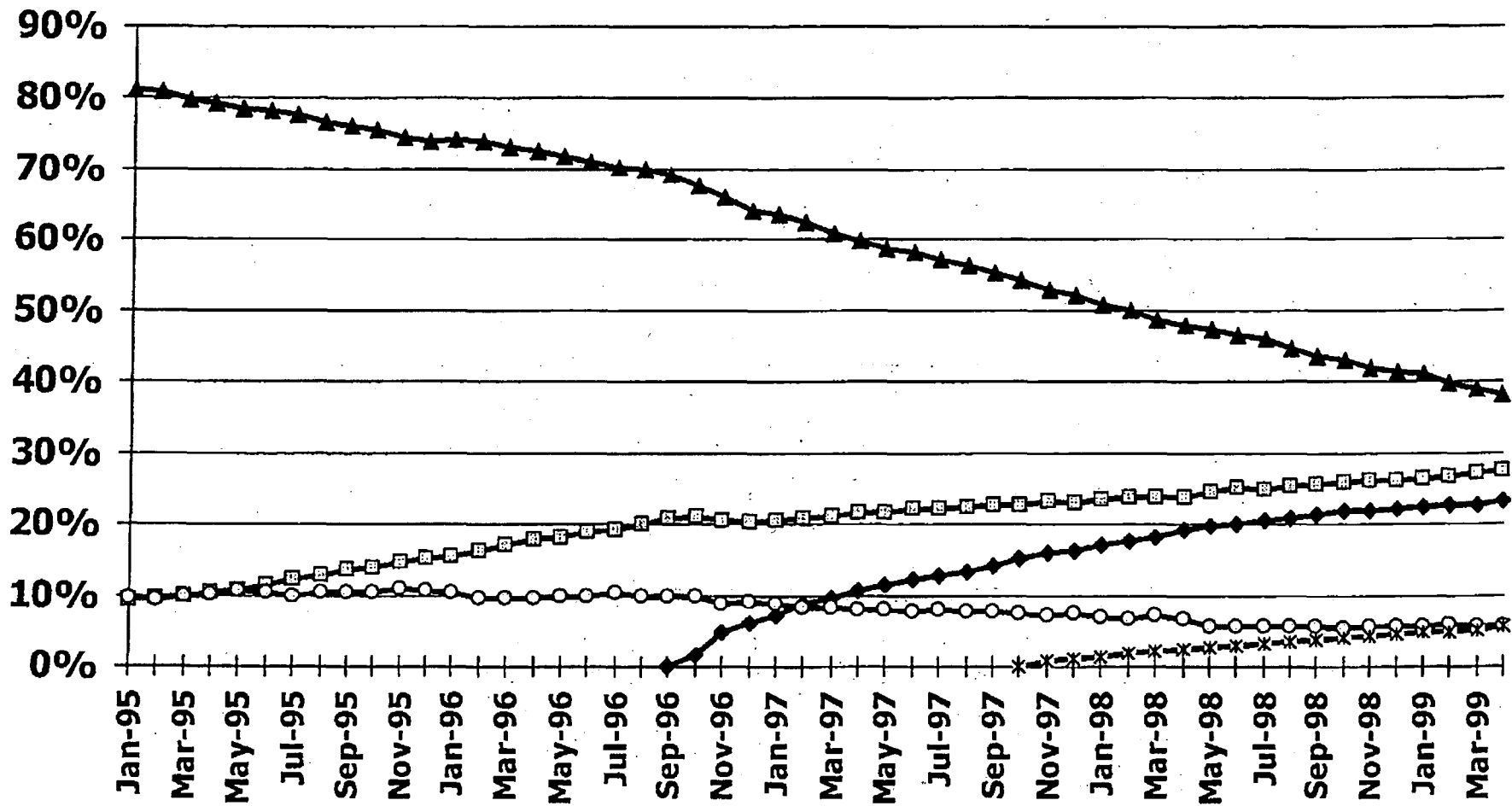
Stop the Growth of Zyprexa!

Maintain #1 Prescribed Position!

Antipsychotic Market New Prescription Share



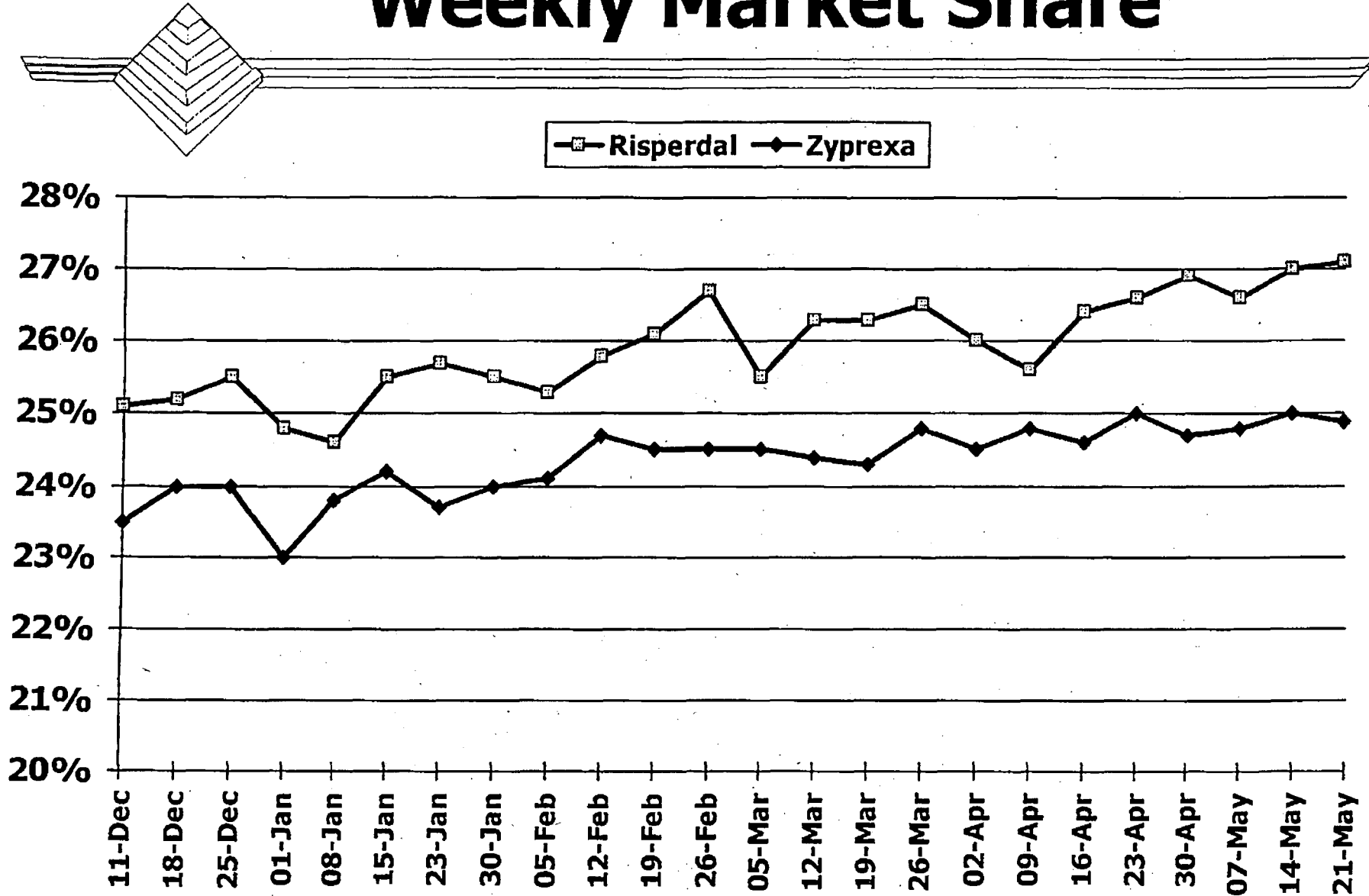
■ Risperdal
 ◆ Zyprexa
 ○ Clozaril
 ▲ Conventionals
 ✱ Seroquel



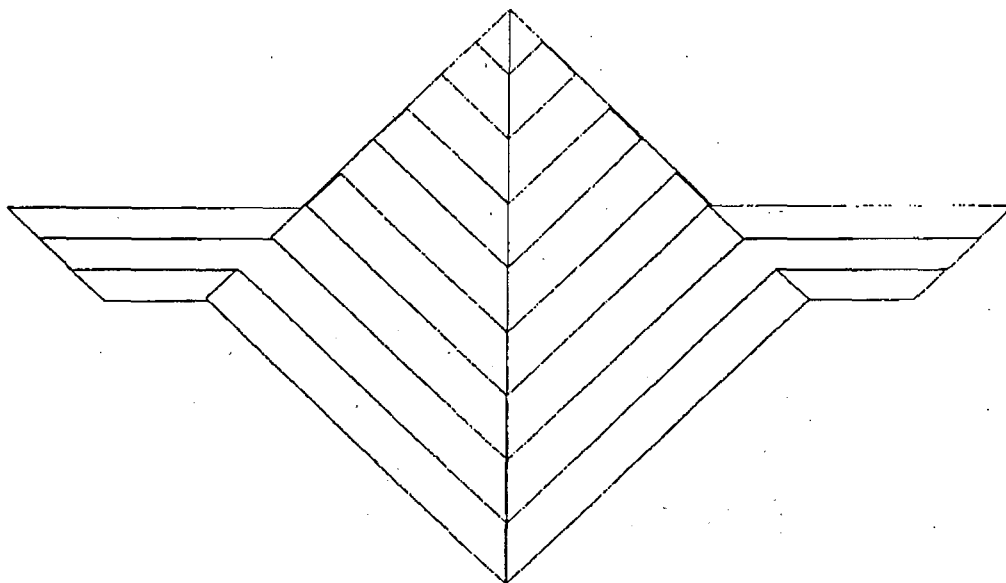
R. 3814

Antipsychotic Market Weekly Market Share

R.3815

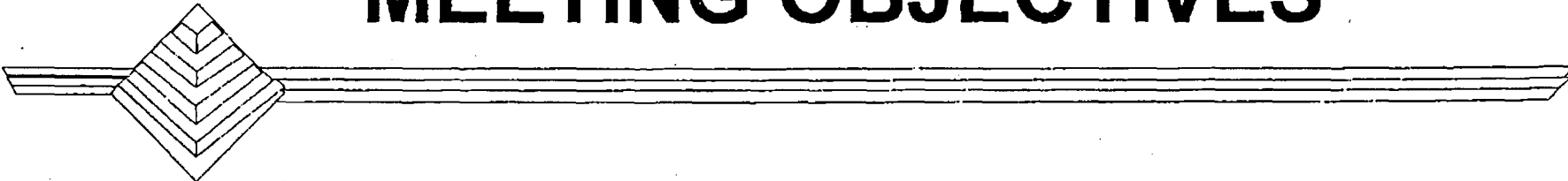


RISPERDAL



Remains

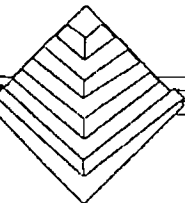
The #1 Prescribed Antipsychotic



MEETING OBJECTIVES

- ***GROW our #1 Position!***
- ***DOMINATE Psychiatry Marketplace!***
 - Use of New Sales materials!
 - Improve our Competitive Selling Skills
 - Maximize Teamwork!

Agenda



Tuesday

- General Session/Brand Breakouts
- CNS/Scios Selling Skills Training
- ElderCare General Session/Breakouts
- Special Evening Function

Wednesday

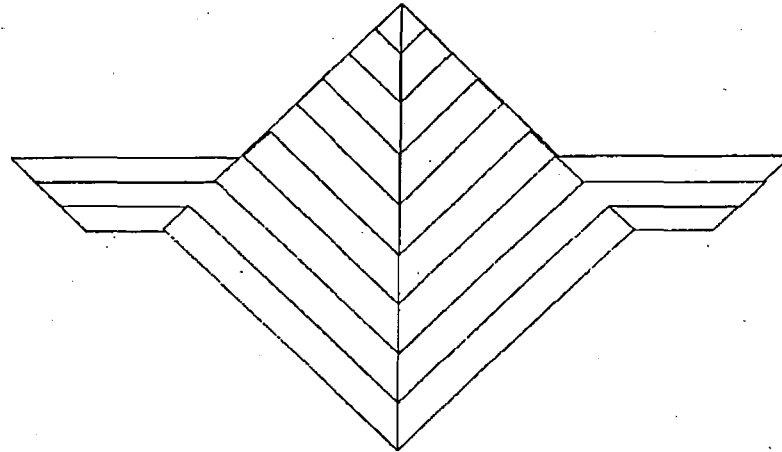
- CNS/Scios Selling Skills Training
- ElderCare General Session/Breakouts
- Scios Awards Banquet
- Janssen 'Free Night'

Thursday

- CNS/ElderCare/Scios Team Day
- District Meetings
- Janssen Awards Banquet

RISPERDAL

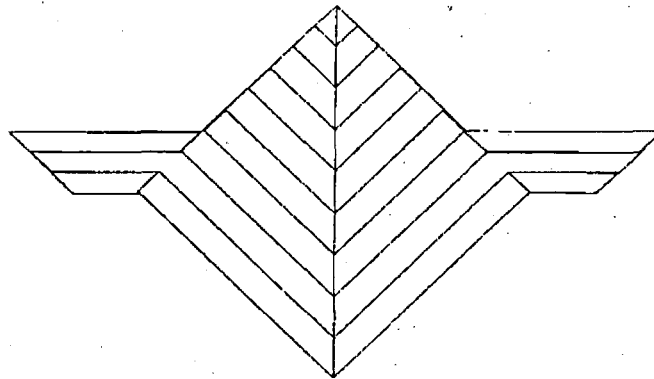
National Sales Meeting



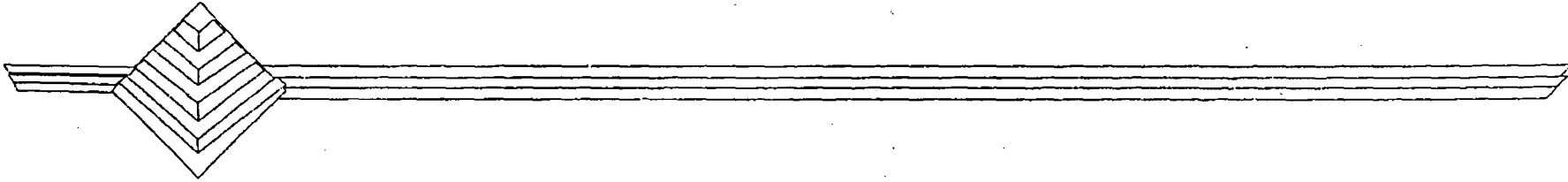
"Every Minute Counts"

DAVID NORTON

President, Janssen Pharmaceutica



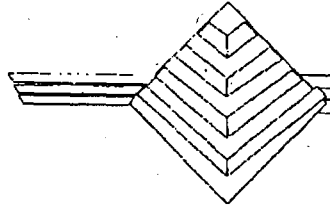
1998 RISPERDAL Sales



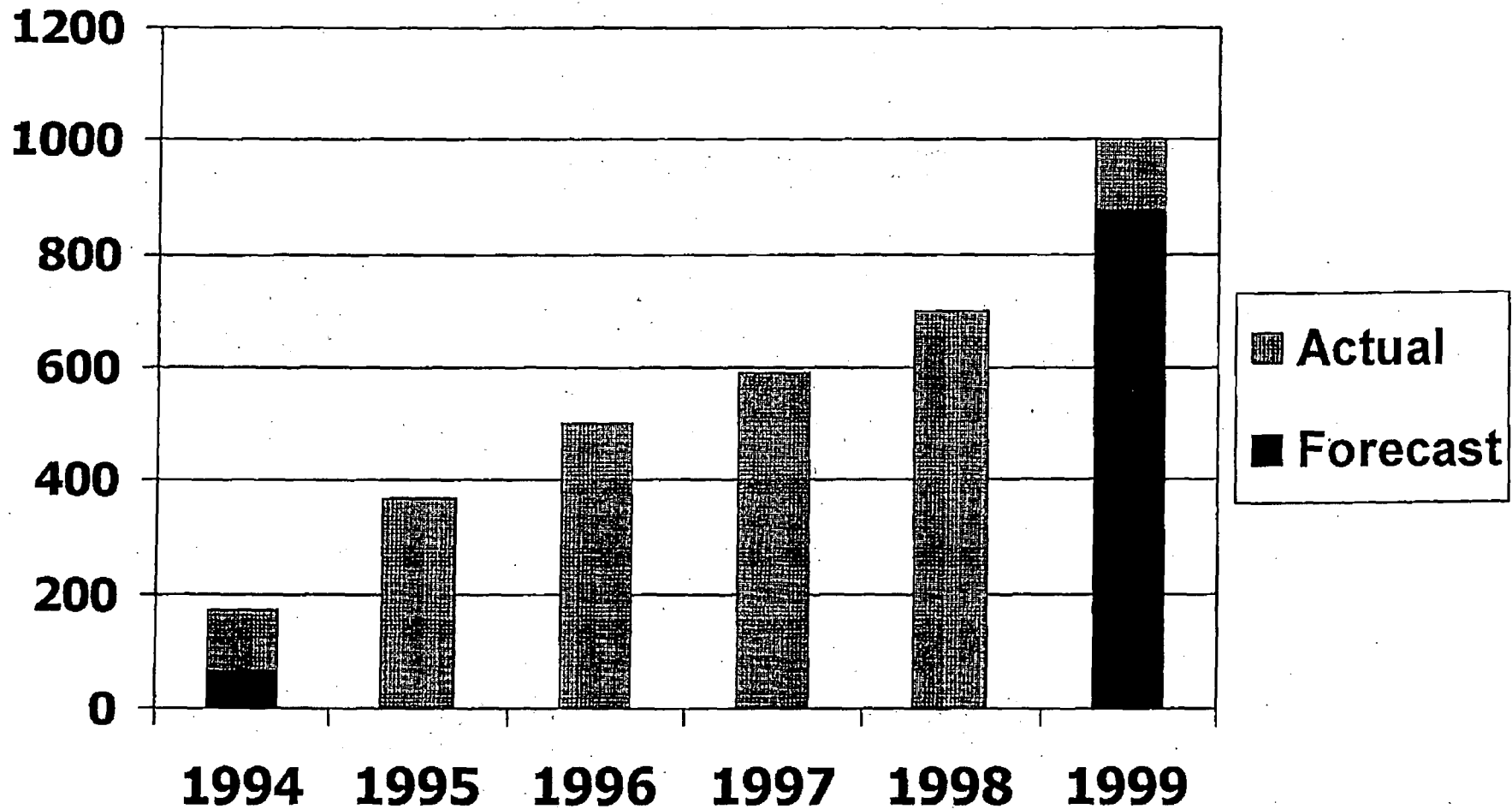
\$698 MM

(Exceeded Forecast by \$_____ MM)

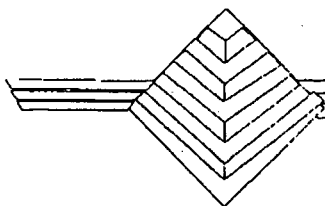
RISPERDAL Annual Sales



R. 3822
\$ Millions



RISPERDAL Milestones



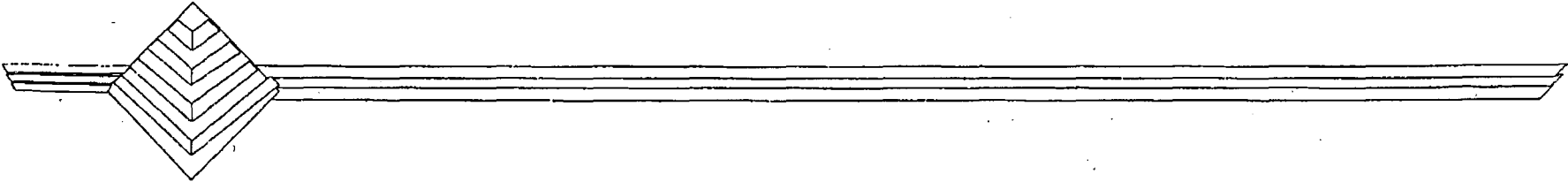
**Only 56 products have reached \$100 MM
(US Sales) in first 12 months on the
market!**

RISPERDAL did!

**Only 11 products have achieved \$500 MM
in annual sales after only 3 years on the
market!**

RISPERDAL did!

RISPERDAL Milestones

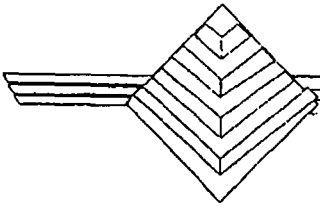


Only 11 products sold \$1 BB last year

RISPERDAL will...

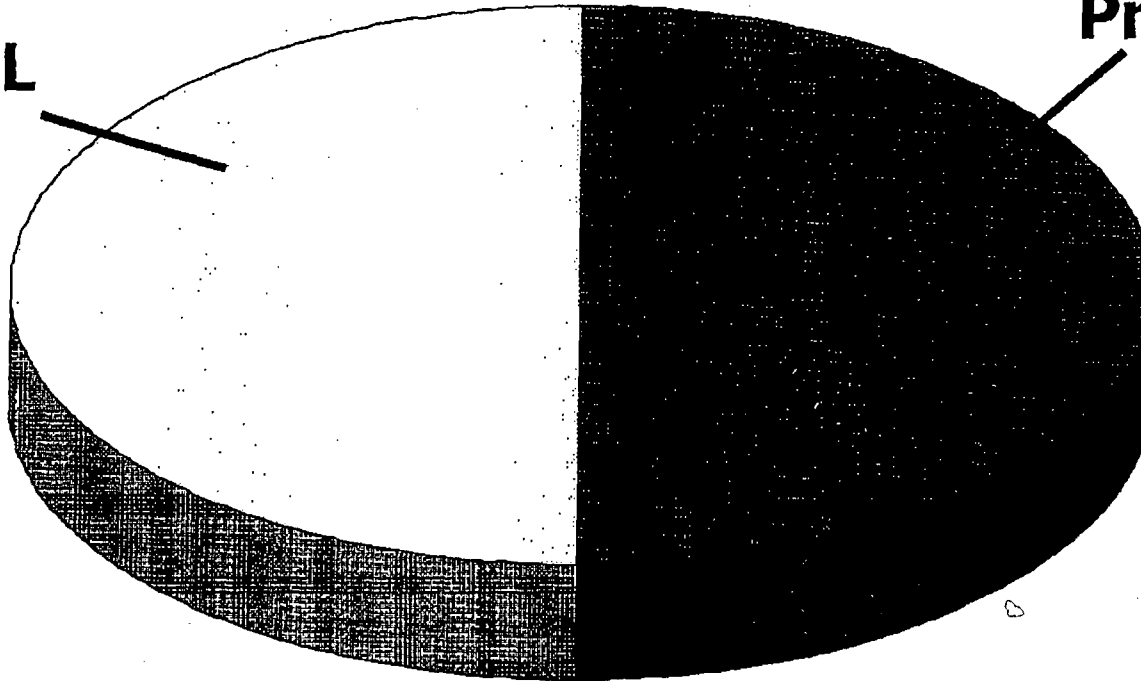
CAN YOU MAKE IT HAPPEN?

Janssen Pharmaceutica 1999 Sales

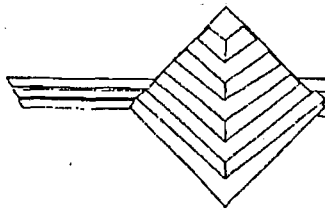


RISPERDAL

**Other Janssen
Products**



Johnson & Johnson



"...Worldwide pharmaceutical sales increased 7.1%...This growth reflects the strong performance of RISPERDAL..." 1997 J&J Annual Report

"J&J attributed the growth in worldwide pharmaceutical sales in the last quarter to RISPERDAL..." 1998 J&J Q3 Report

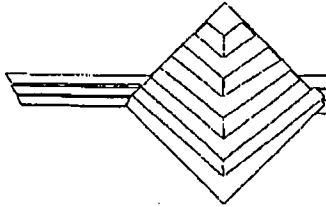
Johnson & Johnson

Credo

**"We believe our first responsibility
is to the doctors, nurses, and
patients..."**

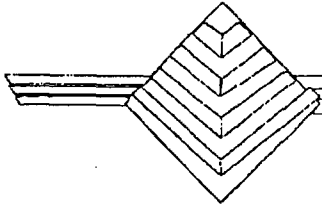
A Profile of Success:

Ken Steele



- **Age 15 - Diagnosed with Paranoid Schizophrenia**
- **Next 30 Years - Homelessness & State Hospitals**
- **1994 - First Treatment with RISPERDAL**
- **Voices Stopped for First Time in 30 Years**

A Profile of Success: Ken Steele - Today

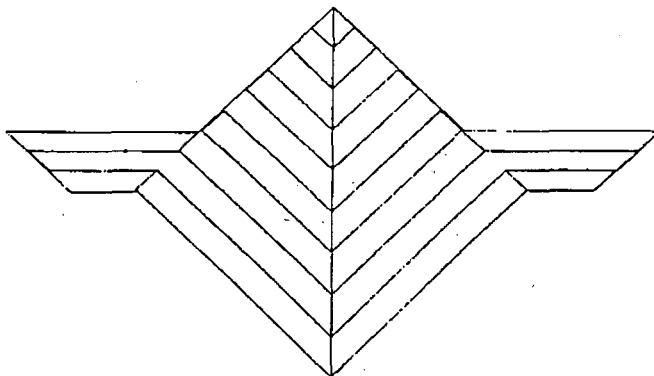


- **Appeared on front page of NY Times**
- **Publisher of New York City Voices**

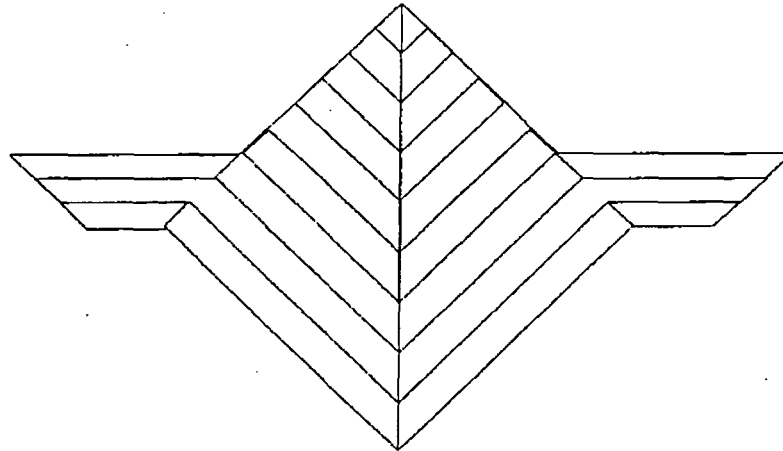
Founder of NY Voter Empowerment Project

Celebrated 4-Years of Being Voice-Free (5/99)...

ALEX GORSKY
Vice President, Marketing

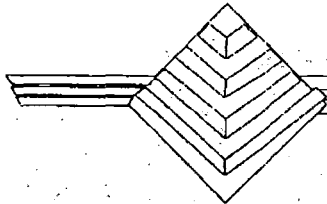


Janssen Pharmaceutica:



A Market Leader in CNS

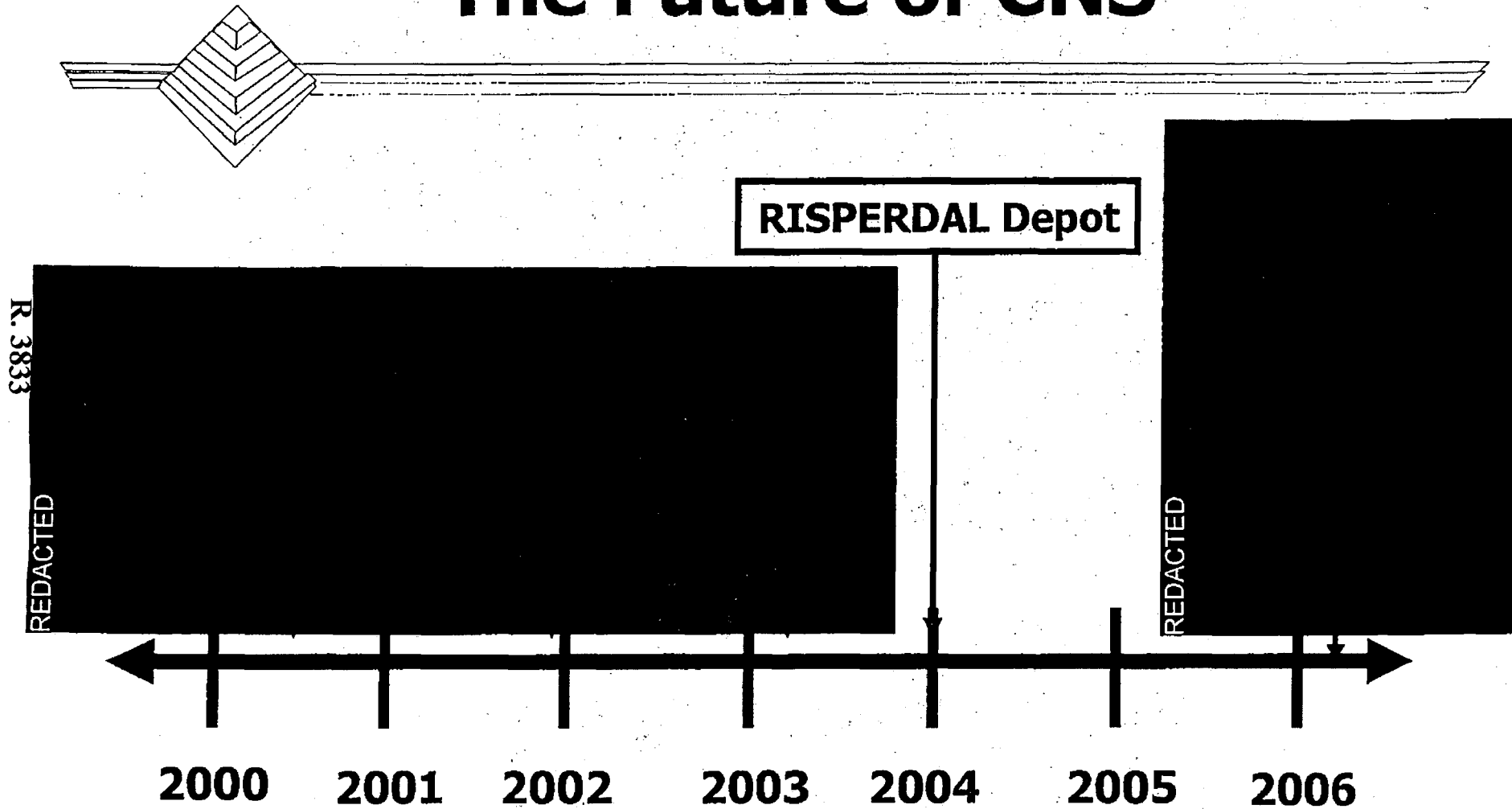
Janssen Pharmaceutica: The Future of CNS



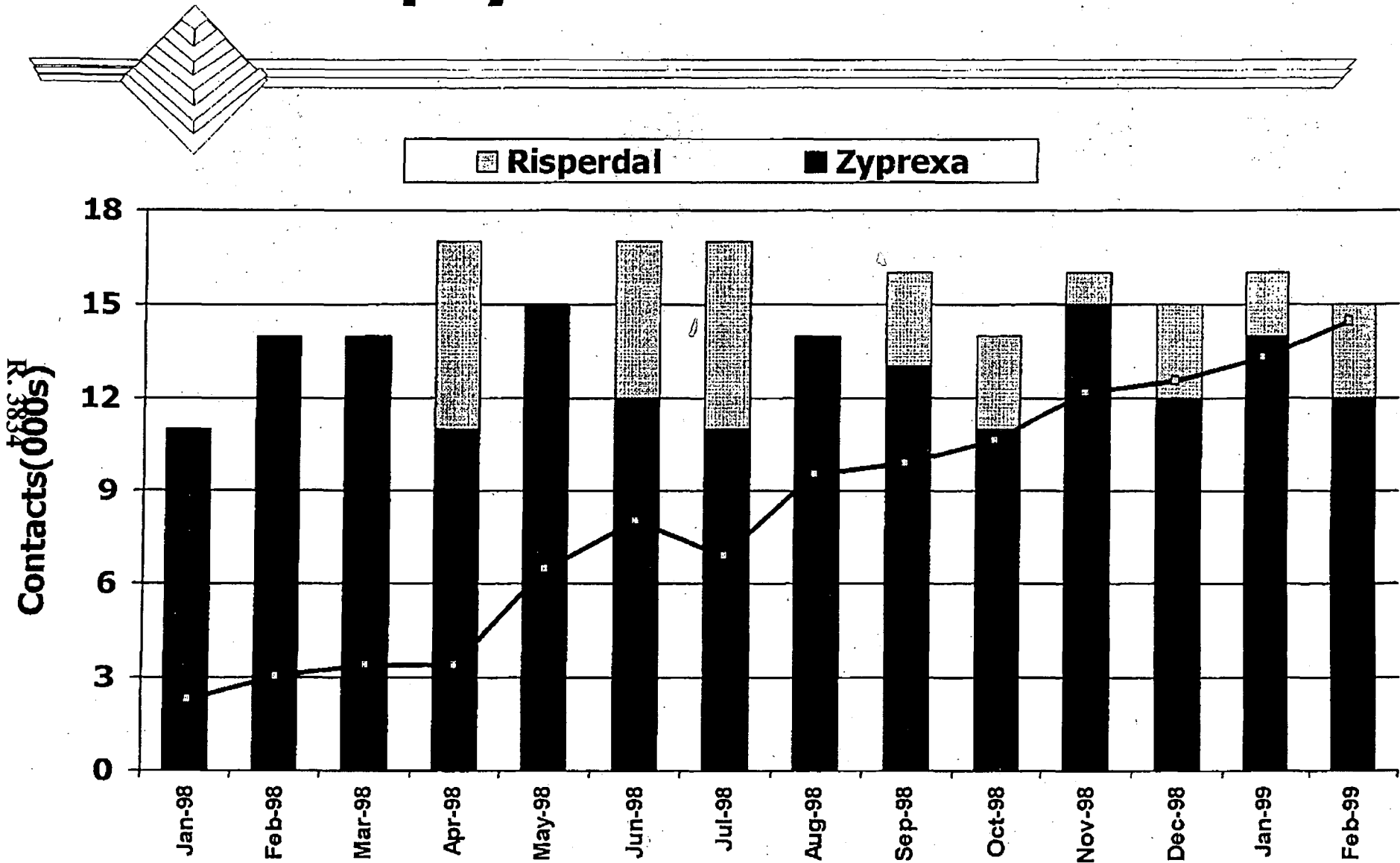
REDACTED

RISPERDAL Depot(s)

Janssen Pharmaceutica: The Future of CNS



Antipsychotic Call Volume

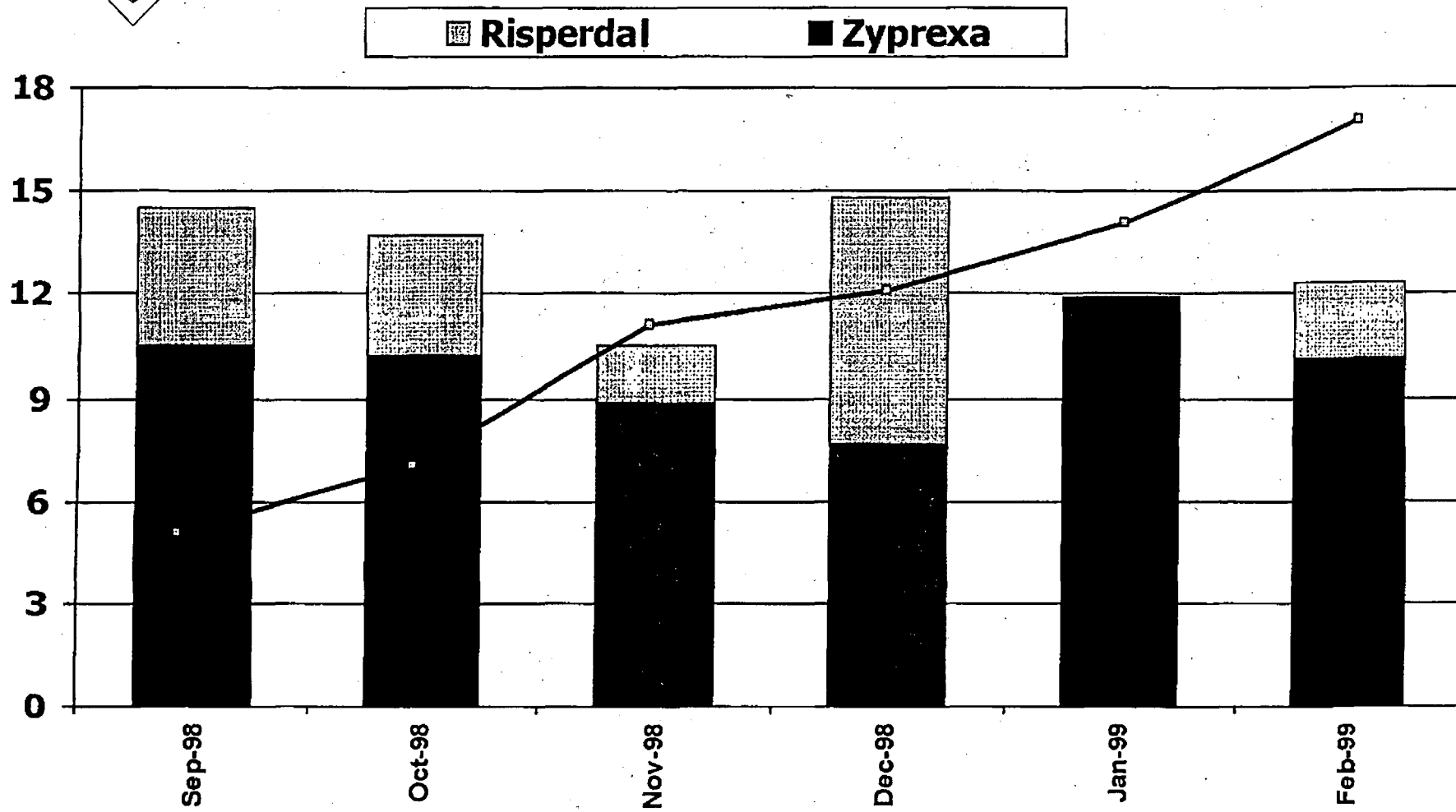


Source: IMS IPS

Risperdal Detailing Includes Janssen, SKB, and Scios

Minutes Per Call

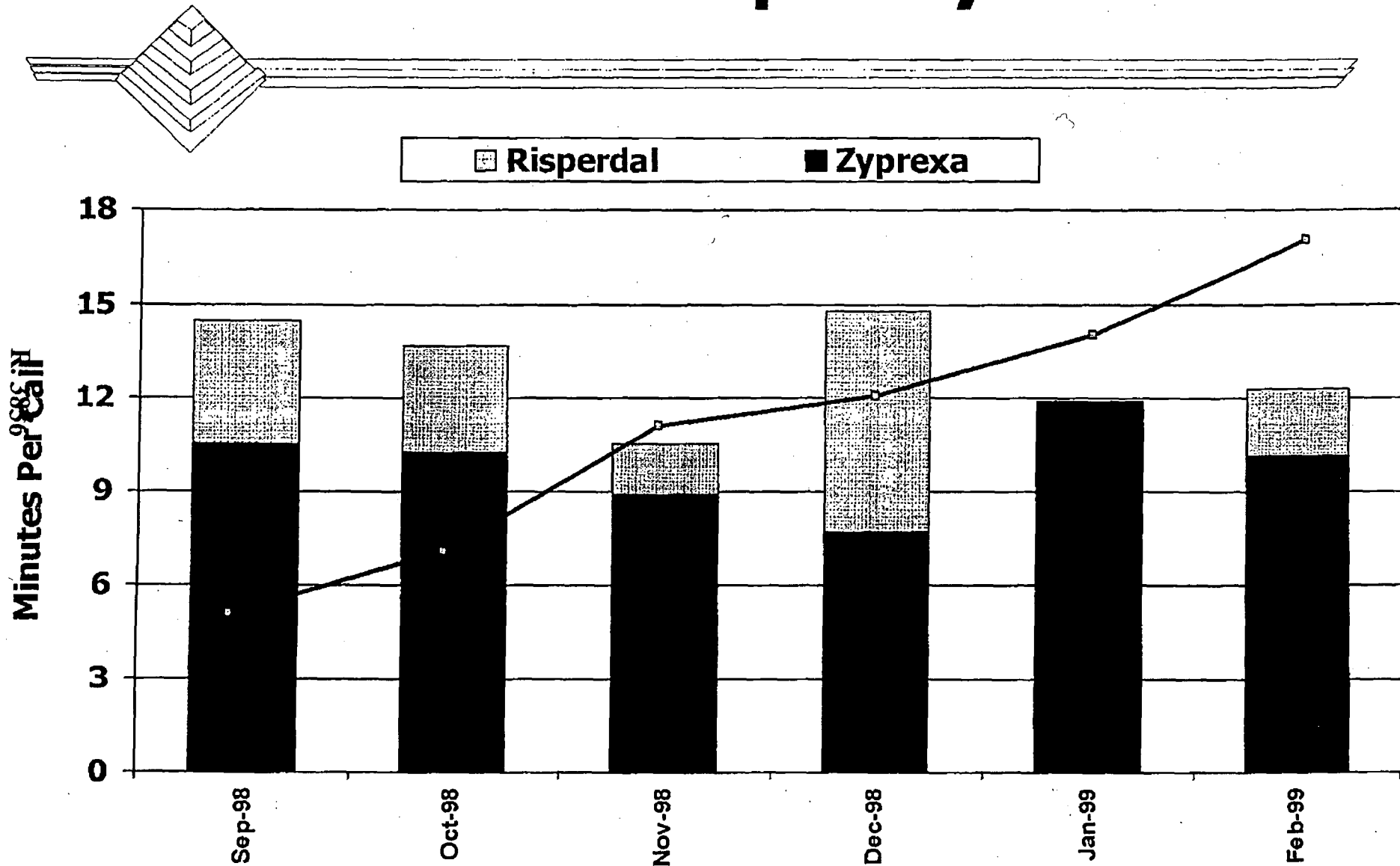
R. 3835
Minutes Per Call



Source: IMS IPS

Risperdal Detailing Includes Janssen, SKB, and Scios

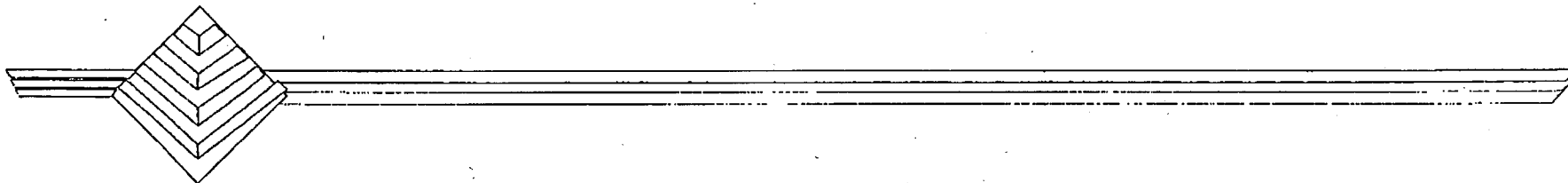
Call Frequency



Source: IMS IPS

Risperdal Detailing Includes Janssen, SKB, and Scios

Message Consistency

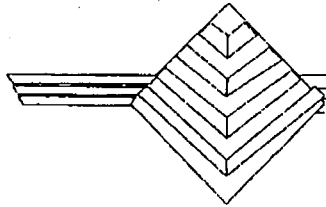


Efficacy

Weight Gain / Safety

Dosing

Home Office Support



Medical Meetings

20,000 MDs

Medical Ed Programs

15,000 MDs

Home Office Visitation

300 Top MDs

RISPERDAL Sales Forces

Partnership & Teamwork

R.3839

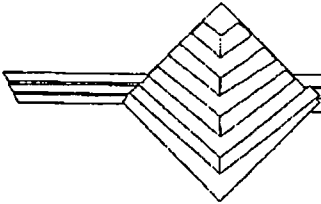
CNS-S
164

Scios
95

Eldercare
85

CNS-I
51

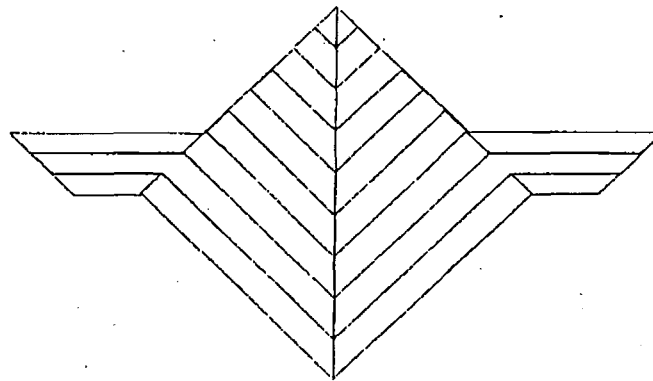
"Every Minute Counts!"



Our Strong Future in CNS...

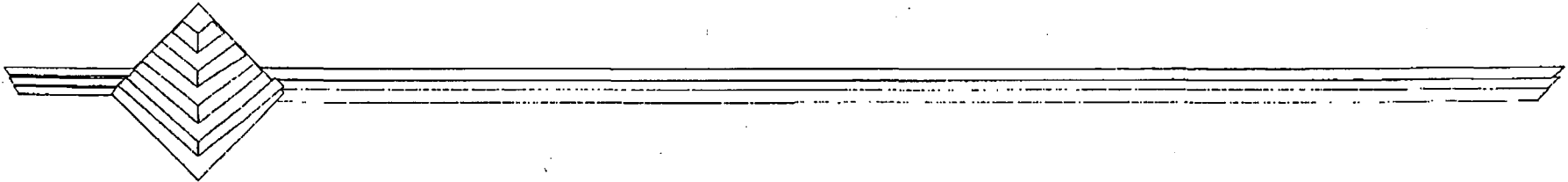
**... Will Be Built With
RISPERDAL!**

JANET VERGIS
Group Product Director, CNS



LUDWIG HANTSON
Franchise Director, CNS

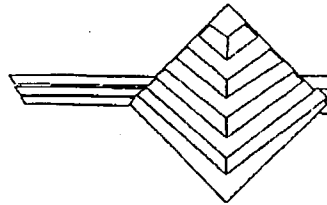
Congratulations!!



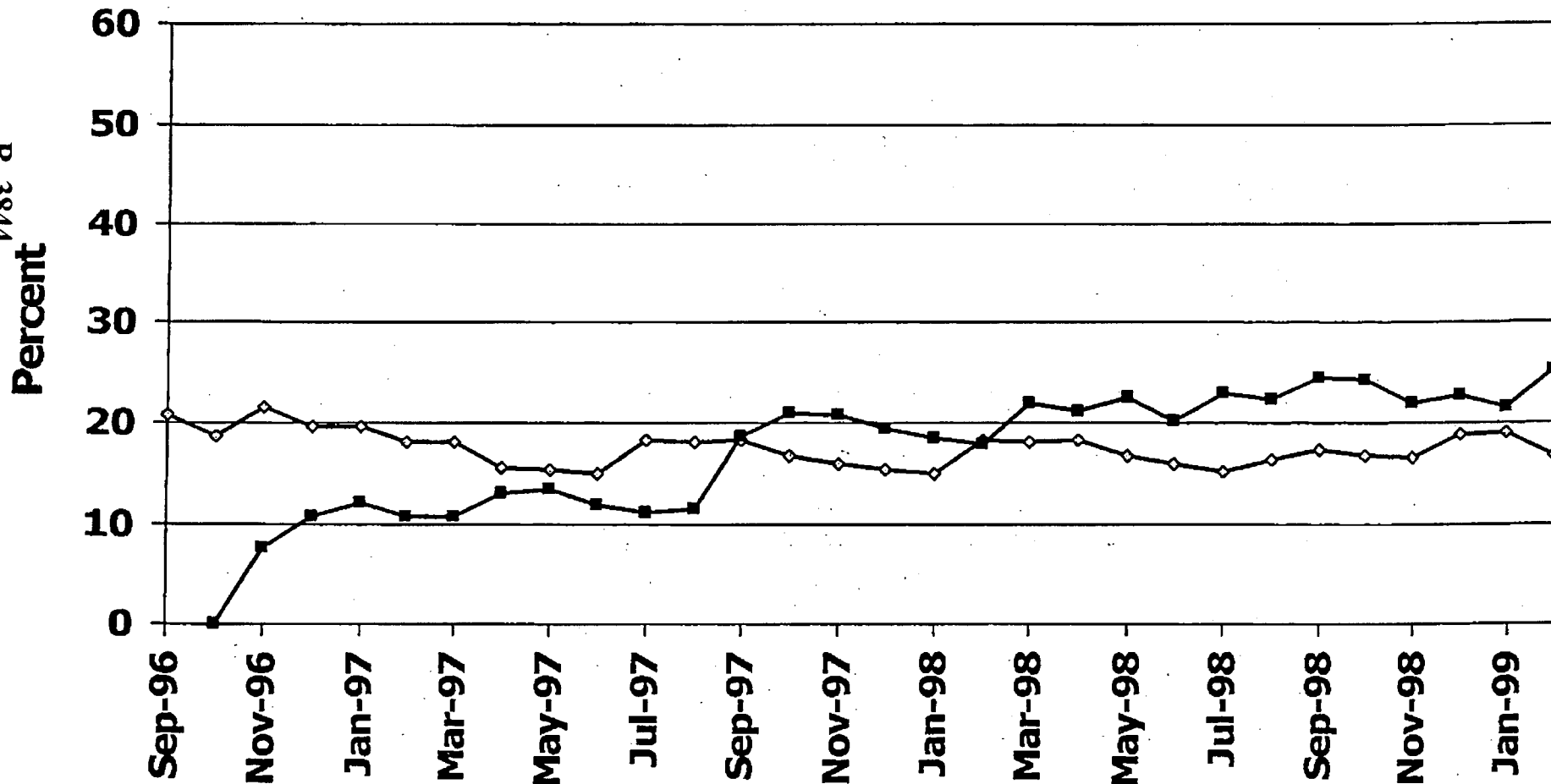
- **New High NRx Share 9-Months Running**
- **RISPERDAL Share Growth = Zyprexa Share Growth in 1999 (+1.1)**
- **Sales are up 39% over last year**
- **Sales are tracking to achieve \$____ in 1999**
- **RISPERDAL has been #1 for nearly 3 years!!**

APA 1999 MARKET RESEARCH

Schizophrenia Market Share



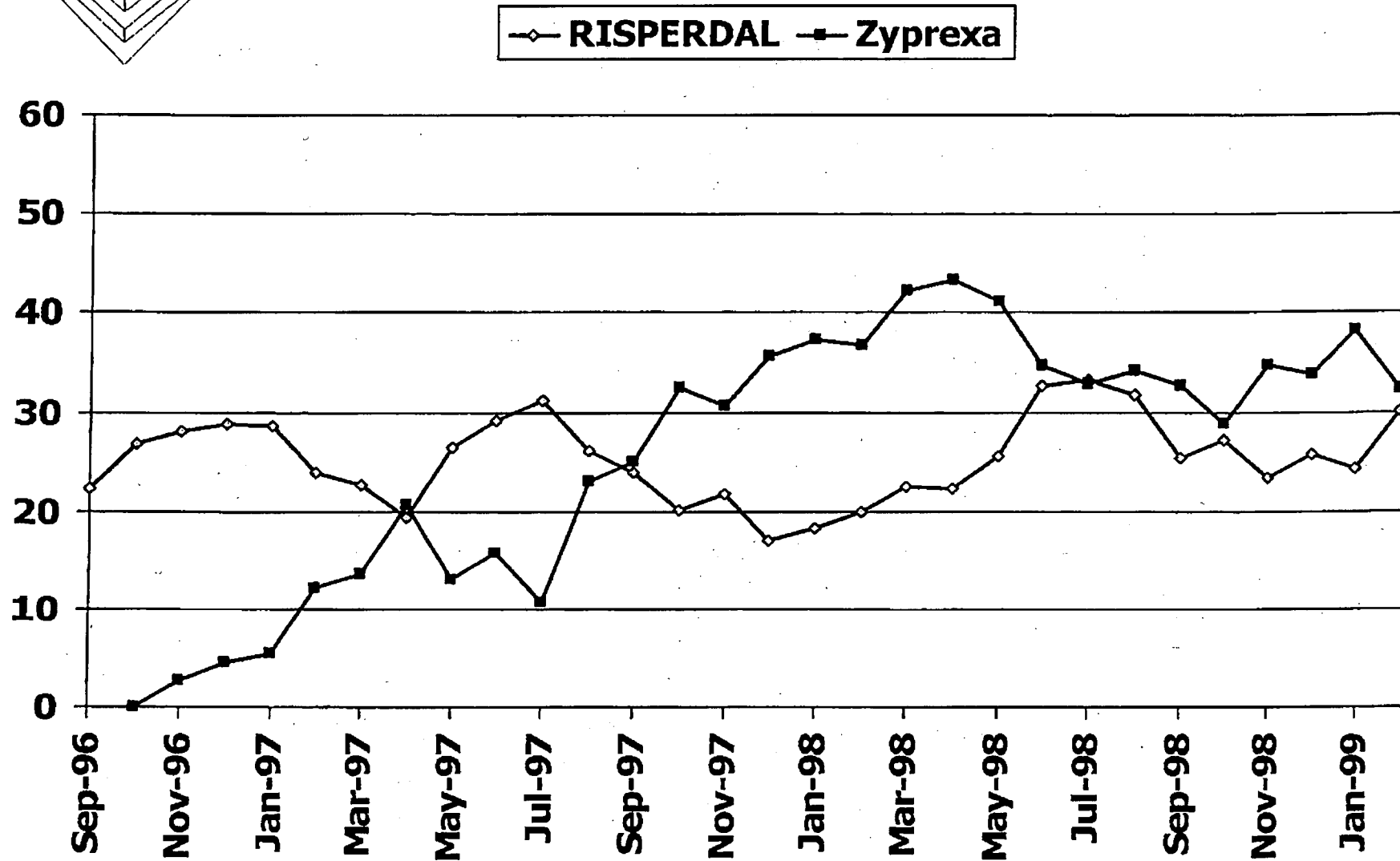
—◇— RISPERDAL —■— Zyprexa



Source: IMS NDTI (Market Share is based on antipsychotic agents only)

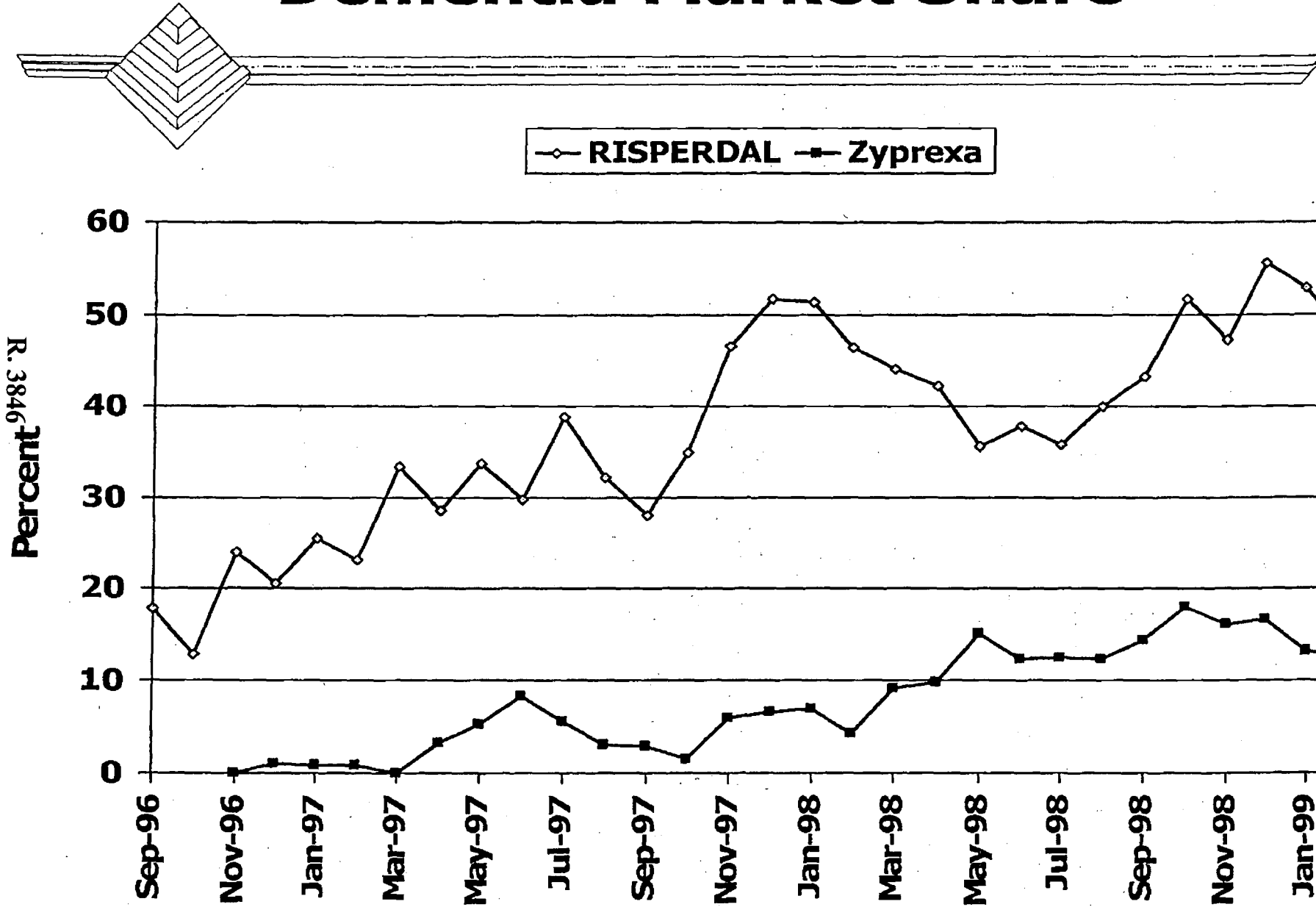
Bipolar Disorder Market Share

R. 3845



Source: IMS NDTI (Market Share is based on antipsychotic agents only)

Dementia Market Share



R. 3846

ce S N (M St s b or antipsychotic agents only)

NEW

RISPERDAL Sales Aids & Journal Ads

BASE

**Special
Populations**



NEW

RISPERDAL
0.25mg & 0.5mg Tablets

**0.25mg /
0.5mg**
Launch Ad

R. 3848

NEW

RISPERDAL

Sample Design

**Photo of
Sample
Put-Ups**

NEW

RISPERDAL

Relapse Prevention Trial

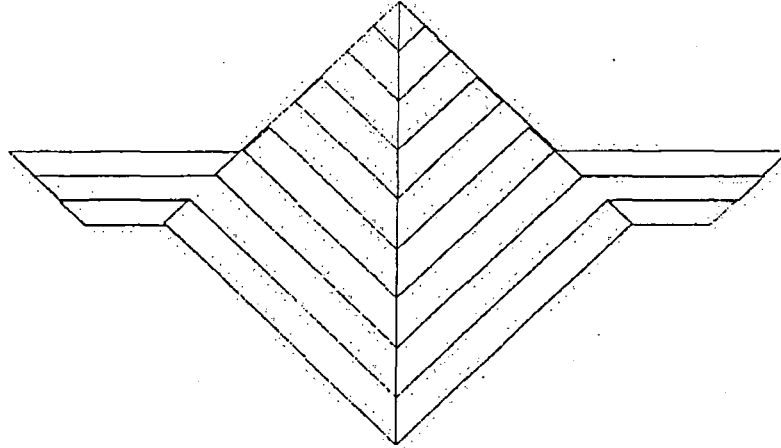
RIS-079
Poster

NEW

Home Office Advisory Programs CNS & ElderCare

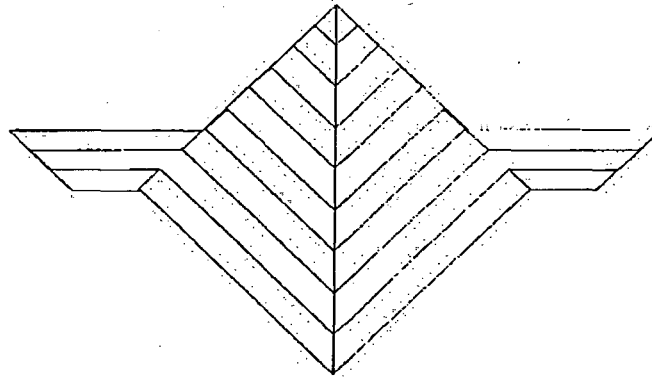
**Picture of
Janssen**

RISPERDAL '99



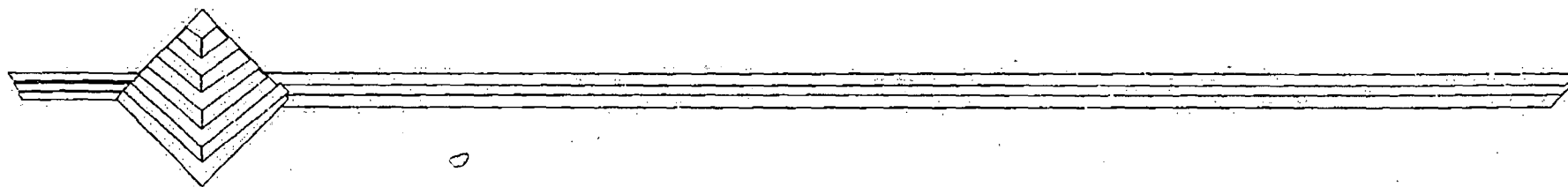
Make Every Minute Count!

MIKE WALSMAN
CNS National Sales Director



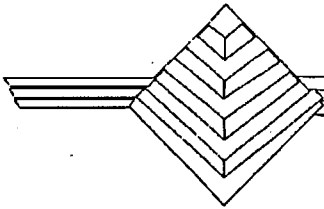
R. 3853

KEY POINTS



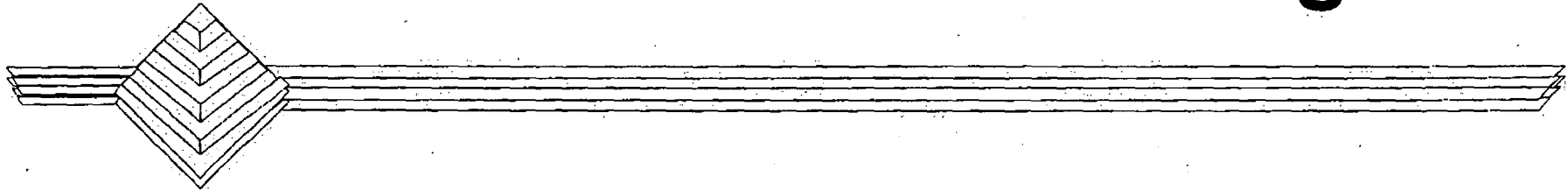
- Risperdal is #1!
- Importance of RISPERDAL!
- Janssen/J&J Commitment!
- Every minute counts-Preparation!

HOUSEKEEPING NOTES



- Check Your Agenda!
- Be on Time!
- This Evening Function!
 - 6:30pm

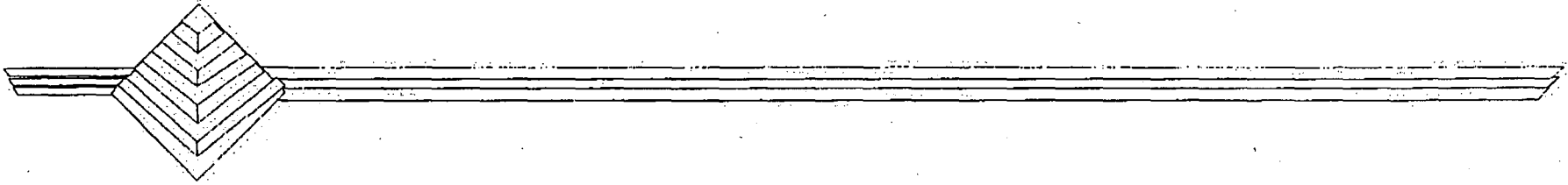
The RISPERDAL Challenge



“...Lilly not only scored all the points, but Janssen didn't even get a first down. They (Lilly) are going to bury them....It's a matter of time..”

K. Huer, SmithBarney, Dec. '96'

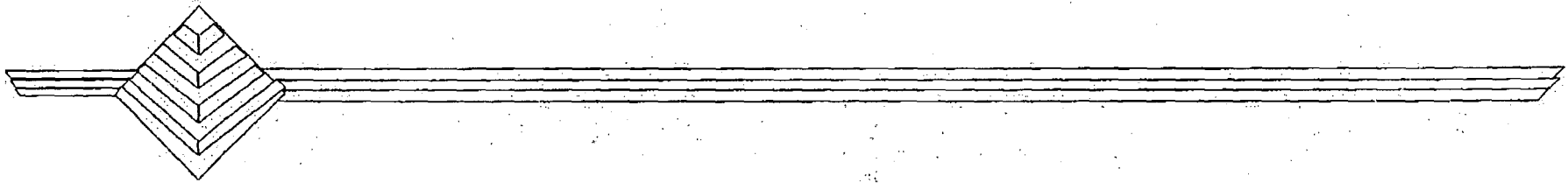
The RISPERDAL CHALLENGE



We woke up above ground today!

We're Still Here!

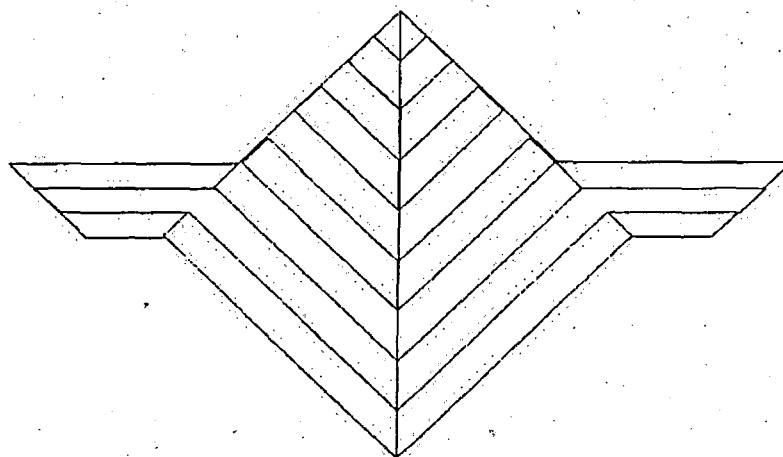
We're Still Growing!



WE'RE STILL #1!!

**WE'RE GOING TO
STAY #1!!!!!!**

RISPERDAL '99

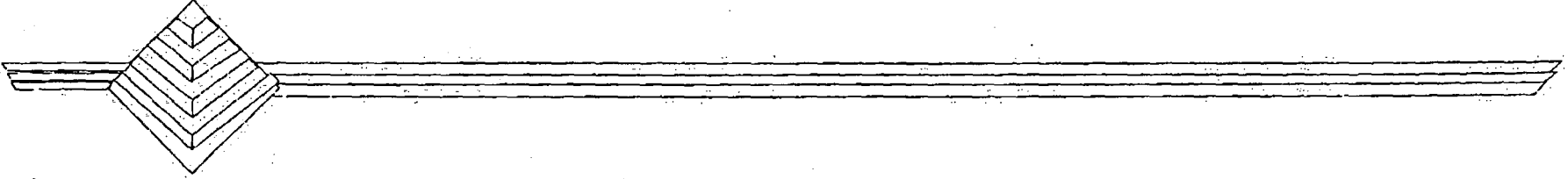


Make Every Minute Count!

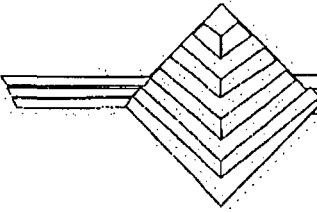
Selling Skills Presentation

Tuesday June 8, 1999

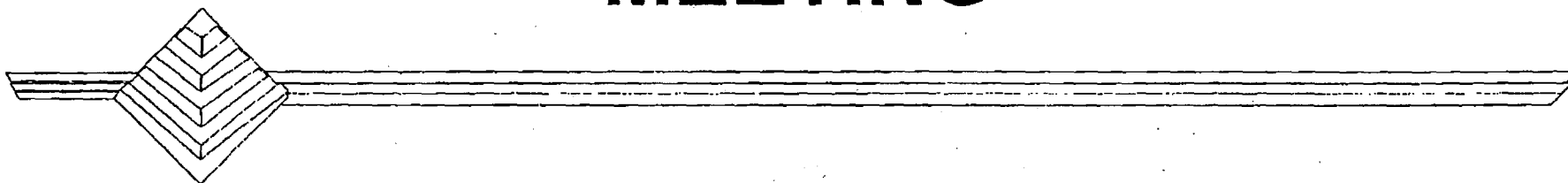
Why A New Selling Program?

- 
- Establish consistent selling platform for all representative/selling partners
 - Establish a consistent selling language for all representatives
 - Improve ability to fully engage physicians during sales calls

Why A New Selling Program?

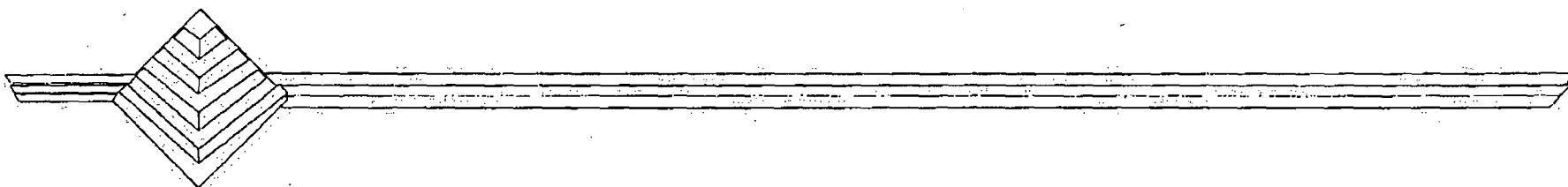
- 
-
- Provide well defined selling skills expectations:
 - Field Work Sessions
 - FCRs/Human Resources Review
 - Enhance competitive selling capability

RISPERDAL NATIONAL TRAINING MEETING



TEAM DAY PRESENTATION

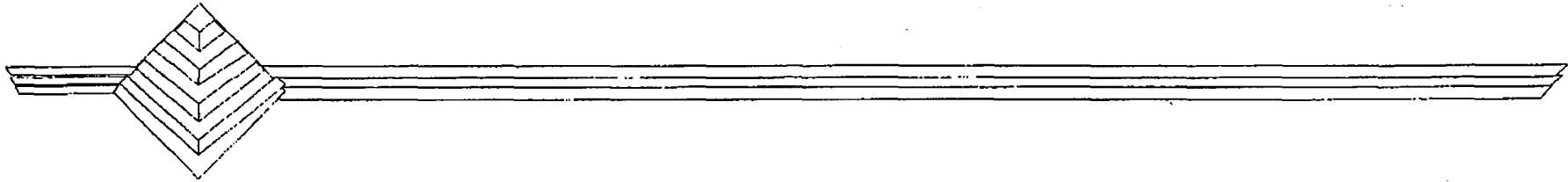
“Welcome to Team Day”



THE BEST OF THE BEST IN CNS

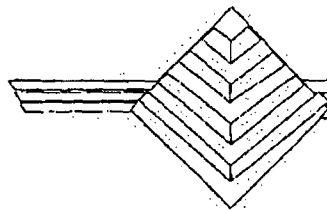
CNS - EC - SCIOS

TEAM DAY AGENDA



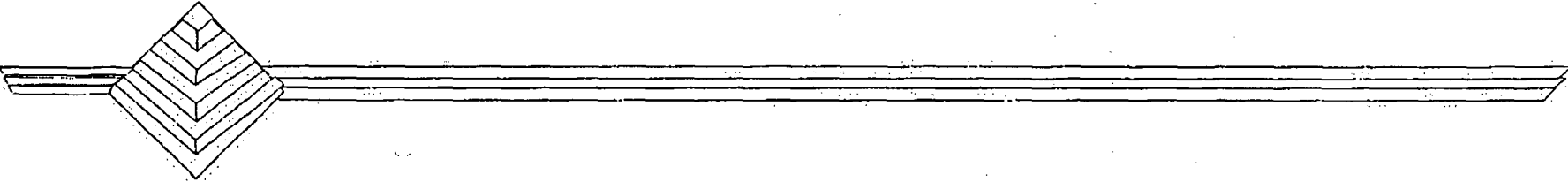
- Review Objectives
- Sales Direction
 - CNS
 - EC
 - SCIOS
- Breakout Session

Objectives



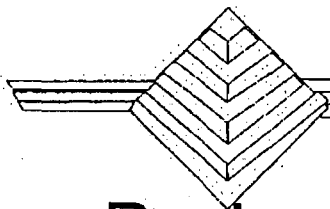
- Maximize 'Teamwork'
- Clarify Roles and Responsibilities
 - CNS - EC - SCIOS
- Understand Sales Direction for each Team
- Enhance Communication
- Maximize RISPERDAL® growth
- Follow up

General Guidelines

- 
- Communication
 - Big Picture

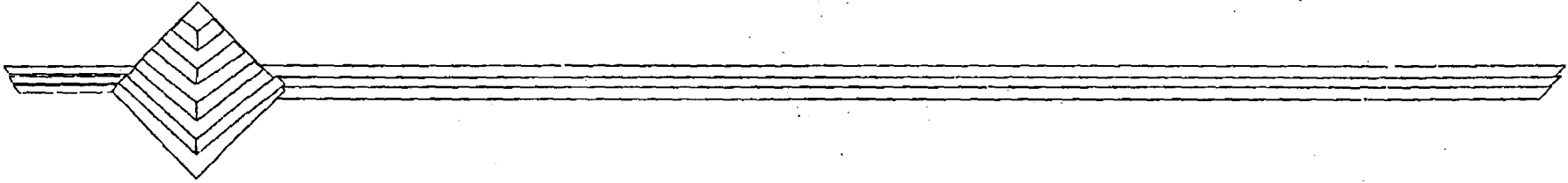
Breakout Session

Co-Promotion Partners



- Review 'Dual called on' key physicians and target accounts
- Develop specific action plans to:
 - Enhance coverage
 - Improve and Exchange Communication
 - Leverage Resources i.e. CME, speaker programs etc.
 - Grow RISPERDAL® share - both - schizophrenia and special population
 - Follow up - Develop a plan - What-Where-When-How?

CNS SALES FORCE

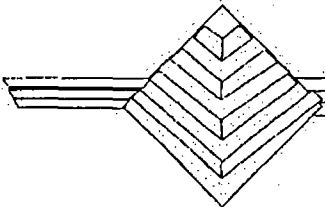


3Q99 SALES DIRECTION

R. 3869

CNS SALES FORCE

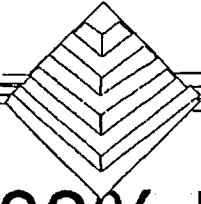
3Q99 OBJECTIVES



- GROW RISPERDAL Market Share!
- STOP the Growth of Zyprexa!
- REGAIN Market Share Leadership with Decile 8-9 Psychiatrists!
- OWN Schizophrenia Segment of Market!
- EXECUTE CNS Call Plan!

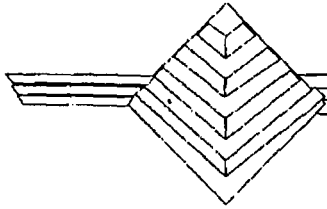
1999 CNS SALES DIRECTION

3Q99 CALL PLAN



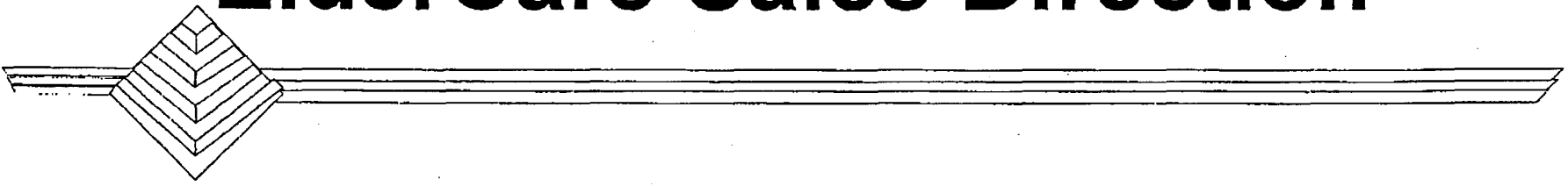
- 100% Reach on all target HVP physicians
 - S-Rep = Top 60 Physicians
 - I-Rep = Top 100 Physicians
- 90% 2X/mo Frequency on Decile 8-9 physicians
- Avoid Distractions - Maintain Focus!
- Maintain 2x/mo Hospital Call Activity!
- Partner with Scios to Maintain Decile 5-7 Call Activity!
- Effectively Utilize Resources!

RISPERDAL KEY COMMUNICATION POINTS



- Focus on ***EFFICACY*** FIRST!
- Emphasize **low weight gain!**
- Stress **appropriate dosing!**
- ***Ask*** for the **BUSINESS!**
 - Specific Patient Types

1999 3rd Cycle ElderCare Sales Direction



- **Target the Right Customers**

- Priority #1 - Prescribers

- Geriatric Psychiatrists/Consultant Psychiatrists
 - Medical Directors
 - Attending Physicians/Physician Extenders

- Priority #2 - Influencers

- Directors of Nursing
 - Facility Staff
 - Consultant Pharmacist

1999 3rd Cycle

ElderCare Sales Direction

- **Achieve Frequency on Targeted Customers**

Goal: 6 Physicians and 2 Nursing Homes/Day

<u>Prescribers</u>	<u>Frequency</u>	<u>Goal</u>
Psychiatrists	3x per Qtr	90%
Medical Directors	3x per Qtr	90%
Attending Physicians	3x per Qtr	65%
Hospice	3x per Qtr	90%
<u>Influcencers</u>		
Top 20 NH	3x per Qtr	80%
Bottom 20 NH	2x per Qtr	65%
Consult. Pharm.	As Needed	As Needed

1999 3rd Cycle ElderCare Sales Direction

- **Execute High Impact Sales Message**

- Consistent Core Message Delivery
- Tailored to Customer Need/Concern
- Execution of Multiple Product Presentations

- Risperdal - 50%

RED [REDACTED]

RED [REDACTED]

1999 3rd Cycle ElderCare Sales Direction

- Teamwork

LTC Manager

CNS

275

500 Blue & Gold

REDACTED

All Products

Risperdal

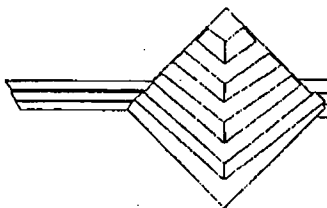
REDACTED

REDACTED

RISPERDAL TRAINING MEETING

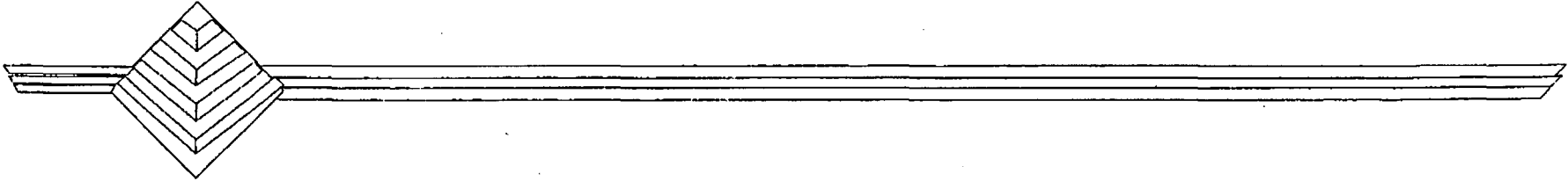
THURSDAY CLOSING SESSION

'THE BEST OF THE BEST'



WELCOME BACK!

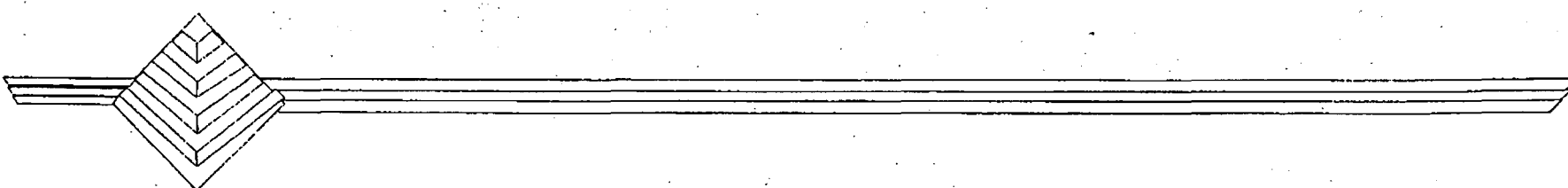
KEY OBJECTIVES



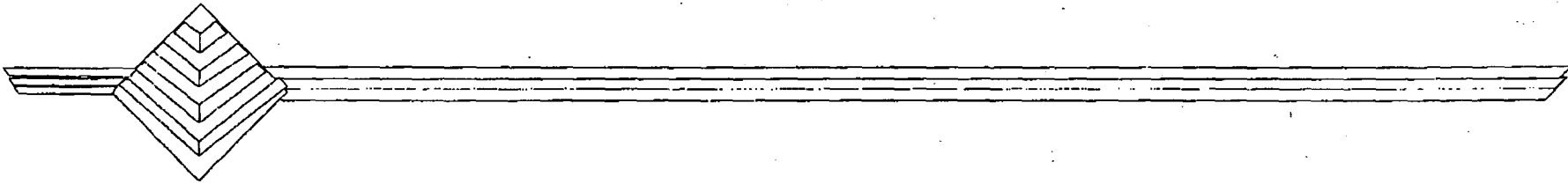
- ***GROW*** RISPERDAL SHARE!
- ***STOP*** THE GROWTH OF OLANZAPINE!

RISPERDAL

CRITICAL SUCCESS FACTORS

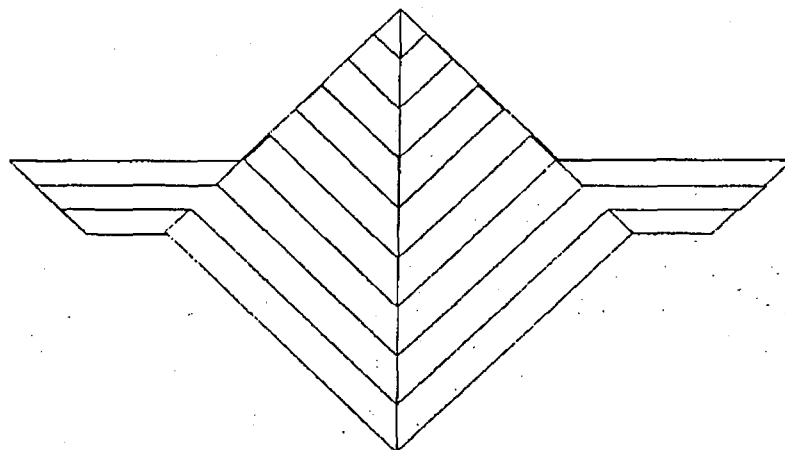
- 
- Pride & Confidence
 - Effective Use of New Sales Materials
 - Successful Execution of Call Plans
 - Effective Selling Skills
 - Maximize Teamwork

RISPERDAL CRITICAL SUCCESS FACTORS



'ASK FOR THE BUSINESS'

RISPERDAL '99



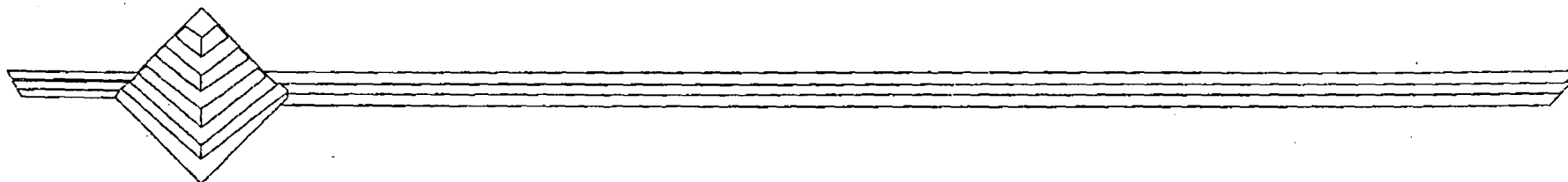
Make Every Minute Count!

RISPERDAL AWARDS BANQUET

Thursday June 10, 1999

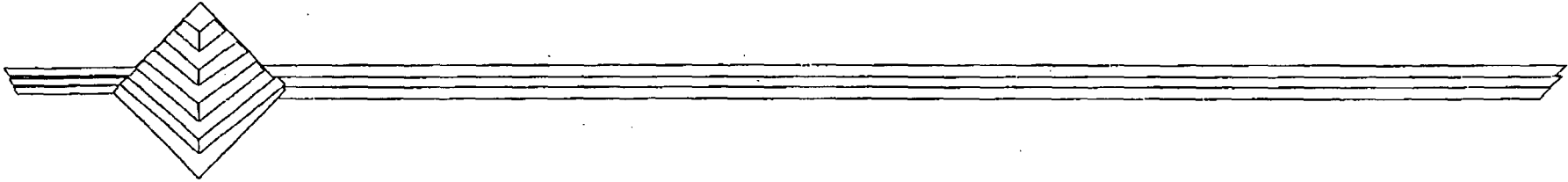
8:00pm

CNS 'SPRINT CONTEST' WINNERS



- Contest Period:
 - October 1998 - March 1999
- Top District per CNS Region (PI)
- Awards:
 - \$5,000 per District Manager
 - \$2,500 per District Members

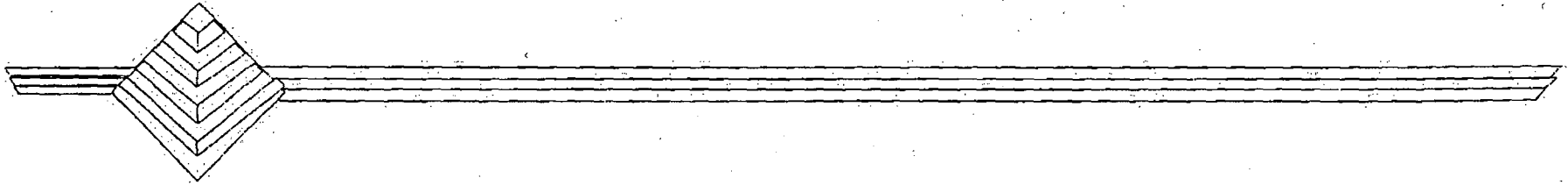
CNS SPRINT CONTEST WINNER EASTERN REGION



NEW YORK DISTRICT

Janet Petrillo, DM

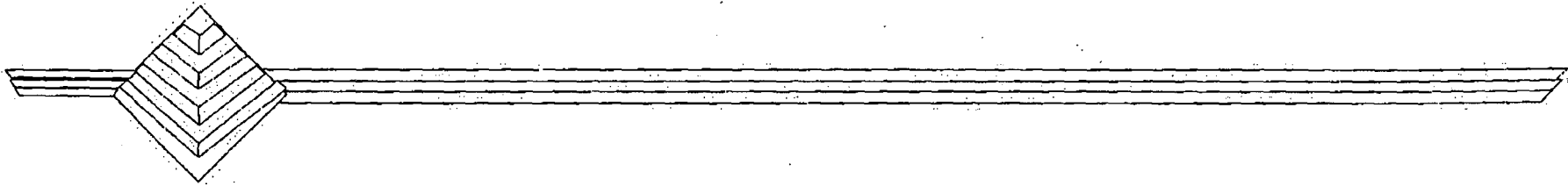
CNS 'SPRINT CONTEST' WINNER CNS CENTRAL REGION



CHICAGO CNS DISTRICT

Jeff Hoover, DM

CNS 'SPRINT CONTEST' WINNER WESTERN REGION



Los Angeles District

Jeff Doherty, DM

**RISPERDAL University Freshman Year
Minneapolis District**

Anthony Cartwright District Manager

Ben Breskovich

Elizabeth Bucholz

David Conforti

Lawrence Danger

Paula Dunnum

Susan Grogan

Rick Hansen

Sarah Kim

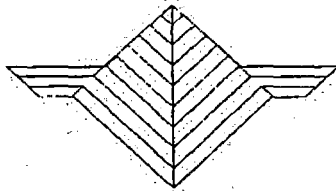
Lamont Roth

Saeed Siddiqui

RISPERDAL TRAINING MEETING

**TUESDAY AM
GENERAL SESSION**

MIKE WALSMAN
CNS National Sales Director



WELCOME TO SAN DIEGO!



'THE BEST OF THE BEST IN CNS'

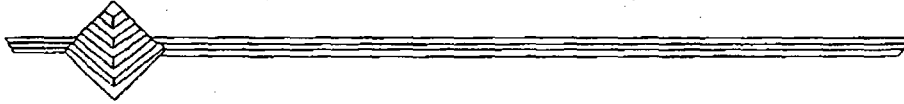
CNS SALES FORCE!

ELDERCARE SALES FORCE!

SCIOS SALES FORCE!

- Welcome Everyone
- 'What's the #1 antipsychotic on the market?
- Why! - Best Product & Best People
- Ask three sales forces to stand - acknowledgement
- Sales Force growth 65-over 350!

'THE BEST OF THE BEST IN CNS'



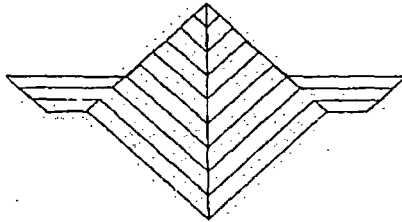
RISPERDAL IS #1!

RISPERDAL IS THE MARKET LEADER!!

**RISPERDAL WILL STAY THE
MARKET LEADER!!!**

RISPERDAL

National Sales Meeting



"Every Minute Counts"

- Theme - Why because our forecast for 1999 is \$874MM!
- Every minute - every day - every call will make the difference

1999 Sales Objective



\$874 MM

- Other way to look at it:
- Everyone needs to sell \$3.5MM/day or \$6,000/min of RISPERDAL to achieve our forecast.
- So far in 1999 you have made every minute count. Let's look back at how we have performed against the sales goals we put in place during our 1998 National Sales Meeting

\$874 Million:
"Every Minute Counts"



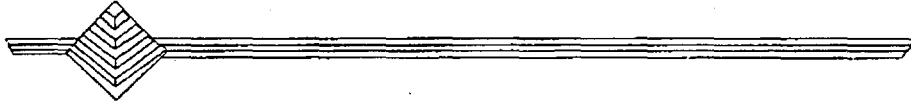
\$874 Million

\$3.5 Million / Day

\$350,000 / Hour

\$6,000 / Minute

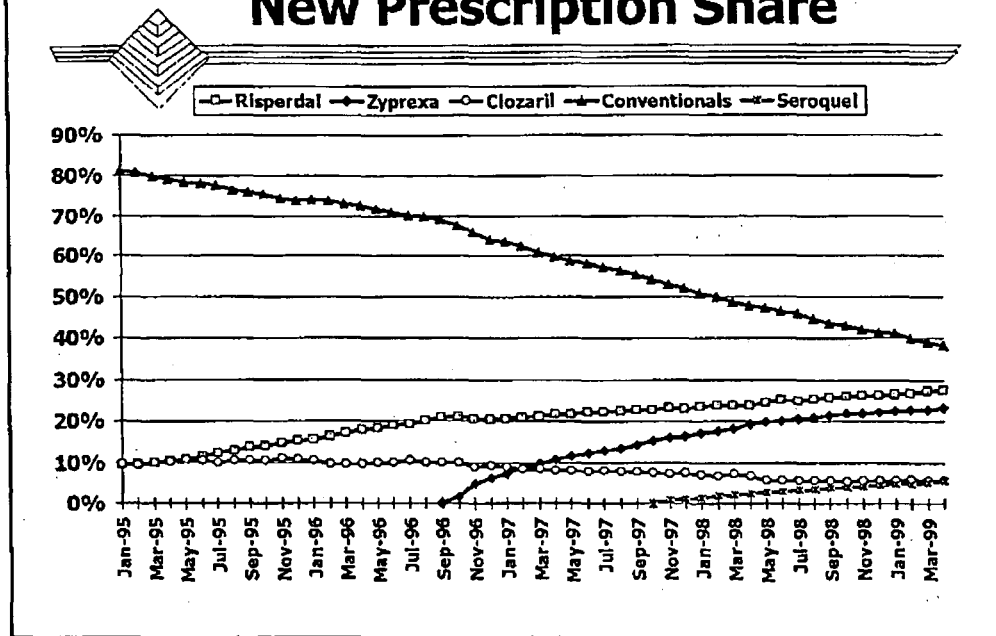
1998 RISPERDAL Sales Meeting: Goals



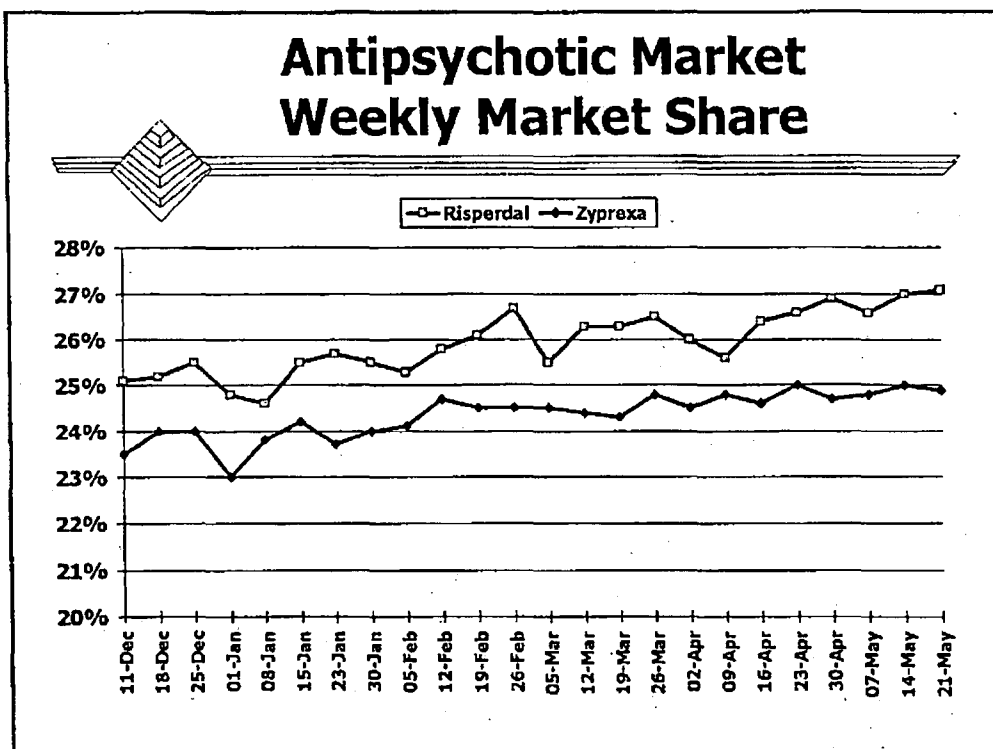
- **Grow RISPERDAL Share!**
- **Stop the Growth of Zyprexa!**
- **Maintain #1 Prescribed Position!**

- Set goals of Growing Risperdal Share
- Next - Stopping the growth of olanzapine
- Lastly, maintaining and growing our #1 prescribed leadership position

Antipsychotic Market New Prescription Share

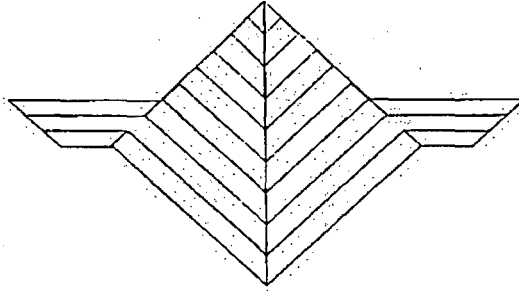


•Grown Risperdal Nrx share for 9 consecutive months



• Looking at weekly share - we are stopping the growth of olanzapine!

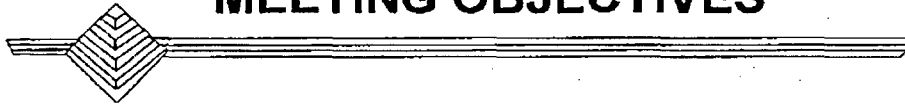
RISPERDAL



**Remains
The #1 Prescribed Antipsychotic**

- Lastly - maintained the #1 position of RISPERDAL in the market!
- Pride in this outstanding accomplishment.
- Congratulations..you are accomplishing ALL three of our critical goals for RISPERDAL and you are making every minute count.

MEETING OBJECTIVES



- ***GROW our #1 Position!***
- ***DOMINATE Psychiatry Marketplace!***
 - Use of New Sales materials!
 - Improve our Competitive Selling Skills
 - Maximize Teamwork!

• Our objectives for this years continue the trends we have established over the past year.

• It's now time to grow our #1 position in the market by achieving a psotion of dominace in Psychiatry.

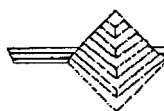
• We will accomplish these objectives at this meeting by

• Effectively using the excellent new selling materials the brand has prepared.

• By improving our competitive selling skills

• And by closely working together to enchance our teamwork

Agenda



Tuesday

- General Session/Brand Breakouts
- CNS/Scios Selling Skills Training
- ElderCare General Session/Breakouts
- Special Evening Function

Wednesday

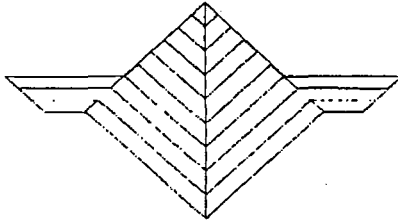
- CNS/Scios Selling Skills Training
- ElderCare General Session/Breakouts
- Scios Awards Banquet
- Janssen 'Free Night'

Thursday

- CNS/ElderCare/Scios Team Day
- District Meetings
- Janssen Awards Banquet

- In order to meet our meeting objectives, let's review our agenda for the next three days.
- Everyone should review their individual agenda and insure you are 'on time' for each session.

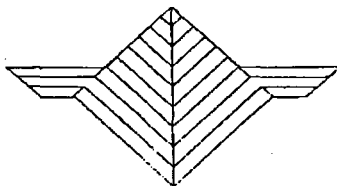
RISPERDAL National Sales Meeting



"Every Minute Counts"

- Let's make every minute count over the next three days!
- Are you ready!!
- Let's do it!!

DAVID NORTON
President, Janssen Pharmaceutica



1998 RISPERDAL Sales



\$698 MM

(Exceeded Forecast by \$_____ MM)

In order to achieve our dollar and share objective, it is incredibly important that we are the market leaders in schizophrenia and bipolar disorder.

Achieving the forecast in 1999 is critical to our goal of \$1 Billion in 2000, and it will also significantly impact Janssen's as well as J&J's bottom line.

This represents a 20.9% growth over last year and in 1998 we grew 20% versus 1997.

(Current monthly NRx - 25.8%, Oct.)

RISPERDAL Annual Sales

