

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 XIII

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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

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NDA 20-272, NDA 20-588
RISPERDAL® (risperidone) Tablets and Oral Solution

Response to FDA Request for Information: Evaluation
of the Effect of Risperidone on Glucose Metabolism

August 10, 2000
Vol. 1 of 15

JJRP 00379863
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D807.1

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• 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.

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R. 5900

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• 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.

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R. 5901

- 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 "Brian J. Maloney R.Ph. 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 <i>(Title 21, Code of Federal Regulations, 314 & 601)</i>		Form Approved: OMB No. 0910-0338 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) 730-3486		FACSIMILE (FAX) Number (Include Area Code) (609) 730-3091
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-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyridin-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, contact, 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 356a (4/97)

JJRP 00379868
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D807.6

R. 5904

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 application 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
<i>Edward G. Brann</i>		August 10, 2000
TYPED NAME AND TITLE		
Edward G. Brann, Asst. Dir., Regulatory Affairs		
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 531-H 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 356h (4/97)

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 D807.7

R. 5905

1 COMPREHENSIVE
INDEX

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D807.8

COMPREHENSIVE INDEX

<u>ITEM</u>	<u>CONTENTS</u>	<u>VOLUME</u>	<u>PAGE</u>
	Cover Letter		
	FDA Form 356h		
1	COMPREHENSIVE INDEX	1	2
	FDA letter (01 May 2000)	1	2
	Foreign Reg. Agencies	1	4
	Sweden	1	4
	United Kingdom	1	11
3	INTEGRATED SUMMARY	1	15
	De Smedt G, et al. Integrated Summary of the effects of risperidone on glucose metabolism and weight. Janssen Research Foundation, August 2000; Integrated Summary Report.	1	15
5	NONCLINICAL	1	28
	Verstynen A, et al. Risperidone: Preclinical observations of glucose metabolism-related changes. Janssen Research Foundation, July 2000; Nonclinical Summary.	1	28
8	CLINICAL DATA	1	40
8.1	Clinical Trial Data	1	40
	List of Trials	1	40
	De Smedt G, et al. Evaluation of the effects of risperidone on glucose metabolism in Phase 1-3 trials. Janssen Research Foundation, July 2000; Clinical Research Report.	1	42
8.2	Pharmacovigilance Data	15	1
	De Deene A., et al. Reported disturbances of the glucose metabolism with risperidone: a post-marketing review. Janssen Research Foundation, June 2000; International Pharmacovigilance Report.	15	1
8.3	Epidemiology Study	15	165
	Grogg A. Antipsychotics and Type II Diabetes. Hecon Associates, Inc., July 2000; Epidemiology Report.	15	165
8.4	Literature Review	15	207

Volume 1/Page 1

JJRP 00379871

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D807.9

FDA letter (01 May 2000)

JJRP 00379872
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D807.10



MAY 1 2000

NDA 20-272

NDA 20-588

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

Dear Ms. Wagner-Weber:

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

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

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

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

Volume 1/Page 2

JJRP 00379873

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D807.11

NDA 19-758

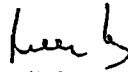
Page 2

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

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

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

Sincerely,



Russell Katz, M.D.

Director

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Volume 1/Page 3

JJRP 00379874
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D807.12

Foreign Reg. Agencies

JJRP 00379875
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D807.13

Janssen Research Foundation
NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

LÄKEMEDELSVERKET
Medical Products Agency
Programmer för medicinsk efterkontroll

Protokoll nr L6E: 14/2000

Protokoll över kontroll av farmaceutisk specialitet

Asp nr
92-0109

Tillverkare/ombud
Janssen-Cilag AB
Box 7073
192 07 SOLLENTUNA

Benämning
RISPERDAL, tabl 1 mg

På Pharmacovigilance Working Party har frågan väckts om en möjlig klasseffekt för atypiska neuroleptika, främst clozapin, olanzapin, risperidon och quetiapin, vad gäller påverkan på glukosmetabolismen i riktning mot nedsatt glukostolerans/diabetes mellitus. Den svenska myndigheten har utsetts att utreda denna fråga inom EU. Utredningen syftar till att fastställa om alla ovanstående substanser har denna biverkning. Informationen om dessa biverkningar i produktresuméerna kommer samtidigt att ses över och det kommer att tas ställning till eventuellt behov av gemensamma texter (klasseffekter).

Vi ber Er därför sammanställa rapporter kumulativt fram till april 2000 avseende påverkan på glukosmetabolismen (nedsatt glukostolerans, hyperglykemi, ketoacidosis, ketonuri, glykuri, diabetes mellitus, förvärrad diabetes mellitus, reaktiverad diabetes mellitus, diabeteskoma etc) för (produktnamn). Vid analysen bör hänsyn tas till dos, behandlingstid, resultat av utsättning och eventuell återinsättning samt till viktiga riskfaktorer såsom kön, obesitas/BMI, viktuppgång, kardiovaskulära riskfaktorer, samtidig annan behandling, tidigare förekomst av hyperglykemi, arvet för diabetes mellitus och etnicitet (vissa folkgrupper har känd hög förekomst av diabetes mellitus). Rapporter avseende olika svårighetsgrader av hyperglykemi (t ex diabeteskoma) bör redovisas separat. Incidensen av dessa biverkningar bör redovisas separat för kliniska prövningar och för spontanrapporteringsdata efter marknadsföring.

Eventuellt förslag till ändring i produktresumé/FASS-text emotses.

Vi vore tacksamma för Ert svar till 2000-06-05

Uppsala 2000-04-20

Karin Hedeumalm
Karin Hedeumalm, specialistläkare

Följande åtgärder föreslås:

Uppsala 2000- _____

Volume 1/Page 4

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D807.14

Janssen Research Foundation

NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

[Translation prepared by Janssen]

Medical Products Agency
Box 26
751 03 Uppsala
Sweden

April 20, 2000

Janssen-Cilag AB
Box 7073
192 07 Sollentuna
Sweden

Re: Protocol L6E: 14/2000

The question has been raised at the Pharmacovigilance Working Party whether there is a possible class-effect for atypical neuroleptics, mainly clozapine, olanzapine, risperidone and quetiapine, concerning an influence on the glucose metabolism towards an impaired glucose-tolerance/diabetes mellitus. The Swedish authorities have been appointed to analyze this question within the EU. The analysis is aiming at establishing if all of the above mentioned substances has this adverse effect. The information regarding these adverse effects in the summary of product characteristics will concomitantly be revised and a commitment for a need for comment texts (class effects).

We would therefore like you to compile reports cumulatively up to April 2000 regarding the influence on glucose metabolism (decreased glucose tolerance, hyperglycemia, ketoacidosis, ketonuria, glycosuria, diabetes mellitus, deteriorated diabetes mellitus, reactivated diabetes mellitus, diabetic coma, etc.) for (product name) [Risperdal]. In the analysis consideration has to be taken to dose, treatment time, results of discontinuation of therapy and possible rechallenge of medication as well as important risk factors such as sex, obesity/BMI, weight increase, cardiovascular risk factors, concomitant other treatment, previous occurrence of hyperglycemia, heredity for diabetes mellitus and ethnicity (some ethnic groups have a high occurrence of diabetes mellitus). Reports concerning different severity of hyperglycemia (e.g., diabetic coma) are to be shown separately. The incidence of these adverse effects is to be shown separately for clinical trials and spontaneous post-marketing data, respectively.

A revised summary of product characteristics is awaited.

Respond no later than June 5, 2000.

Volume 1/Page 5

JJRP 00379877

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D807.15

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-CILAG

Läkemedelsverket
Samordningskansliet
Box 26
751 03 UPPSALA

2000-05-18

ELSA/ellb

Asp nr 92-0109

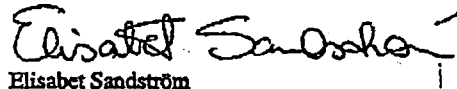
Att: Karin Hedenmalm
Programmet för medicinsk efterkontroll

Risperdal tabletter 1 mg – fråga angående påverkan på glukosmetabolismen
Protokoll över kontroll av farmaceutisk specialitet, protokoll nr L6E: 14/2000

Enligt telefonsamtal med Bengt Lindeskog har vi fått svarsfrist till den 26 juni för att företaget ska kunna samordna med svaret till den brittiska myndigheten.

Med vänlig hälsning

JANSSEN-CILAG AB
Regulatory Affairs


Elisabet Sandström

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Sweden

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Volume 1/Page 6

JJRP 00379878
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D807.16

R. 5914

Janssen Research Foundation

NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

Translation in to English

Medical Product Agency
Box 26
751 03 UPPSALA
Sweden

May 18, 2000

ELSA/ellö

Attn: Karin Hedenmalm
The unit for medical follow-up

Risperdal tablets 1 mg – evaluation of the effects of glucose metabolism
Protocol of control of pharmaceutical speciality, protocol No. L6E: 14/2000

According to telephone call with Bengt Lindeskog, we have been given respite until June 26 to give the company the opportunity to co-ordinate the answer to the British authorities.

Yours sincerely,

JANSSEN-CILAG AB
Regulatory Affairs

Elisabet Sandström

Volume 1/Page 7

JJRP 00379879
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D807.17

R. 5915

26th June 2000

Medical Products Agency
Box 26
SE-751 03 UPPSALA/SWEDEN
Attn: Dr. Örjan Mortimer

Dear,

Re: Risperdal – evaluation of the effects on glucose metabolism

Further to the MPA's request to evaluate the effect of Risperdal on glucose metabolism as it has been raised at the Pharmacovigilance Working Party to investigate a possible class-effect for atypical neuroleptics, we have recently analysed the relevant safety data from our extensive clinical and pharmacovigilance databases.

We hereby enclose two reports which provide all available clinical and pharmacovigilance information in determining whether Risperdal has an effect on glucose metabolism.

- Evaluation of the effects of risperidone on glucose metabolism in phase 1-3 trials
Clinical Report – Summary of safety – glucose related events, 23 June 2000.
- Risperidone and diabetes
International Pharmacovigilance Report, 23 June 2000.

The first clinical report summarises the data from over 11,000 psychiatric patients of 55 Phase 2-3 and 10 Phase 1 world-wide trials encompassing three age groups (adolescent, adult and geriatric) performed over the last 15 years. These data were reviewed for adverse events associated with abnormalities in glucose metabolism.

Four Phase 2-3 trials were not included in the analysis because they were not available in the appropriate database format. These trials represent a total of about 500 patients or 5% of the present database. Based on the relatively low incidence of glucose-related events from the present analysis, it is not expected that the data from these trials will have an important impact on the overall conclusions.

The incidence of adverse events related to abnormalities in glucose metabolism in Phase 2-3 trials was evaluated in patients treated in short-term trials, in long-term trials and in all trials regardless of the design or duration. The overall incidence of these events was very low with risperidone treatment (0.82% in 8402 patients). For the short-term trials, there was a lower incidence with risperidone treatment (0.60% of 5330 patients) compared with placebo or olanzapine treatment (0.81% of 868 patients and 0.89% of 448, respectively). The incidence was higher with both risperidone and placebo treatment when compared with haloperidol and other neuroleptics (0.14% of 712 patients and 0.34% of 293, respectively, in short-term trials) (i.e. zuclopentixol, perphenazine, remoxipride, clozapine, methotrimeprazine). When comparisons were made between patients treated in long-term trials, there was a lower incidence with risperidone treatment (1.2% of 3072 patients) than with haloperidol treatment (1.99% of 302 patients). There are no long-term double blind trials with placebo, olanzapine or other neuroleptic treatments.

About 50% of the events were a worsening of a pre-existing condition rather than an induction of diabetes or abnormal glucose metabolism. The percentage of patients with placebo (57%), risperidone (43%) and haloperidol (57%) treatment who had pre-existing abnormalities in glucose metabolism are similar. Therefore, interpretation of the results was unhampered by possible imbalances in this factor.

Volume 1/Page 8

JJRP 00379880

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D807.18

The occurrence of deaths was indistinguishable between risperidone (0.01%, 1 in 8402 patients) and placebo treatment (0%, 0 in 868 patients), haloperidol (0%, 0 in 1014 patients), and other neuroleptics (0%, 0 in 741 patients). In addition, the incidence of serious glucose-related adverse events was lower with risperidone treatment (0.15% in 8402 patients) than with placebo or haloperidol (0.35% in 868 patients and 0.30% in 741 patients, respectively). No serious adverse events were reported related to abnormalities of glucose metabolism with other neuroleptics. Discontinuations due to glucose-related adverse events was also lowest in risperidone-treated patients (0.04% of 8402 patients) than with placebo (0.12% in 868 patients) or with haloperidol (0.20% in 1014 patients). No discontinuations were reported related to abnormalities of glucose metabolism with the other neuroleptics in 741 patients.

Subgroup analyses showed a higher incidence of glucose abnormalities in elderly and black patients. This is consistent with epidemiological studies reporting a higher risk in black and elderly patients^(1, 2, 3). The higher incidence of adverse events in females is most likely due to the high proportion of elderly women. Two-third of the elderly patients were female.

Data from 10 Phase 1 trials support the finding in the Phase 2 and 3 trials that there is no evidence that treatment with risperidone induces significant abnormalities in glucose metabolism.

Therefore, there appears to be no evidence in a large body of clinical data that abnormalities of glucose metabolism were occurring at a higher rate in patients treated with risperidone compared with those patients treated with placebo. The higher incidences seen in black patients, elderly and female patients are due to the fact that elderly and black patients are more at risk for abnormalities in glucose metabolism and that a higher proportion of elderly women was included as part of the trials.

The clinical report presents the data as requested by the Agency. All adverse events (including severity) related to abnormalities of glucose metabolism (glucose-related adverse events) are listed. The incidence of adverse events were attributed to the treatment at onset of each event and were analysed by treatment, by age group, by trial design (blinding and duration) and by demographics (sex and race). Comparison of risperidone versus placebo, haloperidol, olanzapine and other neuroleptics were performed as well.

Analysis by dose level was not done as part of the aforementioned evaluation because several trials had a flexible dosing regimen and the timeframe of this evaluation did not allow this more extensive analysis. The same applies to the relationship between glucose-related adverse events and weight changes. These time-consuming and in-depth analyses will be further provided upon completion (projected timeline 08-09/00).

The influence of other concomitant medication and/or diseases (e.g. cardiovascular risk factors) has not been examined in detail in this evaluation. Annex 2 of the clinical report however provides information on concomitant medication/disease on an individual patient level. An investigation of the heridity of diabetes mellitus and of a rechallenge was not possible as this information was not recorded.

¹ Incidence, prevalence, and mortality of diabetes in a large population. A report from the Skaraborg Diabetes Registry: Berger B, Stenstrom G, Sundkvist G. Diabetes Care 22(5): 773-8, 1999 May

² Blood pressure increase with impaired glucose tolerance in young adult American blacks. B. Falkner et al. 1999 American Heart Association; Hypertension 1999;34: 1086-1090

³ Increased insulin resistance and insulin secretion in nondiabetic African-Americans and Hispanics compared with non-Hispanic Whites. S. Haffner et al. The insulin resistance atherosclerosis study. Diabetes, Vol 45, June 1996: 741-747

The second pharmacovigilance report provides an overview of all world-wide reported post-marketing spontaneous adverse event (AE) reports on disturbances of the glucose metabolism in association with risperidone, received by the International Pharmacovigilance (IPV) Department of the Janssen Research Foundation since the first marketing of risperidone in May 1993 through 31 March 2000.

In total 202 (1.2%) spontaneous case reports, dealing with WHO-Art dictionary codes indicative for disturbances in the glucose homeostasis, have been retrieved from the international safety database. In 41 of the cases, newly recognised diabetes was diagnosed. In 60 patients diabetes was already pre-existent. In 26 from the remaining 101 cases the onset of the diabetes was not attributable; in the residual 75 cases a concise diagnosis of the underlying cause of the glucose homeostasis disturbance was impossible. Distinction between type I and type II DM is very difficult because of the scarcity of relevant information.

The available information on body weight was very limited. However, in the set of patients with glucose related AEs, the ratio for overweight and BMI was higher than in the none-glucose related group. This was to be expected, since overweight is a known risk factor for diabetes mellitus. The proportion of cases with "weight increase" during risperidone treatment, however, seems not to be higher than in the none-glucose related group.

A distinction in different subgroups in relation to the ethnicity was impossible because this information was not communicated by the reporters.

Given the extensive cumulative exposure estimated at 3,541,514 patient years (through 31 March 2000) and with reference to literature data, the total of 41 cases of possible newly recognised diabetes cases can be considered to be extremely low. Even if the worst case scenario is adopted (meaning that all 202 cases are newly diagnosed diabetes), the reported incidence of diabetes with risperidone exposure, remains extremely low. This report is in line with the previous IPV report on diabetes (dated March 1996) and demonstrates that the incidence of diabetes mellitus doesn't seem to be increased by risperidone. The currently available cumulative spontaneous safety data do not point to a relationship between the use of risperidone and disturbances in glucose homeostasis and do confirm the findings as observed in the clinical report.

In conclusion, the incidence of adverse events related to abnormalities in glucose metabolism was very low with risperidone treatment and comparable with placebo. This low incidence was confirmed by the pharmacovigilance data.

As a result, when considering the data from these two reports together, it can be concluded that the benefit/risk estimation specifically for this condition remains favourable and that the current Company Core Data Sheet does not need to be changed.

On behalf of Janssen-Cilag AB
Regulatory Affairs

Elisabet Sandström

Volume 1/Page 10

JJRP 00379882

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Department of Health

MEDICINES CONTROL AGENCY

Market Towers 1 Nine Elms Lane London SW8 5NQ



Maria Hilling
Senior Drug Safety Scientist
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P.O. Box 79
Saunderton
High Wycombe
Buckinghamshire
HP14 4HJ



17th March 2000

Our ref. CLU-12461

Dear Miss Hilling

Thank you for your recent correspondence regarding Anonymised Single Patient Prints for risperidone.

With regard to the specific ASPPs requested by yourself, I can confirm that further information has subsequently been received regarding the reports listed below. Please find enclosed updated ASPPs for these reports.

ADROIT Registration Number	Janssen-Cilag Number
REDACTED	JAUK23074
	JAUK30023
	JAUK32453

I regret that we are unable to provide copies of any investigations that may be attached to the report, all available information is as stated on the ASPP.

In addition to cardiac reactions, the MCA have highlighted the following areas as being of particular concern and would be grateful if you could address these particular issues during your review of the Safety Profile for risperidone;

1. Blood dyscrasias; particularly disorders with decreased white blood cells and aplastic anaemia - is the current SPC statement regarding blood dyscrasias adequate?
2. Diabetes mellitus and hyperglycaemia; there are a number of foreign reports of these reactions.
3. Thromboses; there are a number of both foreign and UK reports of thromboses associated with risperidone treatment.
4. Pituitary tumour; we are aware of 8 foreign cases of pituitary tumour associated with risperidone.

Volume 1/Page 11

JJRP 00379883

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D807.21

We would be grateful for confirmation that these reviews will be carried out. We request that they be included within the review of cardiac reactions, which should be forwarded to me by 26th May 2000.

Please do not hesitate to contact me on the telephone number below should you require any further help.

Thank you in advance,

Yours sincerely



Jennifer Bailey B.Sc (Hons)
Senior Scientific Classifier
Mutual Recognition Team
Pharmacovigilance Group
Room 14.240, MT
Direct Line: 020 7273 0031

cc: Louise Kerr, Co-ordinator - Mutual Recognition Team

Volume 1/Page 12

JJRP 00379884
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29th June 2000

Jennifer Bailey
Senior Scientific Classifier
Mutual Recognition Team
Pharmacovigilance Group, Room 14.240
Medicines Control Agency
Market Towers
1 Nine Elms Lane
LONDON SW8 5NQ

Dear Ms. Bailey,

Re: Risperidone – Safety Reviews
Your Ref: CLU-12461

Further to your letter of 17th March, and subsequent communications by letter and phone, I have pleasure in enclosing copies of company reviews of the following areas:-

- Blood dyscrasias
- Diabetes mellitus and hyperglycaemia
- Thromboses
- Pituitary tumour

Below is a summary of the overall conclusions for each area -

Blood dyscrasias

The available data do not appear to indicate a relevant relationship between risperidone and serious blood dyscrasias at recommended therapeutic doses. As a result, the benefit/risk estimation specifically with regard to blood dyscrasias remains favourable and no changes are required to the Company Core Data Sheet.

Diabetes mellitus and hyperglycaemia

The Medical Products Agency of Sweden had recently requested to evaluate the effect of risperidone on glucose metabolism, as this issue has been raised by the CPMP Pharmacovigilance Working Party to investigate a possible class-effect for atypical neuroleptics. On Friday 23rd June, two reports were sent to the MPA providing all available clinical and pharmacovigilance information concerning risperidone and potential effects on glucose metabolism (the cover letter sent to the MPA, together with three literature references, is attached to this letter).

These reports conclude that in clinical studies the incidence of adverse events related to abnormalities in glucose metabolism was very low with risperidone treatment and was comparable with placebo. This low incidence was confirmed by

Volume 1/Page 13

JJRP 00379885
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D807.23

post-marketing pharmacovigilance data. Subsequently, the benefit/risk estimation specifically for this condition remains favourable and no changes are required to the Company Core Data Sheet.

Thrombosis and embolism

The available data do not appear to indicate a relevant relationship between risperidone and thrombosis or embolism at recommended therapeutic doses. As a result, the benefit/risk estimation specifically with regard to venous thrombosis and pulmonary embolism remains favourable and no changes are required to the Company Core Data Sheet.

Pituitary tumour

Hyperprolactinemia is a recognized side effect of anti-psychotic therapy. This may be associated with reproductive symptoms such as gynaecomastia, amenorrhoea and infertility. Depending on the degree of investigation, an underlying microadenoma may often be detected, as with other cases of hyperprolactinemia, unrelated to anti-psychotics. Thus it is not surprising to have pituitary microadenoma reported as a suspected adverse reaction in association with risperidone treatment. Pituitary microadenomas are considered to have relatively benign prognosis compared to macroadenomas. There is no evidence that risperidone increases the risk of conversion of a microadenoma into a macroadenoma with symptoms of optic pathway compression or pituitary dysfunction.

Having detected symptomatic hyperprolactinemia with an associated microadenoma caution should always be exercised; but yet, in view of the serious nature of schizophrenia, no definitive recommendation can be made regarding a specific action.

Reports of pituitary tumours in association with risperidone will continue to be closely monitored and will be re-evaluated one year from now. However, on the basis of the pooled safety data analysis of reported pituitary tumours, the benefits of risperidone still exceed the risks

If you have any questions or require any further information please do not hesitate to contact me.

Kind regards,

Mr Chris Marris
UK Drug Safety Manager
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Volume 1/Page 14

JJRP 00379886
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D807.24

3 INTEGRATED
SUMMARY

JJRP 00379887
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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	Non-proprietary Name: Risperidone
Report No.	EDMS-BEBE-1788252	Report date: 8 August 2000
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	

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Volume 1/Page 15

JJRP 00379888
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D807.26

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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

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

Volume 1/Page 17

JJRP 00379890
Confidential/Produced in Litigation Pursuant to Protective Order
D807.28

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 ^{c,d} 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 zuclopenthixol, perphenazine, remoxipride, clozapine, methotrimeprazine.

^e Although originally coded as "coma diabetic", this elderly patient (#1204) experienced hyperglycemia 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

Volume 1/Page 18

JJRP 00379891
Confidential/Produced in Litigation Pursuant to Protective Order
D807.29

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, methotrimeprazine.

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, methotrimeprazine.

Volume 1/Page 19

JJRP 00379892
Confidential/Produced in Litigation Pursuant to Protective Order
D807.30

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 zuclopenthixol, perphenazine, remoxipride, clozapine, methotrimeprazine.

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		
	<18years)	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 $\pm$ 3.54	-1.17 $\pm$ 3.52
Olanzapine	-	3.21 $\pm$ 4.45	-
Other neuroleptics ^a	-	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	-

^a 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.

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.

Volume 1/Page 22

JJRP 00379895
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D807.33

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

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.

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Integrated Summary

12

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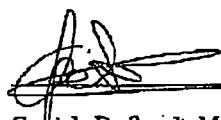
Volume 1/Page 26

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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.



Goedele De Smedt, M.D.
Clinical Project Scientist

8 August 2000

Global Clinical R&D and Regulatory Affairs, Worldwide, CNS

Volume 1/Page 27

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5 NONCLINICAL

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JANSSEN PHARMACEUTICA N.V.

NON-CLINICAL SUMMARY	
R - number: R064766	Non-proprietary Name: Risperidone
EDMS-USTI-2081658	Report date: 31 July 2000
Title:	Risperidone: Preclinical observations of glucose metabolism-related changes
Author(s):	B. Verstynen, A. Lampo and W. Coussement
Department:	Department of Toxicology
Janssen Research Foundation Turnhoutseweg 30 B2340 Beerse, Belgium	

SUMMARY

Diabetes is characterised by an elevated blood glucose concentration (hyperglycemia), which may lead to glucosuria. In the pre-clinical animal data with risperidone, decreases instead of increases in serum glucose levels were seen in rodents and minor histological changes in the rat and mouse pancreas were considered prolactin-mediated, rodent-specific effects. Neither changes in glucose nor any effect on the endocrine pancreas were observed in dogs. Therefore, it can be concluded that the current pre-clinical data in dogs, mice and rats do not indicate any risperidone-induced glucose metabolism-related changes.

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Volume 1/Page 28

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TABLE OF CONTENTS

SUMMARY	1
LIST OF IN-TEXT TABLES AND FIGURES	2
1. INTRODUCTION	3
2. DOGS	3
2.1. Results	3
2.2. Discussion	4
2.3. Conclusion	5
3. MICE	5
3.1. Results	5
3.2. Discussion and conclusion	5
4. RATS	6
4.1. Results	6
4.2. Discussion and conclusion	9
5. OVERALL CONCLUSION:	10
REFERENCES	11

LIST OF IN-TEXT TABLES AND FIGURES

Table of tables

Table 1: Preclinical data on glucose metabolism-related changes in dogs	4
Table 2: Preclinical data on glucose metabolism-related changes in mice	5
Table 3: Preclinical data on glucose metabolism-related changes in rats	7

1. INTRODUCTION

All changes related to glucose metabolism that were seen in repeated-dose toxicity studies in mice, rats and dogs are briefly summarized below.

2. DOGS

2.1. Results

Dogs were dosed with risperidone, orally by capsules, in a 1-month¹, 3-month², 3-month with a 2-month recovery period³ and a 12-month⁴ toxicity study. Detailed results of these studies are noted in Table 1.

Volume 1/Page 30

JJRP 00379904
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Table 1: Preclinical data on glucose metabolism-related changes in dogs

	Doses of risperidone in mg/kg/day						
	0	0.16	0.31	0.63	1.25	2.5	5
1-month study¹							
Serum glucose (mg%)	106	102		100		102	
Urine glucose (score 0-3)	0	0		0		0	
Pancreas weight	NE	NE		NE		NE	
Histology of pancreas	NE	NE		NE		NE	
3-month study²							
Serum glucose (mg%)	86 [#]		109**		106**		109**
Urine glucose (score 0-3)	0		0		0		0
Absolute pancreas weight (g)	26		25		27		28
Relative pancreas weight (g/10 kg)	22		19		21		23
Histology of pancreas	N		N		N		N
3 (+2)-month study³							
Serum glucose (mg%)	106 (83)		101 (95)		96 (91)		102 (100)
Urine glucose (score 0-3)	0 (0)		0 (0)		0 (0)		0 (0)
Absolute pancreas weight (g)	21 (25)		31* (23)		28 (26)		25 (25)
Relative pancreas weight (g/10 kg)	17 (22)		24* (22)		22 (24)		19 (22)
Histology of pancreas	NE		NE		NE		NE
12-month study⁴							
Serum glucose (mg%)	104		100		105		103
Urine glucose (score 0-3)	0		0		0		0
Absolute pancreas weight (g)	25		27		29		32**
Relative pancreas weight (g/10 kg)	19		19		19		21
Histology of pancreas	N		N		N		N

NE = not examined N = within normal limits () = results after the recovery period

Significance: *p<0.05 **p<0.01 ***p<0.001

= The statistically significant increases of the risperidone dosed animals are related to the low value of the control animals

2.2. Discussion

None of the significant changes were regarded as risperidone-related since they were small, not dose-related or within the normal limits of the historical control data.

2.3. Conclusion

Risperidone had no relevant effects on serum and urine glucose levels nor on pancreas weight in dogs after repeated dosing up to 12 months. Histological examination revealed no changes on pancreas tissues either

3. MICE

3.1. Results

Mice were dosed with risperidone, orally through the diet, in a 3-month toxicity study⁵ and in an 18-month carcinogenicity study⁶. Detailed results of these studies are presented in Table 2.

Table 2: Preclinical data on glucose metabolism-related changes in mice

	Doses of risperidone in mg/100 g food/day							
	0		0.63		2.5		10	
	M	F	M	F	M	F	M	F
3-month study⁵								
Serum glucose (mg%)	178	174	184	148**	175	140**	155	131**
Urine glucose (score 0-3)	NE	NE	NE	NE	NE	NE	NE	NE
Absolute pancreas weight (g)	390	374	409	431	429	411	448*	456**
Relative pancreas weight (g/10 kg)	368	1228	1006	1282	992	1195	1121	1354*
Histology of pancreas	NE	NE	NE	NE	NE	NE	NE	NE
Carcinogenicity study⁶								
Serum glucose (mg%)	174	155	171	139**	151**	128***	128***	122***
Urine glucose (score 0-3)	NE	NE	NE	NE	NE	NE	NE	NE
Absolute pancreas weight (g)	465	441	500	518*	500	463	491	444
Relative pancreas weight (g/10 kg)	1046	1253	1100	1298	1125	1183	1081	1167
Histology: non-neoplastic effects in the endocrine pancreas							P	

NE = not examined N = within normal limits P = present

Significance: *p<0.05 **p<0.01 ***p<0.001

3.2. Discussion and conclusion

The following effects were retained as risperidone-related changes in the respective studies:

3-month oral (diet) repeated dose toxicity study:

Serum: decrease in glucose in females at doses of 0.63 mg/100 g food (decrease of 15%), 2.5 mg/100 g food (decrease of 20%), and 10 mg/100g food (decrease of 25%).

Pancreas weight: increase in absolute and relative weight in males and females at 10 mg/100g food.

Oral (diet) carcinogenicity study in mice:

Serum: decrease in glucose at 0.63 mg/100 g food in females (decrease of 10%), decrease in glucose at 2.5 mg/100 g food in males (decrease of 13%) and females (decrease of 17%)
decrease in glucose at 10 mg/100g food in males (decrease of 26%) and females (decrease of 21%).

Histology: increased incidence of prolactin-dependent, non-neoplastic changes in the endocrine pancreas (larger pancreatic islets) in males dosed at 10 mg/100g food.

4. RATS

4.1. Results

Rats were dosed with risperidone, orally by gavage or through the diet, in a 1-month⁷, 3-month⁸, 3-month with 1-month recovery period⁹, a 12-month repeated dose toxicity study¹⁰ and in a 25-month carcinogenicity study¹¹. Detailed results are summarized in Table 3.

Table 3: Preclinical data on glucose metabolism-related changes in rats

	Doses of risperidone in mg/100g food/day ^{a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u, v, w, x, y, z} or mg/kg/day ^a									
	0		0.16		0.63		2.5		10	
	M	F	M	F	M	F	M	F	M	F
1-month study^a										
Serum glucose (mg%)	174	163			178	174	179	170	168	166
Urine glucose (score 0-3)	0	0			0	0	0	0	0	0.20
Absolute pancreas weight (g)	1145	938			1212	1060	1212	1001	1128	884
Relative pancreas weight (g/10kg)	3788	4732			4334	4858	4206	4783	4206	4808
Histology of pancreas	NE	NE			NE	NE	NE	NE	NE	NE
3-month study^a										
Serum glucose (mg%)	167	164			169	175	163	164	164	170
Urine glucose (score 0-3)	0	0			0	0	0	0	0	0
Absolute pancreas weight (g)	1490	1137			1483	1292***	1459	1323***	1392	1112
Relative pancreas weight (g/10kg)	3150	4375			3157	4238	3160	4551*	3271	4568
Histology of pancreas:	N	N			NE	NE	NE	NE	N	N
3 (+1)-month study^a										
Serum glucose (mg%)	152 (157)	169 (154)	141	167	143	153	142	154	146 (155)	143** (157)
Urine glucose (score 0-3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Absolute pancreas weight (g)	1423 (1346)	1130 (1048)	1325	1204	1251*	1083	1287	1126	1196* (1311)	974* (1033)
Relative pancreas weight (g/10kg)	2645 (2277)	3794 (3102)	2533	3626	2417	3331*	2626	3693	2689 (2463)	3476 (3254)
Histology of pancreas:	N	N			NE	NE	NE	NE	N	N

JRF non clinical summary risperidone and glucose metabolism

	Doses of risperidone in mg/100g food/day ^{9,10,11} or mg/kg/day ⁹									
	0		0.16		0.63		2.5		10	
	M	F	M	F	M	F	M	F	M	F
12-month study ¹⁰										
Serum glucose (mg%)	164	154			154	153	153*	149	137***	141**
Urine glucose (score 0-3)	0	0			0	0	0	0	0	0
Absolute pancreas weight (g)	1762	1478			1811	1414	1747	1374	1638	1338
Relative pancreas weight (g/10kg)	2813	4022			3038*	3483**	2932	3441**	3219**	4079
Histology of pancreas:	N	N			NE	NE	NE	NE	N	N
Carcinogenicity study ¹¹										
Serum glucose (mg%)	114	116			102	112	98	116	93*	117
Urine glucose (score 0-3)	NE	NE			NE	NE	NE	NE	NE	NE
Absolute pancreas weight (g)	1931	1572			1680*	1446	1766	1327**	1744*	1358*
Relative pancreas weight (g/10kg)	NE	3940			3348	3452	3666	3539	4230**	4275*
Histology:										
pancreatic endocrine adenoma							P		P	

NE = not examined N = within normal limits P = present () = results after recovery
Significance: *p<0.05 **p<0.01 ***p<0.001

4.2. Discussion and conclusion

The following effects were regarded as risperidone-related changes in the respective rat studies:

1-month oral (diet) repeated dose toxicity:

Serum: no relevant changes in glucose

Urinalysis: no relevant changes in glucose

Pancreas weight: no relevant changes

3-month oral (diet) repeated dose toxicity:

Serum: no relevant changes in glucose

Urinalysis: no relevant changes in glucose

Pancreas weight: no relevant changes

Histology: no changes in the pancreas

3-month oral (gavage) repeated dose toxicity with 1-month recovery):

Serum: decrease in glucose at 10 mg/kg in females (decrease of 15%); normal after recovery period

Urinalysis: no relevant changes in glucose

Pancreas weight: no relevant changes

Histology: no changes in the pancreas

12-month oral (diet) repeated dose toxicity:

Serum: decrease in glucose at 10 mg/100g food in males (decrease of 16%) and females (decrease of 8%)

Urinalysis: no relevant changes in glucose

Pancreas weight: no relevant changes

Histology: no changes in the pancreas

Oral (diet) carcinogenicity study:

Serum: no relevant changes in glucose

Urinalysis: no relevant changes in glucose

Pancreas weight: no relevant changes

Histology: increased incidence of endocrine pancreas adenomas in males dosed at 2.5 and 10 mg/100g food. These pancreatic islet adenomas are also observed with other neuroleptics in the same order of magnitude and are considered to be prolactin-mediated related to the D₂-antagonistic activity of risperidone. These effects are considered rodent-specific.

5. OVERALL CONCLUSION:

Diabetes is characterised by an elevated blood glucose concentration (hyperglycemia), which may lead to glucosuria. In the pre-clinical animal studies with risperidone, decreases instead of increases in serum glucose levels were seen in rodents, and minor histological changes in the rat and mouse pancreas were considered prolactin-mediated, rodent-specific effects. Neither changes in glucose nor any effect on the endocrine pancreas were observed in dogs.

Therefore, it can be concluded that the current pre-clinical data in dogs, mice and rats do not indicate any risperidone-induced glucose metabolism-related changes.

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Volume 1/Page 38

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IRF non-clinical summary: risperidone and glucose metabolism

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Volume 1/Page 39

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B CLINICAL DATA

JJRP 00379914

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List of Trials

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De Smidt G, et al.

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NDA 20-272
Risperdal (risperidone) Tablets

**List of Clinical Trials Evaluated and Reference to the Application
to which the Clinical Reports were Submitted**

The following table lists the clinical trials included in this evaluation and the application (original NDA or supplemental) to which the clinical reports were submitted.

Clinical Trial	Original NDA 4/15/92	Supplemental Application	Date
Phase 1 Trials			
RIS-INT-28		S-011	1/20/98
RIS-BEL-34			
RIS-INT-25			
RIS-INT-38			
RIS-INT-54			
RIS-NED-13			
RIS-USA-3			
RIS-USA-49			
RIS-USA-111			
RIS-USA-122			
Phase 2-3 Trials In Non-Elderly Patients (18-65 yrs)			
RIS-AUT-1			
RIS-BEL-5	X		
RIS-BEL-7	X		
RIS-FIN-1			
RIS-FRA-3	X		
RIS-GER-5	X		
RIS-INT-10		S-007	11/26/96
RIS-INT-2	X		
RIS-INT-3	X		
RIS-INT-5			
RIS-INT-7	X		
RIS-INT-9			
RIS-INT-39 / RIS-GBR-28			
RIS-INT-45			
RIS-INT-46			
RIS-KOR-1			
RIS-SUI-1		S-008	3/12/97
RIS-USA-1	X		
RIS-USA-60		S-007	11/26/96

Volume 1/Page 40

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Janssen Research Foundation

NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

Clinical Trial	Original NDA 4/15/92	Supplemental Application	Date
Phase 2-3 Trials In Non-Elderly Patients (18-65 yrs) Contd.			
RIS-USA-112			
RIS-GBR-17			
RIS-GER-3	X		
RIS-GER-11			
RIS-INT-1	X		
RIS-ITA-1	X		
RIS-USA-54			
RIS-INT-6		S-008	3/12/97
RIS-USA-79		-	5/11/00
RIS-BEL-17	X		
RIS-INT-4	X	S-008	3/12/97
RIS-INT-8	X		
RIS-INT-12			
RIS-INT-17		S-008	3/12/97
RIS-INT-47 / RIS-GBR-29			
RIS-ISR-1			
RIS-NED-2			
RIS-USA-5		S-008	3/12/97
RIS-USA-6		S-008	3/12/97
RIS-USA-7		S-008	3/12/97
RIS-USA-9		S-008	3/12/97
Phase 2-3 Trials In Elderly Patients (> 65 yrs)			
RIS-BEL-14		S-009	3/28/97
RIS-INT-24		S-009	3/28/97
RIS-USA-63		S-009	3/28/97
RIS-BEL-6	X		
RIS-BEL-9	X		
RIS-INT-23		S-009	3/28/97
RIS-INT-26			
RIS-USA-34		S-009	3/28/97
RIS-USA-64		S-009	3/28/97
RIS-USA-70		S-009	3/28/97
Phase 2-3 Trials in Children/Adolescents (<18 yrs)			
RIS-BEL-12			
RIS-BEL-24			
RIS-NED-9			
RIS-CAN-19			
RIS-USA-93			
RIS-BEL-21			
RIS-BEL-22			

NDA 20-588: The only Clinical Study submitted to NDA 20-588 was a single dose – Phase 1 Trial.

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Volume 1/Page 41

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R. 5954

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CLINICAL SUMMARY REPORT	
R - number: R064766	Non-proprietary name: Risperidone
GRIPS No.: USTI-2097011	Report Date: 8 August 2000
Title:	Evaluation of the effects of risperidone on glucose metabolism and weight in Phase 1-3 trials.
Authors:	G. De Smedt, C. Ding, P. Meyvisch, K. Hoffman, L. Masukawa, J. Rosenberg, A. Derivan, I. Caers
Department:	Global Clinical R&D and Regulatory Affairs, Worldwide, and Global Biometrics Sciences and Reporting

ABSTRACT

In summary, the data from over 11,000 psychiatric patients encompassing three age groups (pediatric/adolescent, adult, and geriatric) were reviewed for adverse events associated with abnormalities in glucose metabolism and weight increase in 10 Phase 1 and 56 Phase 2-3 world-wide trials.

Glucose metabolism

The incidence of adverse events related to abnormalities in glucose metabolism in Phase 2-3 trials was evaluated in patients treated in short-term trials, in long-term trials, and in all trials regardless of the design or duration. The overall incidence of these events was low with risperidone treatment (0.87% of 8402 patients). For the short-term trials, there was a lower incidence with risperidone treatment (0.62% of 5330 patients) compared with placebo or olanzapine treatment (0.81% of 868 patients and 0.89% of 448, respectively). The incidence was higher with both risperidone and placebo treatment when compared with haloperidol and other neuroleptics (0.28% of 712 patients and 0.34% of 293, respectively, in short-term trials) (i.e., zuclopenthixol, perphenazine, remoxipride, clozapine, and methotrimeprazine). In long-term trials, there was a lower incidence with risperidone treatment (1.3 % of 3072 patients) or other neuroleptics (0% of 234) than with haloperidol treatment (2.98% of 302 patients). There were no long-term trials with placebo or olanzapine.

The occurrence of deaths associated with glucose-related adverse events was very low and was indistinguishable between risperidone (0.01%, 1 of 8402 patients) and placebo treatment (0%, 0 of 868 patients), haloperidol (0%, 0 of 1014 patients), olanzapine (0%; 0 of 448) and other neuroleptics (0%, 0 of 527 patients). In addition, the incidence of serious glucose-related adverse

Volume 1/Page 42

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events was lower with risperidone treatment (0.15% of 8402 patients) than with placebo or haloperidol (0.35% of 868 patients and 0.30% of 1014 patients, respectively). No serious adverse events with olanzapine or other neuroleptics were related to abnormalities of glucose metabolism. Discontinuation due to glucose-related adverse events was also lower with risperidone (0.04% of 8402 patients) compared with placebo (0.12% of 868 patients) or with haloperidol (0.20% of 1014 patients) treatment. No discontinuations were related to abnormalities of glucose metabolism with olanzapine or other neuroleptics.

Subgroup analyses of risperidone-treated patients showed a higher incidence of glucose-related adverse events in elderly, black, and overweight patients, in general. This is consistent with epidemiological studies. No dose effects were seen.

Data from 10 Phase 1 trials support the findings in the Phase 2-3 trials that there is no evidence that treatment with risperidone induced significant abnormalities in glucose metabolism.

Weight increase adverse events

The incidence of adverse events of weight increase was evaluated in patients treated in short-term trials only, in long-term trials only, and for both short- and long-term trials combined. The overall incidence of these events with risperidone was 2.01% of 8402 patients. For the short-term trials, there was a lower incidence with risperidone treatment (1.39% of 5330 patients) compared with olanzapine treatment (9.38% of 448 patients). The incidence with placebo was 0.92% (of 868 patients), with haloperidol 1.26% (of 712 patients), and with other neuroleptics it was 0.34% (of 293 patients) in short-term trials. Other neuroleptics included zuclopenthixol, perphenazine, remoxipride, clozapine, and methotrimeprazine. In long-term trials, the incidence with risperidone treatment was 3.09% of 3072 patients relative to 1.66% (of 302 patients) with haloperidol treatment and 0.43% (of 234) patients treated with other neuroleptics. There were no long-term trials with placebo or olanzapine.

There were no deaths due to weight increase and no adverse events of weight increase were considered serious. Discontinuations associated with weight increase adverse events occurred in 3 patients from the risperidone treatment group and one in the olanzapine treatment group.

Subgroup analyses of risperidone-treated patients showed a higher incidence of weight increase adverse events males and black patients, in general. No dose effects were seen.

Weight change

Weight gain of more than 14% over baseline body weight occurred more frequently in the 18-65 year-old adults treated with risperidone (2.5%) than

placebo (0.7%) in short-term trials and less frequently than olanzapine (5.2%). Percentages among the elderly were 1.9% and 0.8% for risperidone and placebo, respectively, in short-term trials.

Mean weight change from baseline to endpoint in short-term trials was 1.3 kg for non-elderly adults and 0.4 kg for elderly adults treated with risperidone. These means reflected more weight gain relative to placebo (0.2 kg), haloperidol (0.1 kg) and other neuroleptics (1.0 kg), but less than olanzapine (3.2 kg). In long-term trials, mean change was 1.8 kg for non-elderly and 0.3 kg for elderly risperidone-treated adults. No dose effect was observed. Long-term weight change with haloperidol was a gain of 0.1 kg for non-elderly adults. Risperidone-treated adults with a baseline body mass index (BMI) less than 23 gained more weight on average than patients with a higher BMI.

Weight gain in the pediatric/adolescent patients treated with risperidone was similar to that predicted using standard growth curves, and showed a slight tendency to increase with a higher risperidone mode dose.

Conclusion

In a large body of clinical data, abnormalities of glucose metabolism in patients treated with risperidone occurred at a rate similar to that for patients treated with placebo. Clinically significant weight gain was observed at a rate higher than that for placebo but lower than that observed for patients treated with olanzapine.

TABLE OF CONTENTS

1. Introduction and objective of the report	7
2. Subjects and methods	8
2.1. Subjects	8
2.2. Methods of analysis	13
3. Results	15
3.1. Phase 1 trials	15
3.2. Phase 2-3 trials	17
4. Summary and conclusions	42
5. References	45
6. Supporting Data	48
6.1. Displays	48
6.2. Annexes	Volume 1/Page 163
6.3. Patient Data Listings	Volume 2/Page 1

Volume 1/Page 45

TABLE OF TABLES

Table 1: Phase 1 multidose trials included in evaluation of glucose-related adverse events, clinical laboratory values, and weight-increase adverse events	9
Table 2: Phase 2-3 risperidone trials completed with full analysis of data as of 31 March 2000	11
Table 3: Relationship between double-blind and open-label extension trials	14
Table 4: Incidence (number of patients and %) of laboratory glucose values above or below the normal range with normal baseline values in Phase 1 trials with fasting conditions	16
Table 5: Incidence (number of patients and %) of adverse events related to abnormalities in glucose metabolism in short-term Phase 2-3 trials	18
Table 6: Incidence (number of patients and %) of adverse events related to abnormalities in glucose metabolism in long-term Phase 2-3 trials	18
Table 7: Incidence of deaths, serious adverse events and discontinuations due to adverse events related to abnormalities in glucose metabolism	20
Table 8: Patients who died, had serious adverse events or discontinued due to glucose-related adverse events	22
Table 9: Incidence (number of patients and %) with at least one glucose-related adverse event by age (yrs) and by duration of trial	24
Table 10: Incidence (number of patients and %) of glucose-related adverse events in female and male patients by trial duration	25
Table 11: Incidence (number of patients and %) of glucose-related adverse events by racial group and trial duration	26
Table 12: Glucose-related adverse events by risperidone mode dose	27
Table 13: Treatment-year incidence of glucose-related adverse events	27
Table 14: Baseline body mass index (BMI) and glucose-related adverse events	28
Table 15: Incidence (number of patients and %) of weight increase (preferred term) as an adverse event in Phase 2-3 trials	30
Table 16: Baseline body mass index (BMI) and weight increase adverse	31

TABLE OF TABLES

events (AE)

Table 17: Patients with an adverse event of weight increase (preferred term) for which the action taken was permanent stop of trial medication	31
Table 18: Incidence (number of patients and %) with at least one weight increase adverse event by age grouping (yrs) and by duration of trial	32
Table 19: Incidence (number of patients and %) of weight increase adverse events in female and male patients by trial duration	33
Table 20: Incidence (number of patients and %) of weight increase adverse events by racial group and trial duration	34
Table 21: Weight-increase adverse events by risperidone mode dose	35
Table 22: Treatment-year incidence of weight-increase adverse events	35
Table 23: Weight gain as percentage of baseline weight by trial duration in adults 18-65 years old	36
Table 24: Weight gain as percentage of baseline weight by trial duration in adults older than 65 years	37
Table 25: Weight gain as percentage of baseline weight by trial duration in patients younger than 18 years old	37
Table 26: Incidence of weight gain by baseline BMI	38
Table 27: Weight gain by sex	38
Table 28: Weight gain as percentage of baseline weight by mode dose of risperidone	39
Table 29: Mean $\pm$ SD weight change from baseline at endpoint by trial duration and age group	40
Table 30: Mean $\pm$ SD weight change (kg) by baseline BMI and age group	41
Table 31: Mean weight change of risperidone-treated patients by mode dose	41

1. INTRODUCTION AND OBJECTIVE OF THE REPORT

Risperidone (trade name: Risperdal®) is a benzisoxazole derivative with potent serotonin 5-HT_{2A} and dopamine D₂ receptor-blocking properties.^{1,2} In adults, risperidone has proven to be an effective antipsychotic, ameliorating both positive and negative symptoms of schizophrenia in chronic schizophrenic patients and exhibiting a low rate of extrapyramidal side effects.^{3,4,5,6,7}

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absorption is not affected by food and thus, risperidone can be given with or without meals. Both risperidone and its metabolite, 9-hydroxy-risperidone, form the active fraction. Another metabolic pathway of risperidone is N-dealkylation. After oral administration to psychotic patients, risperidone was eliminated with a half-life of about 3 hours. The elimination half-life of 9-hydroxy-risperidone and the active antipsychotic fraction is 24 hours.

Risperidone (Risperdal®) has been marketed world-wide in more than 70 countries since 1993 and is approved for the treatment of a broad range of patients with schizophrenia, including first episode psychoses, acute schizophrenic exacerbations, chronic schizophrenia, and other psychotic conditions. In addition, risperidone alleviates affective symptoms such as depression, guilt feelings, and anxiety associated with schizophrenia. It is also indicated in maintenance therapy in chronic schizophrenic patients according to the label specifications for each country. Also depending on the specific country, risperidone is indicated for the treatment of behavioral disturbances in patients with dementia who are aggressive, psychotic or have activity disturbances. Based on extensive clinical experience including short- and long-term use, risperidone has been shown to be generally well tolerated.

From the most recent information, total patient exposure to risperidone in the market as of 31 March 2000 (over the last 7 years) has been estimated to be 3,342,755 patient-years.⁸

This clinical report evaluates the available data related to abnormalities of glucose metabolism and weight increase from Phase 1- 3 trials sponsored by Janssen Research Foundation (JRF) to study risperidone from 1 December 1985 to 1 April 2000. This evaluation was performed upon the request of the regulatory authorities to follow the effects of novel antipsychotic treatment on glucose metabolism and weight.

Volume 1/Page 48

JJRPrev 00379925
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2. SUBJECTS AND METHODS

2.1. Subjects

2.1.1. PHASE 1 TRIALS

A total of 26 Phase 1 trials have been performed during the clinical development of risperidone. Only trials with multiple dose design were evaluated for adverse events related to abnormalities in glucose metabolism and increased weight. These 10 trials were RIS-INT-28, RIS-BEL-34, RIS-INT-25, RIS-INT-38, RIS-INT-54, RIS-NED-13, RIS-USA-3, RIS-USA-49, RIS-USA-111, and RIS-USA-122. These trials and the number of patients treated are listed in Table 1.

All subjects were patients except in trials RIS-USA-122 and RIS-INT-28, which enrolled healthy non-elderly non-elderly and elderly subjects, respectively. Data from 148 patients or healthy subjects exposed to multidoses of risperidone contributed to the Phase 1 adverse event analysis. The inclusion/exclusion criteria limited this population of subjects to those who were healthy based on a pre-trial physical examination, medical history, anamnesis, electrocardiogram, the results of blood biochemistry and haematology tests, and urinalysis performed within 2 weeks prior to the first dose. If the results of the laboratory testing were not within the laboratory's reference ranges, the subjects could be included only on condition that the investigator judged that the deviations were not clinically significant.

Glucose levels were reviewed in 4 Phase 1 trials (BEL-34, INT-25, INT-38, and USA-111) where blood samples were taken under fasting conditions (Table 1).

Table 1: Phase 1 multidose trials included in evaluation of glucose-related adverse events, clinical laboratory values, and weight-increase adverse events

Trial	All Patients N=152	Placebo N=48	Risperidone N=148	Donepezil N=24
RIS-INT-28 ^a	20	20	20	0
RIS-BEL-34 (fasting)	8	0	8	0
RIS-INT-25 (fasting)	9	0	9	0
RIS-INT-38 (fasting)	9	0	9	0
RIS-INT-54	14	0	14	0
RIS-NED-13	8	0	8	0
RIS-USA-3 ^a	36	0	36	0
RIS-USA-49	16	4	12	0
RIS-USA-111 (fasting)	8	0	8	0
RIS-USA-122 ^a	24	24	24	24

^a: Cross over design trial**2.1.2. PHASE 2-3 TRIALS****2.1.2.1. Patients in all trials**

All 60 of the Phase 2-3 trials in the risperidone program, that were completed and where data was fully analyzed as of 31 March 2000, were reviewed for adverse events related to abnormalities of glucose metabolism and weight increase (Table 2). The trials were performed in three different populations: non-elderly adult patients (18 to 65 years) with a diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder or bipolar mania (n=8415); elderly patients (> 65 years) with dementia and behavioral disturbances (n=1797); and pediatric or adolescent patients (< 18 years) with mental retardation and conduct or other disruptive behaviour disorders (n=417). A total of 11727 patients were enrolled in all trials. Of these patients, there were 8907 who were treated with risperidone.

The inclusion/exclusion criteria limited the population of patients to those who had no serious, unstable illnesses and were otherwise physically healthy based on a pre-trial physical examination, medical history, anamnesis, electrocardiogram, the results of blood biochemistry and hematology tests, and an urinalysis carried out less than 2 weeks before administration of the first dose. If the results of the biochemistry or haematology tests or the urinalysis testing were not within the laboratory's reference ranges, the patients could be included only on condition that the investigator judged that the deviations were not clinically significant. If an organic illness was present (e.g., diabetes), subjects could be included on condition that the investigator judged the illness to be clinically stable.

2.1.2.2. Patients evaluated for glucose-related and weight increase adverse events

Data from patients treated in 56 of the 60 Phase 2-3 trials listed in Table 2 (non-italicized) were evaluated for glucose-related and weight increase adverse events (data in the electronic database). The 56 trials provided information from a total of 11259 patients in short- and long-term studies combined. Of this total, 868 patients were treated with placebo, 8402 with risperidone, 1014 with haloperidol, 448 with olanzapine, and 527 with other neuroleptics. When only short-term trials were considered, 868 patients were treated with placebo, 5330 with risperidone, 712 with haloperidol, 448 with olanzapine, 293 with other neuroleptics. From only long-term trials, there were 0 patients with placebo, 3072 with risperidone, 302 with haloperidol, 0 patients with olanzapine, and 234 patients with other neuroleptics. Because BEL-11 was a cross-over trial, 37 patients provided data for both risperidone and placebo short-term analysis and therefore were counted twice in the total number of patients evaluated for glucose-related adverse events (11259) while the total number of patients participating in the 56 trials was 11222. Data from 4, of the 60 trials listed in Table 2, (see below, GBR-17, GER-11, BEL-6, and BEL-9) have not been included in the evaluation for glucose-related and weight increase adverse events and account for 505 patients, thus, resulting in 8402 risperidone-treated patients this evaluation. These trials are indicated in italics in Table 2. The total of 505 patients represented 192, 254, 50, and 9 patients, respectively, from these 4 trials in the total of over 11,000 patients in the all trials. Data from these trials were not included because they were among the oldest trials and therefore the data was not available in an appropriate database format for inclusion at this time. Data from these trials were not expected to greatly influence the overall conclusions of this report due to the relatively small percentage (6%) of patients involved.

There were only 21 of 56 trials that had patients in any treatment group reporting glucose-related adverse events. These trials are indicated in bold in Table 2. There were 35 of the 56 trials in which patients in any treatment group reported weight increase adverse events. These trials are underlined in Table 2.

Trial medication doses given to elderly patients were generally lower than those given to younger adults. In addition, the trials were conducted in patients with dementia and behavioral disturbances. Pediatric/adolescent patients were generally dosed according to body weight. Included diagnoses for that population were mental retardation, conduct or other disruptive behaviour disorders.

Table 2: Phase 2-3 risperidone trials completed with full analysis of data as of 31 March 2000

Trial	Total Patients	Risperidone	Haloperidol	Other Neuroleptic ^a	Olanzapine	Placebo
TRIALS NON-ELDERLY PATIENTS (18-65 yrs)						
Double-blind short-term trials						
AUT-1	67	34	0	33	0	0
BEL-5 ³	44	22	22	0	0	0
BEL-7	60	28	32	0	0	0
FIN-1 ⁹	98	48	0	50	0	0
FRA-3 ¹⁰	62	21	20	21	0	0
GER-5 ¹¹	59	39	0	20	0	0
INT-10 ¹²	211	211	0	0	0	0
INT-2 ⁷	1362	1136	226	0	0	0
INT-3 ⁶	523	348	87	0	0	88
INT-5	183	99	84	0	0	0
INT-7 ¹³	107	55	0	52	0	0
INT-9	149	75	0	74	0	0
INT-39/GBR-28	77	39	0	0	0	38
INT-45	490	247	0	0	243 ^b	0
INT-46	150	75	0	0	0	75
KOR-1 ¹⁴	39	19	20	0	0	0
SUI-1 ¹⁵	86	43	0	43	0	0
USA-1 ⁵	160	53	53	0	0	54
USA-60	441	441	0	0	0	0
USA-72	246	163	0	0	0	83
USA-102	156	52	53	0	0	51
USA-112	407	202	0	0	205	0
Open short-term trials						
GBR-17	192	192	0	0	0	0
GER-3	13	13	0	0	0	0
GER-11	254	254	0	0	0	0
INT-1	121	121	0	0	0	0
ITA-1	31	31	0	0	0	0
USA-54	935	935	0	0	0	0
Double-blind long-term trials						
INT-6	190	91	99	0	0	0
USA-79	395	192	203	0	0	0
Open Long-term trials						
BEL-17	116	116	0	0	0	0
INT-4 ¹⁶	386	386	0	0	0	0
INT-8	109	109	0	0	0	0
INT-12	483	483	0	0	0	0
INT-17	492	258	0	234	0	0
INT-47/GBR-29	58	58	0	0	0	0
ISR-1	135	135	0	0	0	0
NED-2	40	40	0	0	0	0
USA-5	7	7	0	0	0	0
USA-6	265	265	0	0	0	0
USA-7	105	105	0	0	0	0
USA-9	107	107	0	0	0	0
TOTAL	9506	7243	899	527	448	389

Trial	Total Patients	Risperidone	Haloperidol	Other Neuroleptic ^a	Olanzapine	Placebo
TRIALS IN ELDERLY PATIENTS (>65 yrs)						
Double-blind short-term trials						
<u>BEL-14</u>	<u>39</u>	20	0	0	0	<u>19</u>
<u>INT-24</u>	<u>344</u>	115	115	0	0	<u>114</u>
<u>USA-63</u>	<u>625</u>	<u>462</u>	0	0	0	<u>163</u>
Open short-term trials						
<u>BEL-6</u>	<u>50</u>	50	0	0	0	0
Double-blind long-term trials						
None						
Open long-term trials						
<u>BEL-9</u>	<u>9</u>	9	0	0	0	0
<u>INT-23</u>	<u>180</u>	<u>180</u>	0	0	0	0
<u>INT-26</u>	<u>83</u>	83	0	0	0	0
<u>USA-34</u>	<u>22</u>	22	0	0	0	0
<u>USA-64</u>	<u>103</u>	<u>103</u>	0	0	0	0
<u>USA-70</u>	<u>330</u>	<u>330</u>	0	0	0	0
TOTAL	1785	1374	115	0	0	296
TRIALS IN PEDIATRIC/ADOLESCENT PATIENTS (<18 yrs)						
Double-blind short-term trials						
<u>BEL-11^d</u>	<u>37^d</u>	<u>37^d</u>	0	0	0	<u>37^d</u>
<u>BEL-24</u>	<u>13</u>	6	0	0	0	7
<u>NED-9</u>	<u>38</u>	<u>19</u>	0	0	0	<u>12</u>
<u>CAN-19</u>	<u>110</u>	<u>53</u>	0	0	0	<u>57</u>
<u>USA-93</u>	<u>118</u>	<u>55</u>	0	0	0	<u>63</u>
Open short-term trials						
<u>BEL-21</u>	<u>6</u>	6	0	0	0	0
<u>BEL-22</u>	<u>7</u>	7	0	0	0	0
Double-blind long-term trials						
N/A						
Open long-term trials						
<u>USA-97</u>	<u>107</u>	<u>107</u>	0	0	0	0
TOTAL	436^d	290	0	0	0	183
OVERALL TOTAL	11727^d	8907^c	1014	527	448	868

Clinical trial reports for all trials are available upon request. In addition, as indicated by reference numbers, some trials have been reported in the literature.

Trials marked in bold are those in which one or more patients reported a glucose-related adverse event.

Trials underlined are those in which one or more patients reported weight gain as an adverse event.

Trials marked in italics are those that were not included in the evaluation of glucose-related or weight increase adverse events because their databases were not in an appropriate format for merging electronically at the time of this report. (c)

a: Other neuroleptics include zuclopenthixol (FIN-1), perphenazine (INT-7), remoxipride (INT-9), clozapine (GER-5, SUI-1), methotrimeprazine (FRA-3).

b: No information on the number of neuroleptic agents is available for this trial.

c: Patients (n=505) from the four trials GBR-17, GER-11, BEL-6, and BEL-9 were not included in the adverse event analysis although all patients received risperidone treatment.

d: BEL-11 was a cross-over study, therefore, the total number of patients is not the sum of the patients in each treatment group. The same patient will be counted in the risperidone as well as the placebo group. Thus, the total number of patients in the Phase 2-3 trials (11727) is different than the number of patients in the electronic database (11764). Of the 37 patients in the trial, 2 were under the age of 18.

Source: Display GAE.2

2.2 Methods of analysis

All adverse events related to abnormalities of glucose metabolism (glucose-related adverse events) and weight-increase adverse events that were reported during the clinical trials for the risperidone program are summarized in this report. In addition, adverse events are described in detail if they were serious or if death or discontinuation occurred due to a glucose-related or weight-increased adverse event. The glucose-related adverse events are as listed: metabolic acidosis, decreased blood sugar, increased blood sugar, diabetic coma, hyperosmolar, diabetes mellitus, diabetes mellitus aggravated, diabetes mellitus deteriorated, new onset diabetes mellitus, diabetes mellitus precipitated, diabetes mellitus reactivated, diabetic ketoacidosis, abnormal glucose tolerance, glucose tolerance decreased, abnormal glucose tolerance test, glycosuria, hyperglycaemia, hypoglycemia, hypoglycemic reaction, ketoacidosis, and ketonuria.

The following 3 separate databases were used for the evaluations in this report:

1) For the *clinical laboratory evaluation of glucose*, four Phase 1 trials that assessed fasting serum glucose levels were analyzed. These trials are listed in Table 1.

2) For the analysis by *mode dose*, the 43 Phase 2-3 trials with sufficient information on treatment duration and/or mode dose were included in the database: AUT-1, BEL-17, BEL-22, BEL-24, BEL-7, CAN-19, FRA-3, GBR-28, GBR-29, GBR-3, GBR-5, INT-10, INT-2, INT-24, INT-3, INT-39, INT-4, INT-45, INT-46, INT-47, INT-6, INT-7, INT-8, INT-9, KOR-1, NED-2, NED-9, SUI-1, USA-063, USA-1, USA-112, USA-34, USA-5, USA-6, USA-60, USA-64, USA-7, USA-70, USA-72, USA-79, USA-9, USA-93, USA-97. The total number of patients was 6617.

3) For the evaluation of *adverse events* related to glucose metabolism or weight-increase, ten Phase 1 trials and 56 Phase 2-3 trials were included in the analysis of adverse events. These trials are listed in Table 1 and Table 2. Unless otherwise specified, this is the database that is referred to throughout this report.

For Phase 1 trials in which blood samples were taken under fasting conditions, laboratory values for glucose are provided as well. For Phase 2-3 trials, because fasting conditions were not required, no analysis of serum glucose levels is presented.

Patients could be exposed to risperidone during double-blind trials and could continue to open-label treatment. The relationship of the trials is shown in Table 3.

The open-label, long-term trial, USA-7 (n=105 with 5 patients having glucose-related adverse events) was the only trial that followed another open-

label, long-term trial. These 105 patients were counted only once in their first open-label, long term trial (USA-6, USA-5, or USA-9).

Table 3: Relationship between double-blind and open-label extension trials

Double-blind, controlled (N)	Open-label (N)	Open-label (N)
GBR-28 (23) →	GBR-29 (19)	
INT-39 (54) →	INT-47 (39)	
INT-24 (334) →	INT-26 (83)	
INT-2 & INT-3 (1362 & 523) →	INT-4 (386)	
INT-3 (523) →	USA-6 (265) →	USA-7 (71)
USA-1 (160) & USA-3 (Phase I) →	USA-5 (4+3) →	USA-7 (3)
USA-8 (not included) →	USA-9 (107) →	USA-7 (31)
USA-63 (625) →	USA-70 (330)	
USA-93 (118) →	USA-97 (107)	

Pre-trial adverse events and post-trial/follow-up non-serious adverse events were excluded from the summary tabulation but were included in patient listings.

Patients in placebo/risperidone crossover trials were included in the total number of patients to determine the incidence for both placebo and risperidone treatment. The incidence of adverse events was attributed to the treatment at onset of each event.

The incidence of glucose-related and weight-increase adverse events in the placebo and active treatment groups (risperidone, haloperidol, olanzapine, other neuroleptics) was summarized by treatment, by trial design (short- and long-term trials), by demographic characteristics (age, race, and sex), and by risperidone mode dose level. Since placebo and olanzapine were only studied in short-term trials, there is a difference in person-time exposure between these groups and the risperidone and haloperidol groups. Therefore, the incidence of glucose-related and weight increase adverse events per patient-year was calculated. Exposure for each patient was calculated as the total treatment duration, in days, divided by 365.25. Patient-years for each treatment were obtained by summing exposures for all patients in a group.

Comorbidity of glucose-related adverse events with weight increase adverse events, and with categories of body mass index (BMI) at baseline (<23; 23<BMI≤27; and >27) was determined. Data showing weight change from baseline to endpoint is presented. Baseline refers to the start of each trial, regardless of whether or not the trial was an extension of a previous trial.

3. RESULTS

3.1. Phase 1 trials

3.1.1. ADVERSE EVENTS

3.1.1.1. Incidence of glucose-related adverse events

Only 1 subject (A30003 in trial INT-54) from a total of 148 multidose risperidone-treated subjects in Phase 1 trials (Table 1) had a glucose-related adverse event. This white 42 year-old woman experienced a glucose-related adverse event (glycosuria/elevated glucose level in urine). The patient was administered a single 50 mg dose of a biweekly risperidone depot formulation on two occasions (09NOV98 and on 22FEB99). The glucose-related adverse event started approximately 3 months after the second injection and lasted for 1 month (7MAY99 to 21JUN99). The patient had an abnormal urine glucose level at the start of the trial (2+) as well as at endpoint (4+). No blood glucose levels were available. This event was not serious nor did it lead to death or discontinuation of treatment. This adverse event was of moderate severity, was doubtfully related to risperidone treatment as reported by the investigator and resolved. Because the half-life for the risperidone depot injection is 3 days and the worsening of glycosuria was reported approximately 3 months after the second injection, a relationship of this event with risperidone treatment is unlikely.

3.1.1.2. Incidence of weight-increased adverse events

Seven subjects from a total of 148 multidose risperidone-treated subjects in Phase 1 trials (Table 1) experienced adverse events of weight increase. The adverse events were all rated mild in severity. The seven subjects all participated in trial INT-54, a multidose trial with a long-lasting (bi-weekly) depot injection of risperidone. Five of them were males. Listings for all seven of these subjects are in Annex 1B.

3.1.2. CLINICAL LABORATORY EVALUATION OF GLUCOSE

In 4 Phase 1 trials assessing blood glucose levels under fasting conditions, there were 9 of 34 patients who showed glucose levels beyond the upper or lower normal limit (Annex 3). Three of the 9 patients had an abnormal glucose level (either high or low) at baseline. In the 6 patients with a normal glucose level at baseline, there were two patients (#5 in BEL-34 and #9 in INT-25) with one or two subsequent glucose levels below normal. Four patients (A3001, A3006, A3008, A3009 in USA-111) had glucose levels above normal. In three of the latter group of patients (A3001, A3008 and A3009 in USA-111), an increased glucose level was observed on one or two occasions while the other measurements were normal. One patient (A3006 in USA-111) had levels above normal on more than two occasions (Table 4). Two patients with a normal baseline had one or more glucose measurements greater than 126 mg/dl (A30009 and A30006 in USA-111).

Table 4: Incidence (number of patients and %) of laboratory glucose values above or below the normal range with normal baseline values in Phase 1 trials with fasting conditions

Trial	Above normal	Below normal	Total No. Patient
BEL-34		1 (12.5%)	8
INT-25	0	1 (11.1%)	9
INT-38	0	0	9
USA-111	4 (50%)	0	8
TOTAL	4 (11.8%)	2 (5.9%)	34

Source: Annex 3

All patients with abnormal glucose levels are described here. Further detailed information for all patients with abnormal fasting glucose values is given in Annex 3.

The following patients had an abnormal glucose level at baseline:

- Patient 6 in BEL-34 received risperidone and had a low glucose value of 65 mg/dl at Visit 1 (baseline), however, all subsequent values were within the normal range of 76 to 110 mg/dl.
- Patient 1 in INT-25 received risperidone and had high glucose values (138 to 107 mg/dl) at all six visits, including baseline (138 mg/dl), however, by the end of the trial at Visit 16, the glucose value (107 mg/dl) had returned near the normal range (75 to 105 mg/dl).
- Patient 7 in INT-25 received risperidone and had a low glucose value at baseline (59 mg/dl) and values that fluctuated above and below (69 to 129 mg/dl) the normal range throughout the trial.

The following patients had a normal glucose level at baseline:

- Patient 5 in BEL-34 received risperidone and had a low glucose value of 24 mg/dl at Visit 2, however, all values preceding and following this visit were within the normal range of 76 to 110 mg/dl.
- Patient 9 in INT-25 received risperidone and had a slightly depressed blood glucose level (72 to 74 mg/dl) during the last two visits of the trial.
- Patient A30001 in trial USA-111 was a 36-year-old white man who had a high glucose value of 181 mg/dl at Visit 4 after 28 days of treatment with risperidone. All other glucose assessments showed values within the normal range.
- Patient A30006 in trial USA-111 was a 48-year-old white man who had high glucose values 6 days after the start of risperidone treatment until the end of treatment. These values ranged from 147 to 205 mg/dl. Upon screening, his baseline glucose value was normal. This patient weighed 146.1 kg at screening.
- Patient A30008 in trial USA-111 was a 42-year-old white man who had an high glucose value of 122 mg/dl at Visit 4 after 28 days of treatment with risperidone. All other glucose assessments showed values within the normal range.

Volume 1/Page 57

JJRPrev 00379934

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- Patient A30009 in trial USA-111 was a 39-year-old Hispanic man who had high glucose values of 160 and 135 mg/dl after 42 days of treatment with risperidone. All other glucose levels were within the normal range. This patient weighed 86.2 kg.

3.2. Phase 2-3 trials

3.2.1. GLUCOSE METABOLISM

3.2.1.1. Adverse events related to abnormalities in glucose metabolism

The incidence of adverse events related to abnormalities in glucose metabolism was evaluated in patients treated in short-term trials only, in long-term trials only, and for both short- and long-term trials combined.

Table 5 shows the incidence of glucose-related adverse events in short-term trials only. There was a lower overall incidence with risperidone treatment (0.62% of 5330 patients) relative to placebo or olanzapine treatment (0.81% of 868 patients and 0.89% of 448, respectively, in short-term trials). The incidence was higher with both risperidone and placebo treatment relative to haloperidol and other neuroleptics (0.28% of 712 patients and 0.34% of 293, respectively). Other neuroleptics included zuclopenthixol (FIN-1), perphenazine (INT-7), remoxipride (INT-9), clozapine (GER-5, SUI-1), methotrimeprazine (FRA-3).

In long-term trials, there was a lower incidence of glucose-related adverse events with risperidone treatment (1.3 % of 3072 patients) or other neuroleptics (0% of 234 patients) than with haloperidol treatment (2.98% of 302 patients) (Table 6). There were no long-term, double-blind trials with placebo or olanzapine. (See also section 3.2.1.5 regarding person-time exposure.)

The overall incidence of adverse events related to abnormalities in glucose metabolism for all trials regardless of the design or duration is shown in Display GAE.4. There was no difference in the overall incidence with risperidone treatment (0.87% of 8402 patients in short-and long-term trials) compared with placebo or olanzapine treatment (0.81% of 868 patients and 0.89% of 448, respectively, in short-term trials). This was lower than the incidence with haloperidol (1.08% of 1014 patients) and higher than for other neuroleptics (0.19% of 527 patients).

Detailed information for individual patients with adverse events related to abnormalities in glucose metabolism is provided in Annex 1A.

Table 5: Incidence (number of patients and %) of adverse events related to abnormalities in glucose metabolism in short-term Phase 2-3 trials

Adverse event preferred term	Placebo N=868	Risperidone N=5330	Haloperidol N=712	Olanzapine N=448	Other Neuroleptics ^a 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 ^b	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

Trials included: AUT-1, BEL-5, BEL-7, FIN-1, GRA-3, GER-5, INT-10, INT-2, INT-3, INT-5, INT-7, INT-9, INT-39/GBR-28, INT-45, INT-46, KOR-1, SUI-1, USA-1, USA-60, USA-72, USA-102, USA-112, GER-3, INT-1, ITA-1, USA-54, BEL-14, INT-24, USA-63, BEL-11, BEL-24, NED-9, CAN-19, USA-93, BEL-21, BEL-22

a: Other neuroleptics include: zuclopenthixol (FIN-1), perphenazine (INT-7), remoxipride (INT-9), clozapine (GER-5, SUI-1), methotrimeprazine (FRA-3).

b: Although originally coded as "coma diabetic", this elderly patient (#1204) experienced hyperglycemia with a hyperosmolar non-ketotic state as a complication of urinary sepsis and acute renal failure.

Source: Display GAE.1, GAE.4

Table 6: Incidence (number of patients and %) of adverse events related to abnormalities in glucose metabolism in long-term Phase 2-3 trials

Adverse event preferred term	Risperidone N=3072	Haloperidol N=302	Other neuroleptics ^a 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

Trials included: INT-6, USA-79, BEL-17, INT-4, INT-8, INT-12, INT-17, INT-47/GBR-29, ISR-1, NED-2, USA-5, USA-6, USA-7, USA-9, INT-23, INT-26, USA-34, USA-64, USA-70, USA-97

a: Other neuroleptics include: zuclopenthixol (FIN-1), perphenazine (INT-7), remoxipride (INT-9), clozapine (GER-5, SUI-1), methotrimeprazine (FRA-3).

Source: Display GAE.1, GAE.4

The events summarized in Table 5 and Table 6 are worsenings of pre-existing conditions and newly diagnosed diabetes or abnormalities in glucose metabolism. Glucose abnormalities were pre-existing in a substantial proportion of patients, as determined from either the available medical history or treatment with concomitant medication for the condition prior to the onset of the first glucose-related adverse event (Annex 2A and 2B). Among the 73 risperidone-treated patients with glucose-related abnormalities 25 had a prior history of abnormalities in glucose metabolism. In the placebo

group, 4 of the 7 patients with glucose-related adverse events had a prior history of glucose abnormalities, as did 3 (of 11) haloperidol patients and 1 of 4 olanzapine patient. Due to the small numbers, no conclusions can be drawn.

3.2.1.2. Deaths, serious adverse events and discontinuations due to adverse events related to abnormalities in glucose metabolism

The incidence of discontinuations due to adverse events related to abnormalities in glucose metabolism with risperidone treatment in short- and long-term trials combined was low (0.04% of 8402 patients) in comparison to placebo (short-term) treatment (0.12% of 868 patients) as well as with short- and long-term haloperidol treatment (0.20% of 1014 patients) (Table 7). No discontinuations due to adverse events related to abnormalities of glucose metabolism were reported with olanzapine or other neuroleptics in short-term trials. Four (4) of the 6 patients who discontinued due to adverse events related to abnormalities in glucose metabolism were elderly. Three (3) of the 6 patients who discontinued had pre-existing abnormalities in glucose metabolism.

The incidence of serious adverse events related to abnormalities in glucose metabolism was also lower (0.15% of 8402 patients) with short- or long-term risperidone treatment compared with placebo (short-term) treatment (0.35% of 868 patients) or haloperidol (short- or long-term treatment, 0.30% of 1014 patients) (Table 7). The distribution of glucose metabolism-related serious adverse events is shown in Table 8. Seven (7) patients experienced hyperglycemia, 7 patients experienced diabetes mellitus, and 5 patients experienced hypoglycemia. One (1) patient had uncontrolled diabetes and another patient had diabetic coma.

The average age of the 19 patients with serious glucose-related adverse events was 69.1 years. Nine (9) were female; 3 were black, 1 was Hispanic, and 15 were white.

There were 10 of the 19 patients with serious glucose-related adverse events who had pre-existing abnormalities in glucose metabolism as shown in Table 8.

Table 7: Incidence of deaths, serious adverse events and discontinuations due to adverse events related to abnormalities in glucose metabolism

Adverse event preferred term	Placebo N=868	Risperidone N=8402	Haloperidol N=1014
Deaths	0	1 (0.01%) ^a	0
Serious adverse events	3 (0.35%)	13 (0.15%)	3 (0.30%)
Discontinuations due to adverse events	1 (0.12%)	3 (0.04%)	2 (0.20%)

a: Two patients (USA-63, #4113 and #1204) died from non-glucose-related adverse events but did report a glucose-related adverse event during treatment. Their narratives are included for completeness in Annex 4 but are not included in the summary table.

No deaths, discontinuation or serious adverse events related to abnormalities of glucose metabolism were reported with olanzapine or other neuroleptic treatment not shown in the table.

Trials: AUT-1, BEL-5, BEL-7, FIN-1, GRA-3, GER-5, INT-10, INT-2, INT-3, INT-5, INT-7, INT-9, INT-39/GBR-28, INT-45, INT-46, KOR-1, SUI-1, USA-1, USA-60, USA-72, USA-102, USA-112, GER-3, INT-1, ITA-1, USA-54, BEL-14, INT-24, USA-63, BEL-11, BEL-24, NED-9, CAN-19, USA-93, BEL-21, BEL-22, INT-6, USA-79, BEL-17, INT-4, INT-8, INT-12, INT-17, INT-47/GBR-29, ISR-1, NED-2, USA-5, USA-6, USA-7, USA-9, INT-23, INT-26, USA-34, USA-64, USA-70, USA-97

There were 3 patients who died and also had an adverse event related to an abnormality in glucose metabolism. In 2 patients (A00367 in trial INT-23 and #44113 in trial USA-63) the cause of death was not due to the glucose-related adverse event and a relationship with risperidone treatment was unlikely. These patients are described as follows and detailed narrative descriptions are provided in Annex 4 for completeness.

- Patient #A00367 in trial INT-23, a 74-year-old white man, developed circulatory failure and hypoglycemia 16 days after completing treatment with risperidone. One week later, the patient developed pneumonia and sepsis. He died due to pneumonia, sepsis and circulatory failure 3 days later.
- Patient #4113 in trial USA-63, a 95-year-old white woman, was treated with placebo. After 8 days on placebo, she stopped eating and drinking, and died due to a non-glucose-related adverse event (multiple organ failure due to her ageing process). The laboratory tests on the day of death, showed, amongst other laboratory abnormalities, hyperglycemia.

The third patient (#1204 in trial USA-63) was an elderly patient who died of urosepsis complicated by hyperglycemia and acute renal failure. The investigator considered the adverse events unrelated to trial medication.

- Patient #1204 in trial USA-63 was an 85-year-old black man with multiple medical problems, including diabetes and chronic renal insufficiency. He discontinued treatment with risperidone after 13 days when he was hospitalised for lethargy and somnolence. Evaluation identified a *Proteus* urinary tract infection, hyperglycemia, hypokalemia, and hypocalcemia. The patient progressed to urosepsis complicated by acute renal failure and a nonketotic hyperosmolality syndrome, and died one day later.

A substantial number of the patients who died, had serious glucose-related adverse events or discontinued due to glucose-related adverse events may have had pre-existing endocrine conditions that could have increased the risk of future abnormalities of glucose metabolism. These events are indicated by the footnote "a" in Table 8 if diabetes or an abnormality in glucose metabolism was suggested by medical history and medications. Glucose-related condition was presumed if the patient had a positive but unspecified history of endocrine disorder and was not taking concomitant medication suggestive of another endocrine disorder (eg, levothyroxine).

Volume 1/Page 62

JJRPrev 00379939
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Table 8: Patients who died, had serious adverse events or discontinued due to glucose-related adverse events

Trial no. Patient no.	Treatment group	Adverse event (WHO preferred term)	DC due to AE	SAE	Death
ADULTS (18-65 years)					
USA-79 (Double-blind)					
0054	RIS	Diabetes mellitus		X	
0601 ^a	RIS	Diabetes mellitus		X	
0076	HAL	Elevated glucose/labs	X ^c		
0084 ^a	HAL	Diabetes mellitus Hypoglycemia		X	
0302	HAL	Diabetes mellitus		X	
0349 ^a	HAL	Hyperglycemia	X	X	
INT-45 (Double-blind)					
A30142 ^a	RIS	Hyperglycemia Hypoglycemia		X	
USA-102 (Double-blind)					
A30030	PLA	Uncontrolled diabetes		X	
USA-6					
0254	RIS	Hypoglycemia		X ^e	
GERIATRICS (>65 years)					
USA-63 (Double-blind)					
0911 ^a	PLA	Hyperglycemia		X	
4113 ^{a,d}	PLA	Hyperglycemia	X	X	(X ^f)
0115 ^a	RIS	Hypoglycemia		X	
1204 ^{a,f}	RIS	Diabetic coma	X	X	X
2613 ^a	RIS	Hyperglycemia	X		
4013	RIS	Hyperglycemia		X	
4014 ^a	RIS	Diabetes mellitus		X	
INT-23 (Open-label)					
A00118 ^a	RIS	Diabetes mellitus		X	
A00367	RIS	Hypoglycemia		X	(X ^f)
USA-70 (Open-label)					
2916 ^a	RIS	Diabetes mellitus		X	
4118	RIS	Hyperglycemia	X	X	
4206	RIS	Hyperglycemia		X	
TOTAL			6	19	1^e

DC: Discontinuation; SAE: Serious adverse event; PLA: placebo; HAL: haloperidol; RIS: risperidone

A patient narrative is provided in Annex 4 for all patients listed in this table.

a: Patient had a pre-existing condition of diabetes either reported during screening or based on treatment with concomitant medication for the condition before the onset of the glucose-related adverse event; or had a history of endocrine disorder that was unspecified and no concomitant medication suggesting presence of an endocrine disorder other than a glucose-related one.

b: This patient was not included in the clinical database listing in Annex 1 as having a serious adverse event that was glucose-related although the patient was hospitalized for hypoglycemia.

c: This patient was not included in the clinical database listing in Annex 1 as having discontinued treatment because of elevated glucose laboratory values.

d: This patient died but death was not due to a glucose-related adverse event. A narrative is provided in Annex 4 for completeness.

e: Only one patient is indicated because only one patient died of a glucose-related adverse event. The additional patients surrounded by parentheses in this column did not die from glucose-related causes but are shown for completeness.

f: Although originally coded as "coma diabetic", this elderly patient (#1204) experienced hyperglycemia with a hyperosmolar non-ketotic state as a complication of urinary sepsis and acute renal failure.

Volume 1/Page 63

JJRPrev 00379940
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Individual case reports (narratives) for deaths, other serious adverse events and adverse events leading to discontinuation are provided in Annex 4.

3.2.1.3. Subgroup analysis

3.2.1.3.1 Age

Overall, elderly patients had a higher incidence of glucose-related adverse events compared to non-elderly adult or pediatric/adolescent patients regardless of the treatment or duration of treatment. This relationship is consistent with epidemiological studies showing a higher incidence of diabetes in elderly as opposed to younger adults in the general population.^{17, 18}

There was also an apparent age-related increase in the overall incidence of glucose-related adverse events with short- and long-term risperidone treatment of 0.34% (1 of 290 patients), 0.51% (35 of 6797 patients), and 2.81% (37 of 1315 patients) for pediatric/adolescent, non-elderly adult, and elderly patients, respectively (Table 9).

When only short-term trial data were considered, there continued to be an age-dependent increase in incidence of glucose-related adverse events with risperidone for pediatric/adolescent, non-elderly adult, and elderly patients (0% of 183 patients, 0.40% of 4550 patients, and 2.51% of 597 patients, respectively) that had a similar pattern to placebo-treated patients (0% of 183 patients, 0.51% of 389 patients, 1.69% of 296 patients).

Non-elderly adult patients treated with risperidone, showed a lower incidence of glucose-related adverse events (0.40%, 18 of 4550 patients) than in olanzapine-treated non-elderly adults (0.89%, 4 of 448 patients) in short-term trials (Table 9). There were no studies in other age groups with olanzapine.

Non-elderly adult patients treated with risperidone in long-term trials showed a lower incidence of glucose-related adverse events (0.76%, 17 of 2247 patients) than haloperidol-treated non-elderly adults, (2.98% , 9 of 302 patients) (Table 9). There were no long-term studies in other age groups with haloperidol.

Table 9: Incidence (number of patients and %) with at least one glucose-related adverse event by age (yrs) and by duration of trial

Trial duration	Pediatric/ Adolescent		Non-elderly Adult		Elderly Adult	
	< 18		18 - 65		> 65	
Treatment	N	n (%)	N	n (%)	N	n (%)
Short-term trial (< 3 months)	366		6277		1008	
Placebo	183	0	389	2 (0.51%)	296	5 (1.69%)
Risperidone	183	0	4550	18 (0.40%)	597	15 (2.51%)
Haloperidol	NA	NA	597	1 (0.17)	115	1 (0.87%)
Olanzapine	NA	NA	448	4 (0.89%)	NA	NA
Other Neuroleptic	NA	NA	293	1 (0.34%)	NA	NA
Long-term trial (> 3 months)	107		2783		718	
Placebo	NA	NA	NA	NA	NA	NA
Risperidone	107	1 (0.93%)	2247	17 (0.76%)	718	22 (3.06%)
Haloperidol	NA	NA	302	9 (2.98%)	NA	NA
Olanzapine	NA	NA	NA	NA	NA	NA
Other Neuroleptic	NA	NA	234	0	NA	NA
Short- and long-term trial	473		9060		1726	
Placebo	183	0	389	2 (0.51%)	296	5 (1.69%)
Risperidone	290	1 (0.34%)	6797	35 (0.51%)	1315	37 (2.81%)
Haloperidol	NA	NA	899	10 (1.11%)	115	1 (0.87%)
Olanzapine	NA	NA	448	4 (0.89%)	NA	NA
Other Neuroleptic	NA	NA	527	1 (0.19%)	NA	NA

Age groupings are confounded by dose and diagnosis. See discussion.

Source: Display GAE.5

3.21.3.2 Sex

In general, there was a higher percentage of men than women who had glucose-related adverse events with placebo, olanzapine, or other neuroleptic treatment. This result is consistent with epidemiological studies.^{17,18} In the risperidone group women (1.09%, all trials combined) had a higher incidence of glucose-related adverse events than men (0.73%, all trials combined) (Table 10 and Display 3). The same held true for those treated with haloperidol.

In short-term trials only, women treated with risperidone had a higher incidence of glucose-related adverse events (0.81%, 16 of 1986 patients) than men (0.51%, 17 of 3338 patients), as did those treated with haloperidol (Table 10).

In long-term trials, there was also a higher incidence of glucose-related adverse events in risperidone-treated women versus men (1.57%, 19 of 1211 patients vs 1.13%, 21 of 1859 patients).

The higher incidence of glucose-related adverse events among risperidone- and haloperidol-treated females in short- and long-term trials is most likely

due to the higher proportion of elderly women. Overall, two-thirds of the elderly patients were female.

Table 10: Incidence (number of patients and %) of glucose-related adverse events in female and male patients by trial duration

Trial duration Treatment	Female		Male	
	N	n (%)	N	n (%)
Short-term trials (< 3 months)	2836		4809	
Placebo	365	2 (0.55%)	503	5 (0.99%)
Risperidone	1986	16 (0.81%)	3338	17 (0.51%)
Haloperidol	247	1 (0.40%)	465	1 (0.22%)
Olanzapine	132	1 (0.76%)	316	3 (0.95%)
Other Neuroleptic	106	0	187	1 (0.53%)
Long-term trials (> 3 months)	1393		2212	
Placebo	NA	NA	NA	NA
Risperidone	1211	19 (1.57%)	1859	21 (1.13%)
Haloperidol	107	4 (3.74%)	195	5 (2.56%)
Olanzapine	NA	NA	NA	NA
Other Neuroleptic	75	0	158	0
Short- and long-term trials	4229		7021	
Placebo	365	2 (0.55%)	503	5 (0.99%)
Risperidone	3197	35 (1.09%)	5197	38 (0.73%)
Haloperidol	354	5 (1.41%)	660	6 (0.91%)
Olanzapine	132	1 (0.76%)	316	3 (0.95%)
Other Neuroleptic	181	0	345	1 (0.29%)

Note: Nine patients with missing sex information were excluded.

Source: Display GAE.5

3.2.1.3.3 Race

Generally, a higher percentage of black patients had glucose-related adverse events regardless of the treatment or the duration of the trial. There was a higher percentage of black patients who reported glucose-related adverse events when treated with risperidone (2.28%, 22 of 966 black patients), olanzapine (2.63%, 2 of 76 black patients) or haloperidol (2.17%, 3 of 318 black patients) compared to white patients (0.75%, 45 of 6005 white patients; 0.30%, 1 of 330 white patients, or 0.58%, 4 of 684 white patients) or patients from other racial groups (0.75%, 6 of 800 other patients; 2.38%, 1 of 42 other patients; or 2.94%, 4 of 136 other patients) as shown in Table 11 for short- and long-term trials combined.

The pattern of a higher incidence of glucose-related adverse events among black patients than white patients was observed whether the trials were short-term or long-term or treatment was with risperidone, haloperidol or olanzapine. This general pattern is consistent with epidemiological studies.^{19,20,18} The exception was patients treated with placebo. With

placebo, there was a lower incidence of glucose-related adverse events in black patients (Table 11). However, the low number of black patients in the placebo group does not allow firm conclusions.

Table 11: Incidence (number of patients and %) of glucose-related adverse events by racial group and trial duration

Trial duration Treatment	Black		White		Other	
	N	n (%)	N	n (%)	N	n (%)
Short-term trials (< 3 months)	984		5346		741	
Placebo	116	0	618	6 (0.97%)	59	1 (1.69%)
Risperidone	720	13 (1.81%)	3701	18 (0.49%)	532	2 (0.38%)
Haloperidol	64	1 (1.56%)	491	1 (0.20%)	101	0
Olanzapine	76	2 (2.63%)	330	1 (0.30%)	42	1 (2.38%)
Other Neuroleptic	8	0	206	1 (0.49%)	7	0
Long-term trials (> 3 months)	320		2709		323	
Placebo	NA	NA	NA	NA	NA	NA
Risperidone	246	9 (3.66%)	2304	27 (1.17%)	268	4 (1.49%)
Haloperidol	74	2 (2.70%)	193	3 (1.55%)	35	4 (11.43%)
Olanzapine	NA	NA	NA	NA	NA	NA
Other Neuroleptic	NA	NA	212	0	20	0
Short- and long-term trials	1304		8055		1064	
Placebo	116	0	618	6 (0.97%)	59	1 (1.69%)
Risperidone	966	22 (2.28%)	6005	45 (0.75%)	800	6 (0.75%)
Haloperidol	138	3 (2.17%)	684	4 (0.58%)	136	4 (2.94%)
Olanzapine	76	2 (2.63%)	330	1 (0.30%)	42	1 (2.38%)
Other Neuroleptic	8	0	418	1 (0.24%)	27	0

Note: Eight hundred thirty-six patients with missing race information were excluded.

Source: Display GAE.5

3.2.1.4. Dose

The database used for the summary by mode dose is described in section 2.2. Several trials had a flexible-dosing regimen with risperidone. The dose was characterized using the following mode dose ranges:

- Dose groups pediatric/adolescent: <0.03mg/kg/day; 0.03-0.04 mg/kg/day; >0.04 mg/kg/day
- Dose groups adult: < 4 mg/day, 4-6 mg/day, >6 mg/day
- Dose groups geriatric: <0.75 mg/day, 0.75-1.5 mg/day, >1.5 mg/day.

The incidence of glucose-related adverse events by risperidone mode dose range is shown in Table 12. No apparent relationship between the mode dose group and incidence of glucose-related adverse events was seen in any of the three populations.

Table 12: Glucose-related adverse events by risperidone mode dose

	Mode dose		
	<0.03mg/kg/day	0.03-0.04 mg/kg/day	>0.04 mg/kg/day
Pediatric/adolescent (<18)			
No glucose AE	43 (100)	33 (100)	146 (99.3)
Glucose AE	0	0	1 (0.7)
Total	43	33	147
Adult (18-65)	<4 mg/day	4-6 mg/day	>6 mg/day
No glucose AE, n (%)	821 (99.9)	2121 (98.8)	2356 (99.7)
Glucose AE, n (%)	1 (0.1)	25 (1.2)	7 (0.3)
Total	822	2146	2363
Elderly (>65)	<0.75 mg/day	0.75-1.5 mg/day	>1.5 mg/day
No glucose AE	512 (96.8)	226 (95.8)	259 (97.0)
Glucose AE	17 (3.2)	10 (4.2)	8 (3.0)
Total	529	236	267

Source: Display GAE.6

3.2.1.5. Incidence of glucose-related adverse events relative to person-time exposure

In addition to displaying the incidence of adverse events separately for short- and long-term trials, as in Table 5 and Table 6, the incidence of glucose-related adverse event rates was explored relative to patient-years of exposure. In the 49 trials with sufficient data for the analysis, 6271 patients were exposed to risperidone treatment for a total of 1900.35 patient-years. Of those, 64 patients had a glucose-related adverse event, yielding an incidence of 3.37% per treatment-year, which is lower than the rate observed with placebo (8.00%) (Table 13). It should be recognized that since there were no long-term trials with placebo, olanzapine, or other neuroleptics in this dataset, individual patients in those groups were treated for a shorter duration than were most patients treated with risperidone or haloperidol. This might underestimate the rate of time-dependent adverse events in those 3 treatment groups. Patient-years of exposure are listed per trial in Display GAE.8.

Table 13: Treatment-year incidence of glucose-related adverse events

Treatment	N	Patient-years exposure	Patients with glucose-related AE (n)	Incidence per treatment-year (%)
Placebo	786	87.49	7	8.00
Risperidone	6271	1900.35	64	3.37
Haloperidol	929	279.57	11	3.93
Olanzapine	447	59.14	4	6.76
Other neuroleptics	293	29.24	1	3.42

There were no long-term trials with placebo, olanzapine, or other neuroleptics in person-time exposure analysis.

Source: Display GAE.8

3.2.1.6. Co-morbidity of abnormalities in glucose metabolism and weight increase or baseline BMI >23

Because being overweight or obese has been identified as a risk factor for diabetes,²¹ glucose-related adverse events were summarized according to baseline body mass index (BMI), using categories of <23, 23-27, and ≥27 kg/m². These categories were derived from The National Health and Nutrition Examination Survey (NHANES),²² which used the sex-specific 85th percentile values from the 1976-1980 survey, corresponding to a BMI of ≥27.8 kg/m² for men and ≥27.3 kg/m² for women, to define overweight.

In active treatment groups, glucose-related adverse events were more common in patients who began the trial with a body mass index greater than 27 (Table 14).

Table 14: Baseline body mass Index (BMI) and glucose-related adverse events

Treatment, N ^a	BMI at baseline		
	BMI<23	23<=BMI<=27	BMI>27
	Glucose-related adverse events number patients (%)	Glucose-related adverse events number patients (%)	Glucose-related adverse events number patients (%)
Placebo, 644	1/351 (0.28)	3/170 (1.76)	1/123 (0.81)
Risperidone, 5975	19/2395 (0.79)	16/1841 (0.87)	33/1739 (1.90)
Haloperidol, 935	1/344 (0.29)	1/300 (0.33)	9/291 (3.09)
Olanzapine, 445	1/117 (0.85)	0/130	3/198 (1.52)
Other neuroleptics, 515	0/211	0/166	1/138 (0.72)

^aPatients for whom BMI at baseline could be calculated.

BMI= weight kg/height m²

Source: Display GAE.7

Of the 8402 risperidone-treated patients, 5 (0.06%) reported both a glucose-related adverse event and a weight increase. All 5 had baseline body mass index (BMI) greater than 27 at baseline (range 30-42). Among the 1014 haloperidol-treated patients, 1 (0.1%) had both types of adverse events. That patient's BMI at baseline was 25. CRF ID numbers for these patients are listed in Display GAE.9. Adverse events of weight increase are discussed in detail in Section 3.2.2.1.

3.2.1.7. Concomitant diseases and medications

Cardiovascular disease is a frequent complication of diabetes. Annexes 2A and 2B contain information on concomitant cardiovascular medication and cardiovascular diseases for individual subjects. As little information is available regarding start dates, no further conclusions can be drawn regarding the co-existence of these types of conditions in these patients.

The relationship between glucose-related adverse events and other concomitant medication has not been examined in detail in this evaluation.

Annexes 2A and 2B contain some information on concomitant medication/diseases for individual subjects.

3.2.1.8. Heredity of diabetes mellitus

An investigation of the presence of diabetes in relatives is not possible because this information was not recorded.

3.2.1.9. Dechallenge/rechallenge

An investigation of the effect on glucose-related adverse events during rechallenge with risperidone was not performed because rechallenge was not part of the protocol for these trials.

The persistence of glucose-related adverse events beyond 4 days after trial completion or discontinuation of treatment was examined. This 4-day period was selected based on the 1-day half-life of risperidone. There were 12 patients with risperidone, 4 patients with haloperidol, and 1 patient with placebo treatment who had glucose-related adverse events with an onset prior to or within 4 days after completion/discontinuation of the trial, but did not recover from the adverse event after the 4-day period (Annex 1 as indicated by the occurrence of adverse event post trial and/or resolution beyond 4 days post trial or discontinuation). The time for resolution of these glucose-related adverse events varied widely. The information obtained is very limited and the data are, therefore, inconclusive.

3.2.1.10. Clinical laboratory evaluation of glucose

No information on the fasting/non-fasting condition for the glucose laboratory values was available, therefore, no evaluation of this assessment was done.

3.2.2. WEIGHT INCREASE

Trials in which weight increase was reported as an adverse event, regardless of treatment group, are underlined in Table 2.

3.2.2.1. Adverse events of weight increase

The incidence of adverse events of weight increase was evaluated in patients treated in short-term trials only, in long-term trials only, and for both short- and long-term trials combined.

As shown in Table 15, in the short-term trials, 74 of 5330 (1.39%) patients receiving risperidone reported weight increase. This was comparable to the percentage in the group receiving haloperidol, 9 of 712 patients, or 1.26%. Weight increase was reported as an adverse event for 9.38% of patients receiving olanzapine (42 of 448). Incidence among the 868 placebo-treated patients was 0.92%, and for the 293 patients treated with other neuroleptics it was 0.34%. Other neuroleptics included zuclopenthixol (FIN-1),

perphenazine (INT-7), remoxipride (INT-9), clozapine (GER-5, SUI-1), methotrimeprazine (FRA-3).

In the long-term trials, the incidence of weight increase was 3.09% among risperidone-treated patients, 1.66% for those taking haloperidol, and 0.43% for those taking other neuroleptics. There were no long-term trials with placebo or olanzapine. (Table 15)

Overall, the incidence of reports of weight increase as an adverse event was highest for olanzapine (9.38%); however this represents only data from short-term trials, since olanzapine was not a comparator in long-term trials. The incidence for risperidone in short- and long-term trials combined was 2.01%, and for haloperidol it was 1.38%. Incidence for other neuroleptics was 0.38%. Placebo was used as a comparator only in the short-term trials, in which the incidence of weight increase as an adverse event was 0.92%.

Detailed information for individual patients with adverse events of weight increase is provided in Annex 1C.

Table 15: Incidence (number of patients and %) of weight increase (preferred term) as an adverse event in Phase 2-3 trials

	Placebo	Risperidone	Haloperidol	Olanzapine	Other Neuroleptics ^a
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Short-term trials ^b	8/868 (0.92)	74/5330 (1.39)	9/712 (1.26)	42/448 (9.38)	1/293 (0.34)
Long-term trials ^c		95/3072 (3.09)	5/302 (1.66)		1/234 (0.43)
TOTAL	8/868 (0.92)	169/8402 (2.01)	14/1014 (1.38)	42/448 (9.38)	2/527 (0.38)

a: Other neuroleptics include: zuclopenthixol (FIN-1), perphenazine (INT-7), remoxipride (INT-9), clozapine (GER-5, SUI-1), methotrimeprazine (FRA-3).

b: Trials included: AUT-1, BEL-5, BEL-7, FIN-1, GRA-3, GER-5, INT-10, INT-2, INT-3, INT-5, INT-7, INT-9, INT-39/GBR-28, INT-45, INT-46, KOR-1, SUI-1, USA-1, USA-60, USA-72, USA-102, USA-112, GER-3, INT-1, ITA-1, USA-54, BEL-14, INT-24, USA-63, BEL-11, BEL-24, NED-9, CAN-19, USA-93, BEL-21, BEL-22

c: Trials included: INT-6, USA-79, BEL-17, INT-4, INT-8, INT-12, INT-17, INT-47/GBR-29, ISR-1, NED-2, USA-5, USA-6, USA-7, USA-9, INT-23, INT-26, USA-34, USA-64, USA-70, USA-97

Source: Display WAE.1

The events summarized in Table 15 represent worsenings of pre-existing conditions or new reports of weight increase. BMI was greater than 23 at the start of the trials in a substantial proportion of patients: 60% (3580/5975) of the risperidone group and 63% (591/935) of the haloperidol group. Table 16 shows reports of weight increase according to body mass index (BMI) at baseline. Except in the haloperidol group, there was no clear relationship between BMI at baseline and subsequent reports of weight increase. In the haloperidol group, there tended to be a higher incidence of weight increase adverse events with higher baseline BMI.

Table 16: Baseline body mass index (BMI) and weight increase adverse events (AE)

Treatment, N ^a	BMI at baseline		
	BMI<23	23<BMI≤27	BMI>27
	Weight increase AE number patients (%)	Weight increase AE Number patients (%)	Weight increase AE number patients (%)
Placebo, 644	4/351 (1.14)	1/170 (0.59)	1/123 (0.81)
Risperidone, 5975	66/2395 (2.76)	35/1841 (1.9)	44/1739 (2.53)
Haloperidol, 935	3/344 (0.87)	3/300 (1.0)	7/291 (2.41)
Olanzapine, 445	10/117 (8.55)	15/130 (11.54)	17/198 (8.59)
Other neuroleptics, 515	1/211 (0.47)	0/166	1/138 (0.72)

^a: Patients for whom BMI at baseline could be calculated.BMI=weight kg/height m²

Source: Display WAE.6

3.2.2.2. Deaths, serious adverse events and discontinuations due to adverse events of weight increase

There were no deaths due to weight increase and no adverse events of weight increase were considered serious. Patients who had adverse events of weight increase for which the outcome was "permanent stop" of trial medication are listed in Table 17: 3 patients treated with risperidone and one treated with olanzapine. In addition, narratives are provided for these patients in Annex 4.

Table 17: Patients with an adverse event of weight increase (preferred term) for which the action taken was permanent stop of trial medication

Trial no. Patient no.	Treatment group	Adverse event (verbatim)
ADULTS (18-65 years)		
INT-3 (Double-blind short-term)		
0468	Risperidone	Weight gain > 15 lbs, bloating, epistaxis, and anemia
USA-112 (Double-blind short-term)		
A30517	Olanzapine	Weight gain
CHILDREN/ADOLESCENTS (<18 years)		
USA-97 (Open-label)		
A3069	Risperidone	Weight gain
A3125	Risperidone	Weight gain

A patient narrative is provided in Annex 4 for all patients listed in this table.

3.2.2.3. Subgroup analysis**3.2.2.3.1 Age**

The incidence of the adverse event of weight increase for each treatment, broken down by age grouping, is shown in Table 18. The majority of the patients were within the ages of 18 and 65 years. Within that cohort, the relative incidence of weight increase for each treatment was similar to that in the sample as a whole.

Elderly patients had a lower incidence of weight increase than did those 18 to 65 years old. This was the case regardless of whether the patients had been treated with risperidone, haloperidol, or placebo. Elderly patients were not treated with olanzapine or other neuroleptics as part of these trials.

In short-term trials (shorter than 3 months), pediatric/adolescent patients treated with risperidone had a higher incidence of reported weight increase (8.2%) than did those treated with placebo (1.09%, or 2 of 183 patients). In the long-term trials, the incidence for weight increase in risperidone-treated adolescents was 20.56%, however, there were no comparator groups in those trials. Since growth and weight gain would be expected in untreated patients younger than 18 years of age, any discussion of this age group will be limited to the short-term trial data, for which another group is available for comparison (in this case, placebo-treated patients).

Table 18: Incidence (number of patients and %) with at least one weight increase adverse event by age grouping (yrs) and by duration of trial

Trial duration Treatment	Pediatric/ Adolescent < 18		Non-elderly Adult 18 - 65		Elderly Adult > 65	
	N	n (%)	N	n (%)	N	n (%)
Short-term trials (< 3 months)	366		6277		1008	
Placebo	183	2 (1.09)	389	5 (1.29)	296	1 (0.34)
Risperidone	183	15 (8.20)	4550	56 (1.23)	597	3 (0.50)
Haloperidol	NA	NA	597	9 (1.51)	115	0
Olanzapine	NA	NA	448	42 (9.38)	NA	NA
Other Neuroleptic	NA	NA	293	1 (0.34)	NA	NA
Long-term trials (> 3 months)	107		2783		718	
Placebo	NA	NA	NA	NA	NA	NA
Risperidone	107	22 (20.56)	2247	64 (2.85)	718	9 (1.25)
Haloperidol	NA	NA	302	5 (1.66)	NA	NA
Olanzapine	NA	NA	NA	NA	NA	NA
Other Neuroleptic	NA	NA	234	1 (0.43)	NA	NA
Short- and long-term trials	473		9060		1726	
Placebo	183	2 (1.09)	389	5 (1.29)	296	1 (0.34)
Risperidone	290	37 (12.76)	6797	120 (1.77)	1315	12 (0.91)
Haloperidol	NA	NA	899	14 (1.56)	115	0
Olanzapine	NA	NA	448	42 (9.38)	NA	NA
Other Neuroleptic	NA	NA	527	2 (0.38)	NA	NA

Age groupings may be confounded by dose and diagnosis.

Source: Display WAE.3

3.2.2.3.2 Sex

Adverse events of weight increase are presented by sex in Table 19. When data from short- and long-term trials were combined, the incidence of weight increase as an adverse event was slightly higher in men compared with

women receiving risperidone. Among those receiving other treatments, a higher percentage of females compared with males reported weight increase. A similar pattern was observed in the data from the short-term trials alone. In the long-term trials, males had a higher incidence than females of reported weight increase with risperidone, haloperidol, or other neuroleptic treatment. The long-term trials did not include treatment with placebo or olanzapine.

Table 19: Incidence (number of patients and %) of weight increase adverse events in female and male patients by trial duration

Trial duration Treatment	Female		Male	
	N	n (%)	N	n (%)
Short-term trials (< 3 months)	2836		4809	
Placebo	365	5 (1.37)	503	3 (0.60)
Risperidone	1986	26 (1.31)	3338	48 (1.44)
Haloperidol	247	5 (2.02)	465	4 (0.86)
Olanzapine	132	18 (13.64)	316	24 (7.59)
Other Neuroleptic	106	1 (0.94)	187	0
Long-term trials (> 3 months)	1393		2212	
Placebo	NA	NA	NA	NA
Risperidone	1211	32 (2.64)	1859	63 (3.39)
Haloperidol	107	1 (0.93)	195	4 (2.05)
Olanzapine	NA	NA	NA	NA
Other Neuroleptic	75	0	158	1 (0.63)
Short- and long-term trials	4229		7021	
Placebo	365	5 (1.37)	503	3 (0.60)
Risperidone	3197	58 (1.81)	5197	111 (2.14)
Haloperidol	354	6 (1.69)	660	8 (1.21)
Olanzapine	132	18 (13.64)	316	24 (7.59)
Other Neuroleptic	181	1 (0.55)	345	1 (0.29)

Note: Nine patients with missing sex information were excluded.

Source: Display WAB.3

3.2.2.3.3 Race

Weight increase by race is shown in Table 20. Blacks had a higher incidence of weight increase than did whites or those of other races treated with risperidone, haloperidol, or olanzapine. This relationship was not evident with placebo, which was only administered during the short-term trials. Race comparisons cannot be made in the category of other neuroleptics since the number of non-white patients treated with them as part of the trials was low. There were very few white patients treated with other neuroleptics who also reported weight increase.

Table 20: Incidence (number of patients and %) of weight increase adverse events by racial group and trial duration

Trial duration Treatment	Black		White		Other	
	N	n (%)	N	n (%)	N	n (%)
Short-term trials (< 3 months)	984		5346		741	
Placebo	116	0	618	5 (0.81)	59	1 (1.69)
Risperidone	720	21 (2.92)	3701	41 (1.11)	532	11 (2.07)
Haloperidol	64	4 (6.25)	491	3 (0.61)	101	1 (0.99)
Olanzapine	76	11 (14.47)	330	28 (8.48)	42	3 (7.14)
Other Neuroleptic	8	0	206	1 (0.49)	7	0
Long-term trials (> 3 months)	320		2709		323	
Placebo	NA	NA	NA	NA	NA	NA
Risperidone	246	21 (8.54)	2304	66 (2.86)	268	7 (2.61)
Haloperidol	74	3 (4.05)	193	2 (1.04)	35	0
Olanzapine	NA	NA	NA	NA	NA	NA
Other Neuroleptic	NA	NA	212	1 (0.47)	20	0
Short- and long-term trials	1304		8055		1064	
Placebo	116	0	618	5 (0.81)	59	1 (1.69)
Risperidone	966	42 (4.35)	6005	107 (1.78)	800	18 (2.25)
Haloperidol	138	7 (5.07)	684	5 (0.73)	136	1 (0.74)
Olanzapine	76	11 (14.47)	330	28 (8.48)	42	3 (7.14)
Other Neuroleptic	8	0	418	2 (0.48)	27	0

Note: Eight hundred thirty-six patients with missing race information were excluded.

Source: Display WAE3

3.2.2.4. Dose

When adverse events of weight increase were summarized by mode dose, no apparent relationship between the dose and weight-increase adverse events was seen (Table 21).

Table 21: Weight-increase adverse events by risperidone mode dose

	Mode dose		
	Pediatric/adolescent (<18)	<0.03mg/kg/day	0.03-0.04 mg/kg/day >0.04 mg/kg/day
No wt increase AE, n (%)	56 (83.6)	30 (90.9)	124 (84.4)
Weight increase AE, n (%)	11 (16.4)	3 (9.1)	23 (15.6)
Total	67	33	147

	Mode dose		
	Adult (18-65)	<4 mg/day	4-6 mg/day >6 mg/day
No wt increase AE, n (%)	805 (97.9)	2095 (97.6)	2327 (98.5)
Wt increase AE, n (%)	17 (2.1)	51 (2.4)	36 (1.5)
Total	822	2146	2363

	Mode dose		
	Elderly (>65)	<0.75 mg/day	0.75-1.5 mg/day >1.5 mg/day
No wt increase AE, n (%)	522 (98.7)	235 (99.6)	264 (98.9)
Wt increase AE, n (%)	7 (1.3)	1 (0.4)	3 (1.1)
Total	529	236	267

Source: Display WAE.5

3.2.2.5. Duration of treatment

In addition to displaying incidence of adverse events separately for short- and long-term trials, as in Table 15, the relationship between duration of treatment and occurrence of weight-increase adverse events was explored relative to patient-years of exposure. In the 49 trials with sufficient data, 6271 patients were exposed to risperidone treatment for a total exposure to risperidone of 1900.35 patient-years. Of those patients, 124 patients had a weight-increase adverse event, yielding a rate per treatment-year of 6.53% (Table 22). No difference was observed between risperidone and placebo.

It should be noted that since there were no long-term trials with placebo, olanzapine, or other neuroleptics in this dataset, individual patients in those groups were treated for a shorter duration than patients in the other treatment groups. The duration of exposure by trial is provided in Display WAE.7.

Table 22: Treatment-year incidence of weight-increase adverse events

Treatment	N	Patient-years exposure	Patients with weight increase AE (n)	Incidence per treatment-year (%)
Placebo	786	87.49	6	6.86
Risperidone	6271	1900.35	124	6.53
Haloperidol	929	279.57	10	3.58
Olanzapine	447	59.14	42	71.02
Other neuroleptics	293	29.24	1	3.42

There were no long-term trials with placebo, olanzapine, or other neuroleptics in the person-time exposure analysis.

Source: Display WAE.7

3.2.2.6. Actual weight change

Trials were of varying lengths and intervals between visits. Therefore, weight change from baseline to endpoint was examined. Because expected weight change would be different for pediatric/adolescent and adult populations, data have been summarized separately for different age groups.

3.2.2.6.1 Weight gain as percentage of baseline weight

Incidence of weight gain as the percentage of baseline weight is presented for short-term and long-term trials and for different age groups separately. The category of <7% includes patients whose weight remained the same or who lost weight.

Among risperidone-treated adults, 2.5% had weight gains greater than 14% of baseline weight in short-term trials, compared to 0.7% among placebo-treated adults, 5.2% among olanzapine-treated adults and 1.5% among those treated with haloperidol or other neuroleptics (Table 23). In long-term trials, 7.3% had weight gains greater than 14% of baseline weight, compared to 0.7% among patients treated long-term with haloperidol. In long-term trial RIS-USA-79 there were more discontinuations by patients in the haloperidol group, resulting in a shorter duration of treatment for that group.

Table 23: Weight gain as percentage of baseline weight by trial duration in adults 18-65 years old

Treatment	Weight gain at endpoint as percentage of baseline weight, n (%)		
	<7%	7-14%	>14%
Short-term trials			
Placebo	285 (92.83)	20 (6.51)	2 (0.65)
Risperidone	2428 (87.46)	280 (10.09)	68 (2.45)
Haloperidol	373 (92.10)	26 (6.42)	6 (1.48)
Olanzapine	296 (73.27)	87 (21.53)	21 (5.20)
Other neuroleptics	176 (87.13)	23 (11.39)	3 (1.49)
Long-term trials			
Risperidone	972 (80.07)	153 (12.60)	89 (7.33)
Haloperidol	272 (96.80)	7 (2.49)	2 (0.71)

Source: Display WEL3

Among the elderly (Table 24), weight increased more than 14% over baseline weight for 1.9% of risperidone-treated patients in short-term trials, and 3.7% in long-term trials.

Table 24: Weight gain as percentage of baseline weight by trial duration in adults older than 65 years

Treatment	Weight gain at endpoint as percentage of baseline weight, n (%)		
	<7%	7-14%	>14%
Short-term trials			
Placebo	226 (93.8)	13 (5.4)	2 (0.8)
Risperidone	471 (89.4)	46 (8.7)	10 (1.9)
Haloperidol	84 (95.5)	4 (4.6)	0
Long-term trials			
Risperidone	350 (85.2)	46 (11.2)	15 (3.7)

Source: Display WEI.3

Among patients younger than 18 (Table 25), there were 9 (of 130; 6.9%) risperidone-treated patients and 2 (of 117; 1.7%) placebo-treated patients with weight gains larger than 14% over baseline. Since growth and weight gain would be expected in a pediatric/adolescent population, drug-related weight gain in this population should be evaluated relative to placebo, as in the short-term trials. Regarding long-term trials, the annual expected weight gain²³ for an 8-year-old male of 34.6 kg (the average age and baseline weight for risperidone-treated patients in the long-term pediatric/adolescent trial) corresponds to a gain of 14.7% over baseline weight. (See section 3.2.2.6.2.)

Table 25: Weight gain as percentage of baseline weight by trial duration in patients younger than 18 years old

Treatment	Weight gain at endpoint as percentage of baseline weight, n (%)		
	<7%	7-14%	>14%
Short-term trials			
Placebo	107 (91.5)	8 (6.8)	2 (1.7)
Risperidone	79 (60.8)	42 (32.3)	9 (6.9)
Long-term trials			
Risperidone	26 (24.8)	25 (23.8)	54 (51.4)

Source: Display WEI.3

3.2.2.6.1.1 Baseline BMI

The weight change summarized by BMI category at baseline is presented in Table 26. In the adult population, more risperidone-treated patients with a baseline BMI below 23 gained more than 14% of baseline weight than did those with higher BMI at baseline. Similar patterns emerged in the elderly and pediatric/adolescent populations (Displays WEI.6A-6E.)

Table 26: Incidence of weight gain by baseline BMI

BMI at baseline	Weight gain at endpoint as percentage of baseline weight, n (%)		
	<7%	7-14%	>14%
Placebo			
BMI <23	49 (94.2)	3 (5.8)	0
23 < BMI ≤ 27	58 (96.7)	2 (3.3)	0
>27	60 (98.4)	1 (1.6)	0
Risperidone			
BMI <23	932 (77.2)	187 (15.5)	88 (7.3)
23 < BMI ≤ 27	1031 (87.2)	114 (9.64)	37 (3.1)
>27	1171 (92.1)	82 (6.45)	18 (1.42)
Haloperidol			
BMI <23	182 (91)	15 (7.5)	3 (1.5)
23 < BMI ≤ 27	202 (94.0)	8 (3.7)	5 (2.3)
>27	234 (96.7)	8 (3.3)	0
Olanzapine			
BMI <23	63 (60.6)	33 (31.7)	8 (7.7)
23 < BMI ≤ 27	84 (71.8)	24 (20.5)	9 (7.7)
>27	149 (82.3)	28 (15.5)	4 (2.2)
Other neuroleptics			
BMI <23	56 (83.6)	9 (13.4)	2 (3.0)
23 < BMI ≤ 27	68 (86.1)	11 (13.9)	0
>27	50 (92.6)	3 (5.6)	1 (1.9)

Patients age 18-65 only.

Source: Display WEL6A-E.

3.2.2.6.1.2 Sex

Weight gain as percentage of baseline weight, for all age groups combined, is shown in Table 27. There was no difference between males and females with respect to degree of weight gain.

Table 27: Weight gain by sex

Treatment	Weight gain (kg) to endpoint as percentage of baseline weight, n (%)		
	<7%	7-14%	>14%
Female			
Placebo	261 (92.2)	18 (6.4)	4 (1.4)
Risperidone	1566 (84.8)	213 (11.5)	67 (3.6)
Haloperidol	257 (94.5)	12 (4.4)	3 (1.1)
Olanzapine	87 (71.3)	29 (23.8)	6 (4.9)
Other neuroleptics	55 (88.7)	5 (8.1)	2 (3.2)
Male			
Placebo	357 (93.5)	23 (6.0)	2 (0.5)
Risperidone	2758 (83.2)	379 (11.4)	178 (5.4)
Haloperidol	472 (94.0)	25 (5.0)	5 (1.0)
Olanzapine	209 (74.1)	58 (20.6)	15 (5.3)
Other neuroleptics	121 (86.4)	18 (12.9)	1 (0.7)

Source: Display WEL4A-E

3.2.2.6.1.3 Race

Weight gain as percentage of baseline weight is presented according to race in Display WE1.5. Racial groups were similar in terms of distribution of degree of weight gain with risperidone.

3.2.2.6.1.4 Dose

In the pediatric/adolescent and adult populations, there was a slight tendency for a higher percentage of patients to have greater than 14% increase in body weight in the highest dose range. In the elderly population there was no dose-related increase in weight (Table 28).

Table 28: Weight gain as percentage of baseline weight by mode dose of risperidone

Mode dose	Weight gain at endpoint as percentage of baseline weight, n (%)		
	<7%	7-14%	>14%
Pediatric/Adolescent (<18)			
<0.03 mg/kg/day	28 (49.1)	17 (29.8)	12 (21.1)
0.03-0.04 mg/kg/day	16 (50.0)	9 (28.1)	7 (21.9)
>0.04 mg/kg/day	61 (41.8)	41 (28.1)	44 (30.1)
Adult (18-65)			
<4 mg/day	485 (88.2)	50 (9.1)	15 (2.7)
4-6 mg/day	1448 (86.3)	168 (10.0)	61 (3.6)
>6 mg/day	1467 (83.2)	215 (12.2)	81 (4.6)
Elderly (>65)			
<0.75 mg/day	400 (84.2)	57 (12.0)	18 (3.8)
0.75-1.5 mg/day	195 (91.6)	16 (7.51)	2 (0.9)
>1.5 mg/day	226 (90.4)	19 (7.6)	5 (2.0)

Source: Display WE1.1A

3.2.2.6.2 Mean weight change from baseline (kg) by trial duration and age group

The mean weight change, in kg, from baseline to endpoint is presented in Table 29 for short-term and long-term trials and for the different age groups separately. In the short-term trials with adults, the mean weight change was 1.32 kg for risperidone-treated patients, 0.17 kg for placebo, 0.07 kg for haloperidol, 0.96 kg for other neuroleptics and 3.21 kg for olanzapine. In the long-term trials, weight change was 1.76 kg for risperidone-treated adults and 0.06 kg for those treated with haloperidol.

In short-term trials with adults older than 65 years, the mean change was 0.37 kg with risperidone, -0.31 kg with placebo and -1.17 kg with haloperidol. In long-term trials average weight change for risperidone-treated elderly patients was 0.25 kg (Table 29).

Weight gain and growth is expected in patients younger than 18 years, and discussion of this age group must take that natural gain into account. Drug-related weight change over time should be evaluated relative to placebo. In the short-term trials, weight change averaged 2.13 kg in risperidone-treated

patients under the age of 18, and 0.57 kg in placebo-treated patients in that age group.

There were no long-term trials with placebo in this population, so natural weight gain can be estimated. According to the National Center for Health Statistics (NCHS) percentiles²³, the annual expected weight gain for an 8-year-old male of 34.6 kg (the average age and baseline weight for risperidone-treated patients in the long-term pediatric/adolescent trial) is 5.1 kg. In the one-year long-term trial (USA-97), mean weight gain with risperidone treatment was 5.48 kg (Table 29).

Table 29: Mean $\pm$ SD weight change from baseline at endpoint by trial duration and age group

Treatment	Mean $\pm$ SD weight change (kg) from baseline to endpoint		
	Pediatric/ adolescent, <18	Adult, 18-65	Elderly, >65
Short-term trials			
(<3 months)			
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 $\pm$ 3.54	-1.17 $\pm$ 3.52
Olanzapine	-	3.21 $\pm$ 4.45	-
Other neuroleptics	-	0.96 $\pm$ 3.28	-
Long-term trials			
(>3 months)			
Risperidone	5.48 $\pm$ 4.51	1.76 $\pm$ 5.66	0.25 $\pm$ 4.34
Haloperidol	-	0.06 $\pm$ 2.41	-

Source: Display WEL8

3.2.2.6.2.1 Baseline BMI

The mean weight change, in kg, from baseline to endpoint is presented in Table 30, summarized by BMI category at baseline. In the adult population, average weight gain in the placebo group did not appear to be affected by baseline BMI. Risperidone-treated adult and elderly patients with a baseline BMI less than 23 gained more weight on average than patients with higher baseline BMI. The opposite was seen in the pediatric/adolescent population.

Table 30: Mean $\pm$ SD weight change (kg) by baseline BMI and age group

Treatment	Baseline BMI		
	<23	23<BMI≤27	>27
Pediatric/Adolescent (<18)			
Placebo	0.49 $\pm$ 1.74	1.17 $\pm$ 0.90	1.15 $\pm$ 1.63
Risperidone	3.27 $\pm$ 3.25	4.63 $\pm$ 4.56	5.71 $\pm$ 5.25
Adult (18-65)			
Placebo	-0.38 $\pm$ 3.41	-0.44 $\pm$ 3.45	-0.41 $\pm$ 3.92
Risperidone	2.21 $\pm$ 4.30	1.44 $\pm$ 4.34	0.62 $\pm$ 4.38
Haloperidol	0.42 $\pm$ 2.82	0.53 $\pm$ 3.16	-0.55 $\pm$ 3.18
Olanzapine	3.78 $\pm$ 3.64	3.25 $\pm$ 4.93	2.84 $\pm$ 4.55
Other neuroleptics	1.54 $\pm$ 2.80	0.89 $\pm$ 3.33	0.33 $\pm$ 3.72
Elderly (>65)			
Placebo	0.20 $\pm$ 2.93	-1.21 $\pm$ 4.16	-0.47 $\pm$ 3.19
Risperidone	0.75 $\pm$ 3.40	-0.42 $\pm$ 3.69	0.27 $\pm$ 4.28
Haloperidol	-0.94 $\pm$ 3.01	-0.53 $\pm$ 3.47	-2.78 $\pm$ 3.66

Weight change from baseline to endpoint.

Source: Displays WEL7A, WEL7B, WEL7C, WEL7D, WEL7E

3.2.2.6.3 Dose

In the adult and elderly populations, no pattern was observed between mean weight change and mode dose of risperidone. In the pediatric/adolescent population, mean weight increased slightly with higher mode dose (Table 31).

Table 31: Mean weight change of risperidone-treated patients by mode dose

Mode dose	Mean $\pm$ SD weight change (kg) from baseline to endpoint
Pediatric/Adolescent	
<0.03 mg/kg/day	3.22 $\pm$ 3.67
0.03-0.04 mg/kg/day	3.50 $\pm$ 2.89
>0.04 mg/kg/day	3.81 $\pm$ 3.89
Adult	
<4 mg/day	1.16 $\pm$ 3.95
4-6 mg/day	1.54 $\pm$ 4.33
>6 mg/day	1.47 $\pm$ 4.53
Elderly	
<0.75 mg/day	0.35 $\pm$ 4.12
0.75-1.5 mg/day	0.15 $\pm$ 3.09
>1.5 mg/day	0.40 $\pm$ 3.25

Source: Display WEL2A

3.2.2.7. Concomitant medications and diseases

The relationship of the incidence of weight change and concomitant medication other than trial medication has not been examined in detail in this evaluation.

3.2.2.8. Dechallenge/rechallenge

The effects of dechallenge/rechallenge on weight increase were not specifically investigated in the individual trials or in this summary. There were 3 risperidone-treated patients and one haloperidol patient who discontinued with an adverse event of weight increase (See Section 3.2.2.2). Their narratives are available in Annex 4. No follow-up information is available and no conclusions can be drawn regarding the effects of dechallenge/rechallenge on weight change.

4. SUMMARY AND CONCLUSIONS

In summary, the data from over 11,000 psychiatric patients encompassing three age groups (pediatric/adolescent, adult, and geriatric) were reviewed for adverse events associated with abnormalities in glucose metabolism and weight increase in 10 Phase 1 and 56 Phase 2-3 world-wide trials.

Glucose metabolism

The incidence of adverse events related to abnormalities in glucose metabolism in Phase 2-3 trials was evaluated in patients treated in short-term trials, in long-term trials, and in all trials regardless of the design or duration. The overall incidence of these events was low with risperidone treatment (0.87% of 8402 patients). For the short-term trials, there was a lower incidence with risperidone treatment (0.62% of 5330 patients) compared with placebo or olanzapine treatment (0.81% of 868 patients and 0.89% of 448, respectively). The incidence was higher with both risperidone and placebo treatment when compared with haloperidol and other neuroleptics (0.28% of 712 patients and 0.34% of 293, respectively, in short-term trials) (i.e., zuclopenthixol, perphenazine, remoxipride, clozapine, and methotrimeprazine). In long-term trials, there was a lower incidence with risperidone treatment (1.3 % of 3072 patients) or other neuroleptics (0% of 234) than with haloperidol treatment (2.98% of 302 patients). There were no long-term trials with placebo or olanzapine.

The occurrence of deaths associated with glucose-related adverse events was very low and was indistinguishable between risperidone (0.01%, 1 of 8402 patients) and placebo treatment (0%, 0 of 868 patients), haloperidol (0%, 0 of 1014 patients), olanzapine (0%; 0 of 448) and other neuroleptics (0%, 0 of 527 patients). In addition, the incidence of serious glucose-related adverse events was lower with risperidone treatment (0.15% of 8402 patients) than with placebo or haloperidol (0.35% of 868 patients and 0.30% of 527 patients, respectively). No serious adverse events with olanzapine or other neuroleptics were related to abnormalities of glucose metabolism. Discontinuation due to glucose-related adverse events was also lower with risperidone (0.04% of 8402 patients) compared with placebo (0.12% of 868 patients) or with haloperidol (0.20% of 1014 patients) treatment. No discontinuations were related to abnormalities of glucose metabolism with olanzapine or other neuroleptics.

Volume 1/Page 83

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Subgroup analyses of risperidone-treated patients showed a higher incidence of glucose-related adverse events in elderly, black, and overweight patients, in general. This is consistent with epidemiological studies. No dose effects were seen.

Data from 10 Phase 1 trials support the findings in the Phase 2-3 trials that there is no evidence that treatment with risperidone induced significant abnormalities in glucose metabolism.

Weight increase adverse events

The incidence of adverse events of weight increase was evaluated in patients treated in short-term trials only, in long-term trials only, and for both short- and long-term trials combined. The overall incidence of these events with risperidone was 2.01% of 8402 patients. For the short-term trials, there was a lower incidence with risperidone treatment (1.39% of 5330 patients) compared with olanzapine treatment (9.38% of 448 patients). The incidence with placebo was 0.92% (of 868 patients), with haloperidol 1.26% (of 712 patients), and with other neuroleptics it was 0.34% (of 293 patients) in short-term trials. Other neuroleptics included zuclopenthixol, perphenazine, remoxipride, clozapine, and methotrimeprazine. In long-term trials, the incidence with risperidone treatment was 3.09 % of 3072 patients relative to 1.66% (of 302 patients) with haloperidol treatment and 0.43% (of 234) patients treated with other neuroleptics. There were no long-term trials with placebo or olanzapine.

There were no deaths due to weight increase and no adverse events of weight increase were considered serious. Discontinuations associated with weight increase adverse events occurred in 3 patients from the risperidone treatment group and one in the olanzapine treatment group.

Subgroup analyses of risperidone-treated patients showed a higher incidence of weight increase adverse events males and black patients, in general. No dose effects were seen.

Weight change

Weight gain of more than 14% over baseline body weight occurred more frequently in the 18-65 year-old adults treated with risperidone (2.5%) than placebo (0.7%) in short-term trials and less frequently than olanzapine (5.2%). Percentages among the elderly were 1.9% and 0.8% for risperidone and placebo, respectively, in short-term trials.

Mean weight change from baseline to endpoint in short-term trials was 1.3 kg for non-elderly adults and 0.4 kg for elderly adults treated with risperidone. These means reflected more weight gain relative to placebo (0.2 kg), haloperidol (0.1 kg) and other neuroleptics (1.0 kg), but less than olanzapine (3.2 kg). In long-term trials, mean change was 1.8 kg for non-elderly and 0.3

kg for elderly risperidone-treated adults. No dose effect was observed. Long-term weight change with haloperidol was a gain of 0.1 kg for non-elderly adults. Risperidone-treated adults with a baseline body mass index (BMI) less than 23 gained more weight on average than patients with a higher BMI.

Weight gain in the pediatric/adolescent patients treated with risperidone was similar to that predicted using standard growth curves, and showed a slight tendency to increase with a higher risperidone mode dose.

Conclusion

In a large body of clinical data, abnormalities of glucose metabolism in patients treated with risperidone occurred at a rate similar to that for patients treated with placebo. Clinically significant weight gain was observed at a rate higher than that for placebo but lower than that observed for patients treated with olanzapine.

5. REFERENCES

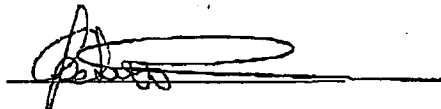
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JRF Clinical Summary Report	
Title	Evaluation of the effects of risperidone on glucose metabolism and weight in Phase 1-3 trials
Authors	G. De Smedt, C. Ding, P. Mayvisch, K. Hoffman, L. Masukawa, J. Rosenberg, A. Derivan, I. Caers

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of this investigation.



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Clinical Project Scientist
Global Clinical R&D and Regulatory Affairs, Worldwide, CNS

8 August 2000

Volume 1/Page 88

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6. SUPPORTING DATA

6.1. Displays

Volume 1/Page 89

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Display GAE.1 Number of glucose related AEs by WHO preferred term and treatment

ADVERSE EVENT PREFERRED TERM	TRIAL DURATION													Total
	LONG-TERM		SHORT-TERM					Short + Long Term						
			Treatment					Treatment						
	Treatment		Treatment					Treatment						
	Halo- peri- dol	Risp- erid- one	Halo- peri- dol	Olan- zapi- ne	Neur- peri- olep- tics	Plac- ebo	Risp- erid- one	Halo- peri- dol	Olan- zapi- ne	Neur- peri- olep- tics	Plac- ebo	Risp- erid- one		
n	n	n	n	n	n	n	n	n	n	n	n	n		
ADVERSE EVENT PREFERRED TERM														
ACIDOSIS	-	1	-	-	-	-	2	-	-	-	-	1	1	
BLOOD SUGAR INCREASED	-	-	-	-	-	-	-	-	-	-	-	-	2	
COMA DIABETIC	-	-	-	-	-	-	1	-	-	-	-	-	1	
DIABETES MELLITUS	5	11	-	1	1	1	4	5	1	1	1	15	23	
DIABETES MELLITUS AGGRAVATED	-	-	-	-	-	-	2	-	-	-	-	2	2	
GLYCOSURIA	-	2	-	-	-	-	-	-	-	-	-	-	2	
HYPERGLYCAEMIA	5	23	2	3	-	5	20	7	3	-	5	43	56	
HYPOGLYCAEMIA	1	5	-	-	-	1	7	1	-	-	1	12	14	
KETOSIS	-	1	-	-	-	-	1	-	-	-	-	2	2	
PLASMA OSMOLALITY INCREASED	-	-	-	-	-	-	1	-	-	-	-	1	1	

Display GAB.2 List of trials and number of patients by treatment

AGE GROUP	TRIAL BLINDING BY DESIGN	TRIAL DURATION	TRIAL ID	Treatment					Total
				Halo-peri-dol	Olanzapine	Neuroleptics	Placebo	Risperidone	
				n	n	n	n	n	
18 - 65	DOUBLE-BLIND	LONG-TERM	INT-6	99	-	-	-	91	190
			USA-79	203	-	-	-	192	395
		SHORT-TERM	AUT-1	-	-	33	-	34	67
			BEL-5	22	-	-	-	22	44
			BEL-7	32	-	-	-	28	60
			FIN-1	-	-	50	-	48	98
			FRA-3	20	-	21	-	21	62
			GER-28	-	-	-	13	10	23
			GER-5	-	-	20	-	39	59
			INT-10	-	-	-	-	211	211
			INT-2	226	-	-	-	1136	1362
			INT-3	87	-	-	88	348	523
			INT-39	-	-	-	25	29	54
			INT-45	-	243	-	-	247	490
			INT-46	-	-	-	75	75	150
			INT-5	84	-	-	-	99	183
			INT-7	-	-	52	-	55	107
			INT-9	-	-	74	-	75	149
			KOR-1	20	-	-	-	19	39
			SUI-1	-	-	43	-	43	86
			USA-1	53	-	-	54	53	160
			USA-102	53	-	-	51	52	156
			USA-112	-	205	-	-	202	407
			USA-66	-	-	-	-	441	441
			USA-72	-	-	-	83	163	246
	OPEN-LABEL	LONG-TERM	BEL-17	-	-	-	-	116	116

(CONTINUED)

Display GAB.2 List of trials and number of patients by treatment

				Treatment							
				Halo- peri- dol	Olan- zapi- ne	Other Neur- olep- tics	Plac- ebo	Risp- erid- one	Total		
				n	n	n	n	n	n		
AGE GROUP	TRIAL BLINDING BY DESIGN	TRIAL DURATION	TRIAL ID								
18 - 65	OPEN- LABEL	LONG- TERM	GER-29	-	-	-	-	19	19		
			INT-12	-	-	-	-	483	483		
			INT-17	-	-	234	-	258	492		
			INT-4	-	-	-	-	386	386		
			INT-47	-	-	-	-	39	39		
			INT-8	-	-	-	-	109	109		
			ISR-1	-	-	-	-	135	135		
			NED-2	-	-	-	-	40	40		
			USA-5	-	-	-	-	4	4		
			USA-5/USA-7	-	-	-	-	3	3		
			USA-6	-	-	-	-	194	194		
			USA-6/USA-7	-	-	-	-	71	71		
			USA-9	-	-	-	-	76	76		
			USA-9/USA-7	-	-	-	-	31	31		
	SHORT- TERM		GER-3	-	-	-	-	13	13		
			INT-1	-	-	-	-	121	121		
			ITA-1	-	-	-	-	31	31		
			USA-054	-	-	-	-	935	935		
			Total			899	448	527	389	6797	9060
			< 18	DOUBLE- BLIND	SHORT- TERM	BEL-11	-	-	-	37	37
BEL-24	-	-				-	7	6	13		
CAN-19	-	-				-	57	53	110		
WED-9	-	-				-	19	19	38		

(CONTINUED)
Display GAE.2 List of trials and number of patients by treatment

				Treatment					Total
				Halo- peri- dol	Olan- zapi- ne	Other Neur- olep- tics	Plac- ebo	Risp- erid- one	
				n	n	n	n	n	
AGE GROUP	TRIAL BLINDING BY DESIGN	TRIAL DURATION	TRIAL ID						
< 18	DOUBLE- BLIND	SHORT- TERM	USA-93	-	-	-	63	55	118
	OPEN- LABEL	LONG- TERM	USA-97	-	-	-	-	107	107
		SHORT- TERM	BEL-21	-	-	-	-	6	6
			BEL-22	-	-	-	-	7	7
	Total				-	-	-	183	290
> 65	TRIAL BLINDING BY DESIGN	TRIAL DURATION	TRIAL ID						
	DOUBLE- BLIND	SHORT- TERM	BEL-14	-	-	-	19	20	39
			INT-24	115	-	-	114	115	344
			USA-063	-	-	-	163	462	625
	OPEN- LABEL	LONG- TERM	INT-23	-	-	-	-	180	180
			INT-25	-	-	-	-	83	83
			USA-34	-	-	-	-	22	22
			USA-64	-	-	-	-	103	103
			USA-70	-	-	-	-	330	330
			Total		115	-	-	296	1315
Total			1014	448	527	868	8402	11259	

Display GAE.1 Number of glucose related AEs by WHO preferred term and demographics

		Treatment																			
		Haloperidol			Olanzapine		Other Neuroleptics		Placebo			Risperidone				All treatments				Total	Total
		AGE GROUP			AGE GROUP		AGE GROUP		AGE GROUP			AGE GROUP				AGE GROUP					
		18 -	> 65	Total	18 -	Total	18 -	Total	18 -	> 65	Total	18 -	< 18	> 65	Total	18 -	< 18	> 65	Total		
		65			65		65		65			65				65					
		n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	
TRIAL DURATION	ADVERSE EVENT																				
LONG-TERM	PREFERRED TERM																				
	ACIDOSIS	-	-	-	-	-	-	-	-	-	-	1	-	-	1	1	-	-	1	1	
	DIABETES MELLITUS	9	-	9	-	-	-	-	-	-	-	9	-	3	11	13	-	3	16	16	
	GLYCOSURIA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	2	
	HYPERGLYCAEMIA	5	-	5	-	-	-	-	-	-	-	7	-	16	23	12	-	16	28	28	
	HYPOGLYCAEMIA	1	-	1	-	-	-	-	-	-	-	2	-	3	5	3	-	3	6	6	
	KETOSIS	-	-	-	-	-	-	-	-	-	-	-	1	-	1	-	1	1	1	1	
SHORT-TERM	BLOOD SUGAR	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	INCREASED	-	-	-	-	-	-	-	-	-	-	2	-	-	2	2	-	-	2	2	
	COMA DIABETIC	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	1	1	1	
	DIABETES MELLITUS	-	-	-	1	1	1	1	1	1	1	2	-	2	4	5	-	2	7	7	
	DIABETES MELLITUS AGGRAVATED	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	2	2	
	GLYCOSURIA	-	-	-	-	-	-	-	-	-	-	-	-	-	2	2	-	-	1	1	
	HYPERGLYCAEMIA	1	1	2	3	3	-	-	1	4	5	11	-	9	20	16	-	14	30	30	
	HYPOGLYCAEMIA	-	-	-	-	-	-	-	-	-	-	1	-	-	7	5	-	3	8	8	
	KETOSIS	-	-	-	-	-	-	-	-	-	-	1	-	-	1	1	-	1	1	1	
	PLASMA OSMOLALITY	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	INCREASED	-	-	-	-	-	-	-	-	-	-	-	-	1	1	1	-	1	1	1	
	ACIDOSIS	-	-	-	-	-	-	-	-	-	-	1	-	-	1	1	-	1	1	1	
	BLOOD SUGAR	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	INCREASED	-	-	-	-	-	-	-	-	-	-	2	-	-	2	2	-	-	2	2	
	COMA DIABETIC	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	1	1	1	
	DIABETES MELLITUS	5	-	5	1	1	1	1	1	1	1	10	-	5	15	18	-	5	23	23	
	DIABETES MELLITUS AGGRAVATED	-	-	-	-	-	-	-	-	-	-	-	-	-	2	2	-	2	2	2	
	GLYCOSURIA	-	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	3	3	
	HYPERGLYCAEMIA	6	1	7	3	3	-	-	1	4	5	18	-	25	43	28	-	30	58	58	
	HYPOGLYCAEMIA	1	-	1	-	-	-	-	-	-	-	1	-	7	12	8	-	6	14	14	
	KETOSIS	-	-	-	-	-	-	-	-	-	-	1	-	1	2	1	-	2	2	2	
	PLASMA OSMOLALITY	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	INCREASED	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	1	1	1	

Display GAE.3 Number of glucose related AEs by WHO preferred term and demographics

		Treatment															All treatments				Total
		Haloperidol			Olanzapine			Other Neuroleptics		Placebo			Risperidone								
		SEX		Total	SEX		Total	SEX		Total	SEX		Total	SEX		Total					
		FEMA-LE	MALE		FEMA-LE	MALE		FEMA-LE	MALE		FEMA-LE	MALE		FEMA-LE	MALE						
		n	n		n	n		n	n		n	n		n	n						
TRIAL DURATION	ADVERSE EVENT																				
LONG-TERM	PREFERRED TERM																				
	ACIDOSIS												5	1	11	7	1	15	16		
	DIABETES MELLITUS	2	3	5									2	2	2		3	2	2		
	GLYCOSURIA																				
	HYPERGLYCAEMIA	2	3	5									13	10	23	15	13	28	28		
	HYPOLYCAEMIA	1		1									2	3	5	3	3	6	6		
	KETOSIS																1	1	1		
SHORT-TERM	BLOOD SUGAR																				
	INCREASED														2	2		2	2		
	COMA DIABETIC														1	1		1	1		
	DIABETES MELLITUS				1		1	1	1		1	1	3	1	4	4	3	7	7		
	AGGRAVATED																				
	GLYCOSURIA												1	1	2	1	1	2	2		
	HYPERGLYCAEMIA	1	1	2		3	3			1	4	5	9	11	20	11	19	30	30		
	HYPOLYCAEMIA									1		1	4	3	7	5	3	8	8		
	KETOSIS														1		1	1	1		
	PLASMA OSMOLALITY																				
	INCREASED														1	1		1	1		
Short + Long Term	ACIDOSIS														1	1		1	1		
	BLOOD SUGAR																				
	INCREASED																2	2	2		
	COMA DIABETIC																				
	DIABETES MELLITUS	2	3	5	1		1	1	1		1	1	8	7	15	11	12	23	23		
	AGGRAVATED																				
	GLYCOSURIA						1	1						1	1	2	1	1	2		
	HYPERGLYCAEMIA	3	4	7		3	3			1	4	5	22	21	43	26	32	58	58		
	HYPOLYCAEMIA	1		1									6	6	12	8	8	14	14		
	KETOSIS														2		2	2	2		
	PLASMA OSMOLALITY																				
	INCREASED														1	1		1	1		

Display GAE.3 Number of glucose related AEs by WHO preferred term and demographics

		Treatment																		All treatments					
		Haloperidol				Olanzapine				Other Neuroleptics		Placebo			Risperidone										
		RACE			Total	RACE			Total	RACE	Total	RACE		Total	RACE			Total	RACE			Total			
		Other	Black	White		Other	Black	White				Other	White		Other	Black	White		Other	Black	White				
		n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	
TRIAL DURATION	ADVERSE EVENT																								
LONG-TERM	PREFERRED TERM																								
	ACIDOSIS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	-	1		
	DIABETES MELLITUS	4	1	-	5	-	-	-	-	-	-	-	-	-	-	4	7	11	4	5	1	7	4		
	GLYCOSURIA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	2	1	1	-	-	1		
	HYPERGLYCAEMIA	1	1	3	5	-	-	-	-	-	-	-	-	-	-	4	5	14	5	6	17	17	4		
	HYPOGLYCAEMIA	1	-	-	1	-	-	-	-	-	-	-	-	-	-	1	4	5	1	1	-	-	1		
	KETOSIS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	-	1		
SHORT-TERM	BLOOD SUGAR	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	INCREASED	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	2	-	2	-	-	-		
	COMA DIABETIC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1	-	1	-	-	-		
	DIABETES MELLITUS	-	-	-	-	-	-	1	1	1	1	-	1	1	-	2	2	4	-	2	5	-	-		
	AGGRAVATED	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	GLYCOSURIA	-	-	-	-	-	-	1	1	-	-	-	-	-	-	1	1	2	-	1	1	-	-		
	HYPERGLYCAEMIA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	HYPOGLYCAEMIA	-	1	1	2	1	2	-	3	-	-	1	4	5	1	6	13	20	3	9	18	4	4		
	KETOSIS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3	7	1	3	-	-	-		
	PLASMA OSMOLALITY	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1	1	-	-	-	-		
	INCREASED	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Short + Long Term	ACIDOSIS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	1	-	-	1		
	BLOOD SUGAR	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	INCREASED	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	2	-	2	-	-	-		
	COMA DIABETIC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1	-	1	-	-	-		
	DIABETES MELLITUS	4	1	-	5	-	-	1	1	1	1	-	1	1	-	6	9	15	4	7	12	-	-		
	AGGRAVATED	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	GLYCOSURIA	-	-	-	-	-	-	1	1	-	-	-	-	-	-	1	1	2	-	1	1	-	-		
	HYPERGLYCAEMIA	1	2	4	7	1	2	-	3	-	-	1	4	5	5	11	27	38	15	35	8	1	1		
	HYPOGLYCAEMIA	1	-	-	1	-	-	-	-	-	-	-	-	-	1	4	7	12	3	4	-	-	-		
	KETOSIS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	2	1	-	-	-	-		
	PLASMA OSMOLALITY	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	INCREASED	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1	-	1	-	-	-		

(CONTINUED)
Display GAS.3 Number of glucose related AEs by WHO preferred term and demographics

		All trea- tmen- ts	
		Total	Total
		n	n
TRIAL DURATION	ADVERSE EVENT		
LONG-TERM	PREFERRED TERM		
	ACIDOSIS	1	1
	DIABETES MELLITUS	16	16
	GLYCOSURIA	2	2
	HYPERGLYCAEMIA	28	28
	HYPOGLYCAEMIA	6	6
	KETOSIS	1	1
SHORT-TERM	BLOOD SUGAR		
	INCREASED	2	2
	COMA DIABETIC	1	1
	DIABETES MELLITUS	7	7
	DIABETES MELLITUS		
	AGGRAVATED	2	2
	GLYCOSURIA	1	1
	HYPERGLYCAEMIA	30	30
	HYPOGLYCAEMIA	8	8
	KETOSIS	1	1
	PLASMA OSMOLALITY		
	INCREASED	1	1
Short + Long Term	ACIDOSIS	1	1
	BLOOD SUGAR		
	INCREASED	2	2
	COMA DIABETIC	1	1
	DIABETES MELLITUS	23	23
	DIABETES MELLITUS		
	AGGRAVATED	2	2
	GLYCOSURIA	3	3
	HYPERGLYCAEMIA	58	58
	HYPOGLYCAEMIA	14	14
	KETOSIS	2	2
	PLASMA OSMOLALITY		
	INCREASED	1	1

Display GAB.4 Number of patients with/without glucose related AEs by treatment and trial duration

run

	TRIAL DURATION															
	LONG-TERM								SHORT-TERM							
	Treatment								Treatment							
	Haloperidol				Other Neuroleptics				Risperidone				Haloperidol			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Glucose related AE																
NO	293	97.02	234	100.0	3032	98.70	710	99.72	444	99.11	292	99.66	861	99.19	5297	99.38
YES	9	2.98	-	-	40	1.30	2	0.28	4	0.89	1	0.34	7	0.81	33	0.62
Total	302	100.0	234	100.0	3072	100.0	712	100.0	448	100.0	293	100.0	868	100.0	5330	100.0

(CONTINUED)

	Short + Long Term		
	Treatment		
	Risperidone		Total
	n	%	n
Glucose related AE			
NO	8329	99.13	11163
YES	73	0.87	96
Total	8402	100.0	11259

Display GAE.5 Number of patients with/without glucose related AEs by demographics

			AGE GROUP								Total
			18 - 65		< 18		> 65				
			n	%	n	%	n	%			
Glucose related AE	TRIAL DURATION	Treatment									
NO	LONG-TERM	Haloperidol	293	97.02	-	-	-	-	-	293	
		Other Neuroleptics	234	100.0	-	-	-	-	-	234	
		Risperidone	2230	99.24	106	99.07	696	96.94	3032		
		All treatments	2757	99.07	106	99.07	696	96.94	3559		
		SHORT-TERM	Treatment								
	Haloperidol	596	99.83	-	-	114	99.13	710			
	Olanzapine	444	99.11	-	-	-	-	444			
	Other Neuroleptics	292	99.66	-	-	-	-	292			
	Placebo	387	99.49	183	100.0	291	98.31	861			
	Risperidone	4532	99.60	183	100.0	582	97.49	5297			
	All treatments	6251	99.59	366	100.0	987	97.92	7604			
	Short + Long Term	Treatment									
		Haloperidol	889	98.89	-	-	114	99.13	1003		
		Olanzapine	444	99.11	-	-	-	-	444		
		Other Neuroleptics	526	99.61	-	-	-	-	526		
		Placebo	387	99.49	183	100.0	291	98.31	861		
		Risperidone	6762	99.49	289	99.66	1278	97.19	8329		
		All treatments	9008	99.43	472	99.79	1683	97.51	11163		
	YES	LONG-TERM	Treatment								
Haloperidol			9	2.98	-	-	-	-	9		
Risperidone			17	0.76	1	0.93	22	3.06	40		
All treatments			26	0.93	1	0.93	22	3.06	49		
SHORT-TERM		Treatment									
		Haloperidol	1	0.17	-	-	1	0.87	2		
		Olanzapine	4	0.89	-	-	-	-	4		

(CONTINUED)

Display GAE.5 Number of patients with/without glucose related AEs by demographics

			AGE GROUP						Total n	
			18 - 65		< 18		> 65			
			n	%	n	%	n	%		
Glucose related AE	TRIAL DURATION	Treatment								
YES	SHORT-TERM	Other Neuroleptics	1	0.34	-	-	-	-	1	
		Placebo	2	0.51	-	-	5	1.69	7	
		Risperidone	18	0.40	-	-	15	2.51	33	
		All Treatments	25	0.41	-	-	21	2.08	47	
		Treatment								
	Short + Long Term	Haloperidol	10	1.11	-	-	1	0.87	11	
		Olanzapine	4	0.89	-	-	-	-	4	
		Other Neuroleptics	1	0.19	-	-	-	-	1	
		Placebo	2	0.51	-	-	5	1.69	7	
		Risperidone	35	0.51	1	0.34	37	2.81	73	
		All treatments	52	0.57	1	0.21	43	2.49	96	
		Treatment								
	Total	LONG-TERM	Haloperidol	302	100.0	-	-	-	-	302
			Other Neuroleptics	234	100.0	-	-	-	-	234
			Risperidone	2247	100.0	107	100.0	718	100.0	3072
All treatments			2783	100.0	107	100.0	718	100.0	3608	
Treatment										
SHORT-TERM		Haloperidol	597	100.0	-	-	115	100.0	712	
		Olanzapine	448	100.0	-	-	-	-	448	
		Other Neuroleptics	293	100.0	-	-	-	-	293	
		Placebo	389	100.0	183	100.0	296	100.0	868	
		Risperidone	4550	100.0	183	100.0	597	100.0	5330	
		All treatments	6277	100.0	366	100.0	1008	100.0	7651	
		Treatment								

(CONTINUED)
Display CAE-5 Number of patients with/without glucose related AEs by demographics

			AGE GROUP							
			18 - 65		< 18		> 65		Total	
			n	%	n	%	n	%	n	
Total	Short + Long Term	Treatment								
		Haloperidol	899	100.0	-	-	115	100.0	1014	
		Olanzapine	448	100.0	-	-	-	-	448	
		Other Neuroleptics	527	100.0	-	-	-	-	527	
		Placebo	189	100.0	183	100.0	296	100.0	868	
		Risperidone	6797	100.0	290	100.0	1315	100.0	8402	
All treatments		9060	100.0	473	100.0	1726	100.0	11259		

Display GAE.5 Number of patients with/without glucose related AEs by demographics

			SEX								
							FEMALE		MALE		Total
			n	%	n	%	n	%	n		
Glucose related AE	TRIAL DURATION	Treatment									
NO	LONG-TERM	Haloperidol	-	-	103	96.26	190	97.44	293		
		Other Neuroleptics	1	100.0	75	100.0	158	100.0	234		
		Risperidone	2	100.0	1192	98.43	1838	98.87	3032		
		All treatments	3	100.0	1370	98.35	2186	98.82	3559		
		Treatment									
	SHORT-TERM	Haloperidol	-	-	246	99.60	464	99.78	710		
		Olanzapine	-	-	131	99.24	313	99.05	444		
		Other Neuroleptics	-	-	106	100.0	186	99.47	292		
		Placebo	-	-	363	99.45	498	99.01	861		
		Risperidone	6	100.0	1970	99.19	3321	99.49	5297		
		All treatments	6	100.0	2816	99.29	4782	99.44	7604		
		Treatment									
	Short + Long Term	Haloperidol	-	-	349	98.59	654	99.09	1003		
		Olanzapine	-	-	131	99.24	313	99.05	444		
		Other Neuroleptics	1	100.0	181	100.0	344	99.71	526		
		Placebo	-	-	363	99.45	498	99.01	861		
		Risperidone	8	100.0	3162	98.91	5159	99.27	8329		
		All treatments	9	100.0	4186	98.98	6968	99.25	11163		
		Treatment									
YES	LONG-TERM	Haloperidol	-	-	4	3.74	5	2.56	9		
		Risperidone	-	-	19	1.57	21	1.13	40		
		All treatments	-	-	23	1.65	26	1.18	49		
		Treatment									
	SHORT-TERM	Haloperidol	-	-	1	0.40	1	0.22	2		
		Olanzapine	-	-	1	0.76	3	0.95	4		
		Treatment									

(CONTINUED)
Display GAE.5 Number of patients with/without glucose related AEs by demographics

			SEX								Total n
							FEMALE		MALE		
			n	%	n	%	n	%			
Glucose related AE	TRIAL DURATION	Treatment									
YES	SHORT-TERM	Other Neuroleptics	-	-	-	-	1	0.53	1		
		Placebo	-	-	2	0.55	5	0.99	7		
		Risperidone	-	-	16	0.81	17	0.51	33		
		All treatments	-	-	20	0.71	27	0.56	47		
	Short + Long Term	Treatment									
		Haloperidol	-	-	5	1.41	6	0.91	11		
		Olanzapine	-	-	1	0.76	3	0.95	4		
		Other Neuroleptics	-	-	-	-	1	0.29	1		
		Placebo	-	-	2	0.55	5	0.99	7		
		Risperidone	-	-	35	1.09	38	0.73	73		
		All treatments	-	-	43	1.02	53	0.75	96		
Total	LONG-TERM	Treatment									
		Haloperidol	-	-	107	100.0	195	100.0	302		
		Other Neuroleptics	1	100.0	75	100.0	158	100.0	234		
		Risperidone	2	100.0	1211	100.0	1859	100.0	3072		
		All treatments	3	100.0	1393	100.0	2212	100.0	3608		
	SHORT-TERM	Treatment									
		Haloperidol	-	-	247	100.0	465	100.0	712		
		Olanzapine	-	-	132	100.0	316	100.0	448		
		Other Neuroleptics	-	-	106	100.0	187	100.0	293		
		Placebo	-	-	365	100.0	503	100.0	868		
		Risperidone	6	100.0	1986	100.0	3338	100.0	5330		
		All treatments	6	100.0	2836	100.0	4809	100.0	7651		

(CONTINUED)

Display GAB.5 Number of patients with/without glucose related AEs by demographics

		SEX							
		FEMALE				MALE			
		n	%	n	%	n	%	n	Total
Total	Short + Long Term	Treatment							
		Haloperidol	-	-	354	100.0	660	100.0	1014
		Olansapine	-	-	132	100.0	316	100.0	448
		Other Neuroleptics	1	100.0	181	100.0	345	100.0	527
		placebo	-	-	365	100.0	503	100.0	868
		Risperidone	8	100.0	3197	100.0	5197	100.0	8402
		All treatments	9	100.0	4229	100.0	7021	100.0	11259

Display GAE.5 Number of patients with/without glucose related AEs by demographics

			RACE								Total n
					Other		Black		White		
			n	%	n	%	n	%	n	%	
Glucose related AE	TRIAL DURATION	Treatment									
NO	LONG-TERM	Haloperidol	-	-	31	88.57	72	97.30	190	98.45	293
		Other Neuroleptics	2	100.0	20	100.0	-	-	212	100.0	234
		Risperidone	254	100.0	264	98.51	237	96.34	2277	98.83	3032
		All treatments	256	100.0	315	97.52	309	96.56	2679	98.89	3559
	SHORT-TERM	Treatment									
		Haloperidol	56	100.0	101	100.0	63	98.44	490	99.80	710
		Olanzapine	-	-	41	97.62	74	97.37	329	99.70	444
		Other Neuroleptics	72	100.0	7	100.0	8	100.0	205	99.51	292
		Placebo	75	100.0	58	98.31	116	100.0	612	99.03	861
		Risperidone	377	100.0	530	99.62	707	98.19	3683	99.51	5297
		All treatments	580	100.0	737	99.46	968	98.37	5319	99.49	7604
	Short + Long Term	Treatment									
		Haloperidol	56	100.0	132	97.06	135	97.83	680	99.42	1003
		Olanzapine	-	-	41	97.62	74	97.37	329	99.70	444
		Other Neuroleptics	74	100.0	27	100.0	8	100.0	417	99.76	526
		Placebo	75	100.0	58	98.31	116	100.0	612	99.03	861
		Risperidone	631	100.0	794	99.25	944	97.72	5960	99.25	8329
		All treatments	836	100.0	1052	98.87	1277	97.93	7998	99.29	11163
YES	TRIAL DURATION	Treatment									
	LONG-TERM	Haloperidol	-	-	4	11.43	2	2.70	3	1.55	9
		Risperidone	-	-	4	1.49	9	3.66	27	1.17	40
		All treatments	-	-	8	2.48	11	3.44	30	1.11	49
	SHORT-TERM	Treatment									
		Haloperidol	-	-	-	-	1	1.56	1	0.20	2
		Olanzapine	-	-	1	2.38	2	2.63	1	0.30	4

(CONTINUED)

Display CAE.5 Number of patients with/without glucose related AEs by demographics

			RACE								Total n
					Other		Black		White		
			n	%	n	%	n	%	n	%	
Glucose related AE	TRIAL DURATION	Treatment									
YES	SHORT-TERM	Other Neuroleptics	-	-	-	-	-	-	1	0.49	1
		Placebo	-	-	1	1.69	-	-	6	0.97	7
		Risperidone	-	-	2	0.38	13	1.81	18	0.49	33
		All treatments	-	-	4	0.54	16	1.63	27	0.51	47
	Short + Long Term	Treatment									
		Haloperidol	-	-	4	2.94	3	2.17	4	0.58	11
		Olanzapine	-	-	1	2.38	2	2.63	1	0.30	4
		Other Neuroleptics	-	-	-	-	-	-	1	0.24	1
		Placebo	-	-	1	1.69	-	-	6	0.97	7
		Risperidone	-	-	6	0.75	22	2.28	45	0.75	73
		All treatments	-	-	12	1.13	27	2.07	57	0.71	96
	Total	TRIAL DURATION	Treatment								
		LONG-TERM	Haloperidol	-	-	35	100.0	74	100.0	193	100.0
Other Neuroleptics			2	100.0	20	100.0	-	-	212	100.0	234
Risperidone			254	100.0	268	100.0	246	100.0	2304	100.0	3072
All treatments			256	100.0	323	100.0	320	100.0	2709	100.0	3608
SHORT-TERM		Treatment									
		Haloperidol	56	100.0	101	100.0	64	100.0	491	100.0	712
		Olanzapine	-	-	42	100.0	76	100.0	330	100.0	448
		Other Neuroleptics	72	100.0	7	100.0	8	100.0	206	100.0	293
		Placebo	73	100.0	59	100.0	116	100.0	618	100.0	868
		Risperidone	377	100.0	532	100.0	720	100.0	3701	100.0	5330
		All treatments	580	100.0	741	100.0	884	100.0	5346	100.0	7651

(CONTINUED)

Display GAE.5 Number of patients with/without glucose related AEs by demographics

			RACE								Total n
					Other		Black		White		
			n	%	n	%	n	%	n	%	
Total	Short + Long Term	Treatment									
		Haloperidol	56	100.0	136	100.0	138	100.0	684	100.0	1014
		Olanzapine	-	-	42	100.0	76	100.0	330	100.0	448
		Other Neuroleptics	74	100.0	27	100.0	8	100.0	418	100.0	527
		Placebo	75	100.0	59	100.0	116	100.0	618	100.0	868
		Risperidone	631	100.0	800	100.0	966	100.0	6005	100.0	8402
All treatments		836	100.0	1064	100.0	1304	100.0	8055	100.0	11259	

Display GAE.6 Number of patients with Glucose Related AEs by Mode Dose

	AGE GROUP																											Total n
	< 18																> 65											
	18 - 65																											
	MODE DOSE RANGES								MODE DOSE RANGES								MODE DOSE RANGES											
	MISSING		<4 mg/day		4-6 mg/day		>6 mg/day		MISSING		<0.03 mg/kg/day		0.03-0.04 mg/kg/day		>0.04 mg/kg/day		MISSING		<0.75 mg/day		0.75-1.5 mg/day		>1.5 mg/day					
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%		
Glucose related AE																												
NO	1464	99.9	821	99.9	2121	98.8	2356	99.7	43	100.0	67	100.0	33	100.0	146	99.3	281	99.3	512	96.8	226	95.8	259	97.0			8329	
YES	2	0.1	1	0.1	25	1.2	7	0.3	-	-	-	-	-	-	1	0.7	2	0.7	17	3.2	10	4.2	8	3.0			73	
Total	1466	100.0	822	100.0	2146	100.0	2363	100.0	43	100.0	67	100.0	33	100.0	147	100.0	283	100.0	529	100.0	236	100.0	267	100.0			8402	

Display GAE.7 Number of patients with/without glucose related AEs by BMI at baseline

		Treatment										Total
		Haloperidol		Olanzapine		Other Neuroleptics		Placebo		Risperidone		
		n	%	n	%	n	%	n	%	n	%	
BMI Category	Glucose related AE											
BMI<23	NO	343	99.71	116	99.15	211	100.0	350	99.72	2376	99.21	3396
	YES	1	0.29	1	0.85	-	-	1	0.28	19	0.79	22
23<BMI<=27	NO	299	99.67	130	100.0	166	100.0	167	98.24	1825	99.13	2587
	YES	1	0.33	-	-	-	-	3	1.76	16	0.87	20
BMI>27	NO	282	96.91	195	98.48	137	99.28	122	99.19	1706	98.10	2442
	YES	9	3.09	3	1.52	1	0.72	1	0.81	33	1.90	47
Total		935	100.0	445	100.0	515	100.0	644	100.0	5975	100.0	8514

Display GAE.8 Total Exposure of Risperidone Patients and Glucose Related AEs

OBS	TRIAL ID.	Treatment	Patients in Trial	Patient Years of Exposure	Patients who had AEs
1	BEL-5	Haloperidol	22	4.31	0
2	BEL-7	Haloperidol	32	0.81	0
3	FRA-3	Haloperidol	20	1.38	0
4	INT-2	Haloperidol	226	29.66	0
5	INT-24	Haloperidol	115	22.15	1
6	INT-3	Haloperidol	87	8.27	0
7	INT-6	Haloperidol	99	49.87	0
8	KOR-1	Haloperidol	19	2.95	0
9	USA-1	Haloperidol	53	3.93	0
10	USA-102	Haloperidol	53	2.36	1
11	USA-79	Haloperidol	203	153.88	9
12	INT-45	Olanzapine	242	31.58	1
13	USA-112	Olanzapine	205	27.56	3
14	AUT-1	Other Neuro	33	3.11	0
15	FIN-1	Other Neuro	50	4.18	0
16	FRA-3	Other Neuro	21	1.41	0
17	GER-5	Other Neuro	20	1.30	0
18	INT-7	Other Neuro	52	6.67	0
19	INT-9	Other Neuro	74	6.89	1
20	SUI-1	Other Neuro	43	5.68	0
21	CAN-19	Placebo	57	5.65	0
22	GER-28	Placebo	13	0.89	0
23	INT-24	Placebo	114	21.10	1
24	INT-3	Placebo	88	7.22	0
25	INT-39	Placebo	25	1.79	0
26	INT-46	Placebo	75	3.02	0
27	USA-063	Placebo	163	30.97	4
28	USA-1	Placebo	54	3.58	0
29	USA-102	Placebo	51	2.08	2
30	USA-72	Placebo	83	5.06	0
31	USA-93	Placebo	63	6.13	0
32	AUT-1	Risperidone	34	3.35	0
33	BEL-17	Risperidone	115	73.92	0
34	BEL-21	Risperidone	6	0.02	0
35	BEL-22	Risperidone	7	0.60	0
36	BEL-24	Risperidone	6	0.48	0
37	BEL-5	Risperidone	22	4.80	0
38	BEL-7	Risperidone	28	0.56	0
39	CAN-19	Risperidone	53	5.78	0
40	FIN-1	Risperidone	48	4.34	0
41	FRA-3	Risperidone	21	1.52	0
42	GER-28	Risperidone	10	0.70	0
43	GER-29	Risperidone	19	13.53	1
44	GER-3	Risperidone	13	0.88	0
45	GER-5	Risperidone	39	2.28	0
46	INT-1	Risperidone	121	8.91	0
47	INT-10	Risperidone	211	21.20	1
48	INT-2	Risperidone	1136	153.13	1
49	INT-24	Risperidone	115	19.68	1
50	INT-3	Risperidone	348	38.00	0
51	INT-39	Risperidone	29	2.00	0
52	INT-4	Risperidone	384	311.01	0
53	INT-45	Risperidone	247	30.91	2
54	INT-46	Risperidone	75	9.04	0
55	INT-47	Risperidone	39	25.70	0
56	INT-6	Risperidone	91	56.35	1
57	INT-7	Risperidone	55	7.10	0
58	INT-8	Risperidone	109	67.67	0
59	INT-9	Risperidone	75	7.53	0
60	ITA-1	Risperidone	31	2.19	0
61	KOR-1	Risperidone	16	2.14	0
62	NED-2	Risperidone	40	16.05	0
63	NED-9	Risperidone	19	2.16	0
64	SUI-1	Risperidone	43	5.89	0
65	USA-063	Risperidone	462	84.91	14
66	USA-1	Risperidone	53	4.28	0

Display GAE.8 Total Exposure of Risperidone Patients and Glucose Related AEs

OBS	TRIAL ID.	Treatment	Patients in Trial	Patient Years of Exposure	Patients who had AEs
67	USA-102	Risperidone	52	4.90	1
68	USA-112	Risperidone	202	25.77	7
69	USA-34	Risperidone	22	4.88	2
70	USA-5	Risperidone	7	5.48	0
71	USA-6	Risperidone	265	133.35	1
72	USA-60	Risperidone	441	28.47	3
73	USA-64	Risperidone	103	20.23	2
74	USA-7	Risperidone	105	140.57	0
75	USA-70	Risperidone	330	208.19	16
76	USA-72	Risperidone	163	10.28	1
77	USA-79	Risperidone	192	182.20	9
78	USA-9	Risperidone	107	71.57	0
79	USA-93	Risperidone	55	5.43	0
80	USA-97	Risperidone	107	70.42	1

Display GAE.8 Total Exposure of Risperidone Patients and Glucose Related AEs

OBS	Treatment	Patients who had AEs	Total Patients	Patient Years of Exposure	Per Treatment Year (%)
1	Haloperidol	11	929	279.57	3.93
2	Olanzapine	4	447	59.14	6.76
3	Other Neuro	1	293	29.24	3.42
4	Placebo	7	786	87.49	8.00
5	Risperidone	64	6271	1900.35	3.37

Display GAE.9 Listing of patients with Glucose Related AEs and Weight Increase AEs

TRIAL ID	CRF ID	Treatment	BMI	SEX	RACE	AGE, YEARS	WEIGHT, KG	HEIGHT, CM	TRIAL DURATION
USA-112	A30394	Risperidone	41.65	FEMALE	Black	52	117.0	167.6	SHORT-TERM
USA-6/USA-7	000263	Risperidone	34.15	MALE	Black	42	108.2	178	LONG-TERM
USA-6/USA-7	000263	Risperidone	34.15	MALE	Black	42	108.2	178	LONG-TERM
USA-6/USA-7	000626	Risperidone	31.24	MALE	White	39	90.5	170.2	LONG-TERM
USA-6/USA-7	000712	Risperidone	30.31	MALE	Black	37	90.7	173	LONG-TERM
USA-70	002004	Risperidone	30.76	FEMALE	Black	86	76.3	157.5	LONG-TERM
USA-79	000366	Haloperidol	25.13	MALE	White	41	77.2	175.26	LONG-TERM

Display MAE.1 Number of Weight Increase ABs by WHO preferred term and treatment

	TRIAL DURATION													Total	
	LONG-TERM						SHORT-TERM						Short + Long Term		
	Treatment			Treatment			Treatment			Treatment					
	Halo- peri- dol	Other Neur- olep- tics	Risp- erid- one	Halo- peri- dol	Olan- zap- ine	Other Neur- olep- tics	Plac- ebo	Risp- erid- one	Halo- peri- dol	Olan- zap- ine	Other Neur- olep- tics	Plac- ebo			Risp- erid- one
	n	n	n	n	n	n	n	n	n	n	n	n			n
ADVERSE EVENT PREFERRED TERM															
WEIGHT INCREASE	5	1	95	9	42	1	8	74	14	42	2	8	169	235	

Display WAB.2 Number of Weight Increase AEs by WHO preferred term and demographics

		Treatment																									
		Haloperidol				Olanzapine				Other Neuroleptics				Placebo				Risperidone				All treatments					
		AGE GROUP		AGE GROUP		AGE GROUP		AGE GROUP		AGE GROUP		AGE GROUP		AGE GROUP		AGE GROUP		AGE GROUP									
		18 - 65	Total	18 - 65	Total	18 - 65	Total	18 - 65	< 18	> 65	Total	18 - 65	< 18	> 65	Total	18 - 65	< 18	> 65	Total			Total					
		n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n			n	n				
		TRIAL DURATION	ADVERSE EVENT																								
LONG-TERM	PREFERRED TERM																										
	WEIGHT INCREASE	5	5	-	-	1	1	-	-	-	-	64	22	9	95	70	22	9	101	101							
SHORT-TERM	WEIGHT INCREASE	9	9	42	42	1	1	5	2	1	8	56	15	3	74	113	17	4	134	134							
Short + Long Term	WEIGHT INCREASE	14	14	42	42	2	2	5	2	1	8	120	37	12	169	183	39	13	235	235							

Display WAB.2 Number of Weight Increase AEs by WHO preferred term and demographics

		Treatment																		
		Haloperidol			Olanzapine			Other Neuroleptics			Placebo			Risperidone			All treatments			
		SEX			SEX			SEX			SEX			SEX			SEX			
		FEMA-LE	MALE	Total	FEMA-LE	MALE	Total	FEMA-LE	MALE	Total	FEMA-LE	MALE	Total	FEMA-LE	MALE	Total	FEMA-LE	MALE	Total	Total
		n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
TRIAL DURATION	ADVERSE EVENT																			
LONG-TERM	PREFERRED TERM																			
	WEIGHT INCREASE	1	4	5	-	-	-	-	1	1	-	-	-	32	63	95	33	68	101	101
SHORT-TERM	WEIGHT INCREASE	5	4	9	18	24	42	1	-	1	5	3	8	26	48	74	55	79	134	134
Short + Long Term	WEIGHT INCREASE	6	8	14	18	24	42	1	1	2	5	3	8	58	111	169	88	147	235	235

Display WAE.2 Number of Weight Increase AEs by WHO preferred term and demographics

		Treatment																				
		Haloperidol					Olanzapine				Other Neuroleptics		Placebo				Risperidone					
		RACE				Total	RACE			Total	White	Total	RACE		Total	RACE				Total		
		Black	White	Other	Black		White	Other	White				Other	Black		White	Other					
		n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
TRIAL DURATION	ADVERSE EVENT																					
LONG-TERM	PREFERRED TERM																					
	WEIGHT INCREASE	-	3	2	-	5	-	-	-	-	1	1	-	-	-	-	1	21	66	7	95	
SHORT-TERM	WEIGHT INCREASE	1	4	3	1	9	11	28	3	42	1	1	1	2	5	1	8	1	21	41	11	74
Short + Long Term	WEIGHT INCREASE	1	7	5	1	14	11	28	3	42	2	2	2	5	1	8	2	42	107	18	169	

(CONTINUED)

		All treatments						
		RACE				Total	Total	
		Black	White	Other				
		n	n	n	n	n	n	n
		n	n	n	n	n	n	n
TRIAL DURATION	ADVERSE EVENT							
LONG-TERM	PREFERRED TERM							
	WEIGHT INCREASE	1	24	69	7	101	101	
SHORT-TERM	WEIGHT INCREASE	4	36	78	16	134	134	
Short + Long Term	WEIGHT INCREASE	5	60	147	23	235	235	

Display WAE.3 Number of patients with/without Weight Increase AEs by demographics

			AGE GROUP							
			18 - 65		< 18		> 65		Total	
			n	%	n	%	n	%	n	
Weight Increase AE	TRIAL DURATION	Treatment								
NO	LONG-TERM	Haloperidol	297	98.34	-	-	-	-	297	
		Other Neuroleptics	233	99.57	-	-	-	-	233	
		Risperidone	2183	97.15	85	79.44	709	98.75	2977	
		All treatments	2713	97.48	85	79.44	709	98.75	3507	
		Treatment								
	SHORT-TERM	Haloperidol	588	98.49	-	-	115	100.0	703	
		Clonazapine	406	90.63	-	-	-	-	406	
		Other Neuroleptics	292	99.66	-	-	-	-	292	
		Placebo	384	98.71	181	98.91	295	99.66	860	
		Risperidone	4494	98.77	168	91.80	594	99.50	5256	
		All treatments	6164	98.20	349	95.36	1004	99.60	7517	
		Treatment								
	Short + Long Term	Haloperidol	885	98.44	-	-	115	100.0	1000	
		Clonazapine	406	90.63	-	-	-	-	406	
		Other Neuroleptics	525	99.62	-	-	-	-	525	
		Placebo	384	98.71	181	98.91	295	99.66	860	
		Risperidone	6677	98.23	253	87.24	1303	99.09	8233	
		All treatments	8877	97.98	434	91.75	1713	99.25	11024	
Treatment										
YES	LONG-TERM	Haloperidol	5	1.66	-	-	-	-	5	
		Other Neuroleptics	1	0.43	-	-	-	-	1	
		Risperidone	64	2.85	22	20.56	9	1.25	95	
		All treatments	70	2.52	22	20.56	9	1.25	101	
		Treatment								

(CONTINUED)

Display WAE.3 Number of patients with/without Weight Increase AEs by demographics

			AGE GROUP						Total
			18 - 65		< 18		> 65		
			n	%	n	%	n	%	
Weight increase AE	TRIAL DURATION	Treatment							
YES	SHORT-TERM	Haloperidol	9	1.51	-	-	-	-	9
		Olanzapine	42	9.38	-	-	-	-	42
		Other Neuroleptics	1	0.34	-	-	-	-	1
		Placebo	5	1.29	2	1.09	1	0.34	8
		Risperidone	56	1.23	15	8.20	3	0.50	74
		All treatments	113	1.80	17	4.64	4	0.40	134
	Short + Long Term	Treatment							
		Haloperidol	14	1.56	-	-	-	-	14
		Olanzapine	42	9.38	-	-	-	-	42
		Other Neuroleptics	2	0.38	-	-	-	-	2
		Placebo	5	1.29	2	1.09	1	0.34	8
		Risperidone	120	1.77	37	12.76	12	0.91	169
	All treatments	183	2.02	39	8.25	13	0.75	235	
Total	LONG-TERM	Treatment							
		Haloperidol	302	100.0	-	-	-	-	302
		Other Neuroleptics	234	100.0	-	-	-	-	234
		Risperidone	2247	100.0	107	100.0	718	100.0	3072
		All treatments	2783	100.0	107	100.0	718	100.0	3608
	SHORT-TERM	Treatment							
		Haloperidol	597	100.0	-	-	115	100.0	712
		Olanzapine	448	100.0	-	-	-	-	448
		Other Neuroleptics	293	100.0	-	-	-	-	293
		Placebo	389	100.0	183	100.0	296	100.0	868
		Risperidone	4550	100.0	183	100.0	597	100.0	5330

(CONTINUED)

Display WAF.3 Number of patients with/without Weight Increase AEs by demographics

			AGE GROUP						Total
			18 - 65		< 18		> 65		
			n	%	n	%	n	%	
Total	TRIAL DURATION	All treatments							
	SHORT-TERM		6277	100.0	366	100.0	1008	100.0	7651
	Short + Long Term	Treatment							
		Haloperidol	899	100.0	-	-	125	100.0	1024
		Olanzapine	448	100.0	-	-	-	-	448
		Other Neuroleptics	527	100.0	-	-	-	-	527
		Placebo	389	100.0	183	100.0	296	100.0	868
		Risperidone	6797	100.0	290	100.0	1315	100.0	8402
	All treatments	9060	100.0	473	100.0	1726	100.0	11259	

Display WAE.3 Number of patients with/without Weight Increase AEs by demographics

			SEX						Total n
			FEMALE		MALE				
			n	%	n	%	n	%	
Weight increase AE	TRIAL DURATION	Treatment							
NO	LONG-TERM	Haloperidol	-	-	106	99.07	191	97.95	297
		Other Neuroleptics	1	100.0	75	100.0	157	99.37	233
		Risperidone	2	100.0	1179	97.36	1796	96.61	2977
		All treatments	3	100.0	1360	97.63	2144	96.93	3507
		Treatment							
	SHORT-TERM	Haloperidol	-	-	242	97.98	461	99.14	703
		Olanzapine	-	-	114	86.36	292	92.41	406
		Other Neuroleptics	-	-	105	99.05	187	100.0	292
		Placebo	-	-	360	98.63	500	99.40	860
		Risperidone	6	100.0	1960	98.69	3290	98.56	5256
		All treatments	6	100.0	2781	98.06	4730	98.36	7517
		Treatment							
	Short + Long Term	Haloperidol	-	-	348	98.31	652	98.79	1000
		Olanzapine	-	-	114	86.36	292	92.41	406
		Other Neuroleptics	1	100.0	180	99.45	344	99.71	525
		Placebo	-	-	360	98.63	500	99.40	860
		Risperidone	8	100.0	3139	98.19	5086	97.86	8233
		All treatments	9	100.0	4141	97.92	6874	97.91	11024
Treatment									
YES	LONG-TERM	Haloperidol	-	-	1	0.93	4	2.05	5
		Other Neuroleptics	-	-	-	-	1	0.63	1
		Risperidone	-	-	32	2.64	63	3.39	95
		All treatments	-	-	33	2.37	68	3.07	101
		Treatment							
		Treatment							

(CONTINUED)

Display WAE.3 Number of patients with/without Weight Increase AEs by demographics

			SEX						Total n	
			FEMALE		MALE					
			n	%	n	%	n	%		
Weight increase AE	TRIAL DURATION	Treatment								
YES	SHORT-TERM	Haloperidol	-	-	5	2.02	4	0.86	9	
		Olanzapine	-	-	18	13.64	24	7.59	42	
		Other Neuroleptics	-	-	1	0.94	-	-	1	
		Placebo	-	-	5	1.37	3	0.60	8	
		Risperidone	-	-	26	1.31	48	1.44	74	
		All treatments	-	-	55	1.94	79	1.64	134	
	Short + Long Term	Treatment								
		Haloperidol	-	-	6	1.69	8	1.21	14	
		Olanzapine	-	-	18	13.64	24	7.59	42	
		Other Neuroleptics	-	-	1	0.55	1	0.29	2	
		Placebo	-	-	5	1.37	3	0.60	8	
		Risperidone	-	-	58	1.81	111	2.14	169	
		All treatments	-	-	88	2.08	147	2.09	235	
Total	LONG-TERM	Treatment								
		Haloperidol	-	-	107	100.0	195	100.0	302	
		Other Neuroleptics	1	100.0	75	100.0	158	100.0	234	
		Risperidone	2	100.0	1211	100.0	1859	100.0	3072	
		All treatments	3	100.0	1393	100.0	2212	100.0	3608	
	SHORT-TERM	Treatment								
		Haloperidol	-	-	247	100.0	465	100.0	712	
		Olanzapine	-	-	132	100.0	316	100.0	448	
		Other Neuroleptics	-	-	106	100.0	187	100.0	293	
		Placebo	-	-	365	100.0	503	100.0	868	
		Risperidone	6	100.0	1986	100.0	3338	100.0	5330	

(CONTINUED)

Display WAE.3 Number of patients with/without Weight Increase AEs by demographics

			SEX						Total
					FEMALE		MALE		
			n	%	n	%	n	%	
Total	TRIAL DURATION	All treatments							
		SHORT-TERM	6	100.0	2836	100.0	4809	100.0	7651
	Short + Long Term	Treatment							
		Haloperidol	-	-	354	100.0	660	100.0	1014
		Olanzapine	-	-	132	100.0	316	100.0	448
		Other Neuroleptics	1	100.0	181	100.0	345	100.0	527
		Placebo	-	-	365	100.0	503	100.0	868
		Risperidone	8	100.0	3197	100.0	5197	100.0	8402
		All treatments	9	100.0	4229	100.0	7021	100.0	11259

Display WAB.3 Number of patients with/without Weight Increase AEs by demographics

			RACE										Total n	
					Other		Black		White					
			n	%	n	%	n	%	n	%	n	%		
Weight increase AE	TRIAL DURATION	Treatment												
NO	LONG-TERM	Haloperidol	-	-	35	100.0	71	95.95	191	98.96			297	
		Other Neuroleptics	2	100.0	20	100.0	-	-	211	99.53			233	
		Risperidone	253	99.61	261	97.39	225	91.46	2238	97.14			2977	
		All treatments	255	99.61	316	97.83	296	92.50	2640	97.45			3507	
		Treatment												
	SHORT-TERM	Haloperidol	55	98.21	100	99.01	60	93.75	488	99.39			703	
		Olanzapine	-	-	39	92.86	65	85.53	302	91.52			406	
		Other Neuroleptics	72	100.0	7	100.0	8	100.0	205	99.51			292	
		Placebo	73	97.33	58	98.31	116	100.0	613	99.19			860	
		Risperidone	376	99.73	521	97.93	699	97.08	3660	98.89			5256	
		All treatments	576	99.31	725	97.84	948	96.34	5268	98.54			7517	
		Treatment												
	Short + Long Term	Haloperidol	55	98.21	135	99.26	131	94.93	679	99.27			1000	
		Olanzapine	-	-	39	92.86	65	85.53	302	91.52			406	
		Other Neuroleptics	74	100.0	27	100.0	8	100.0	416	99.52			525	
		Placebo	73	97.33	58	98.31	116	100.0	613	99.19			860	
		Risperidone	629	99.68	782	97.75	924	95.65	5898	98.22			8233	
		All treatments	831	99.40	1041	97.84	1244	95.40	7908	98.18			11024	
Treatment														
YES	LONG-TERM	Haloperidol	-	-	-	-	3	4.05	2	1.04			5	
		Other Neuroleptics	-	-	-	-	-	-	1	0.47			1	
		Risperidone	1	0.39	7	2.61	21	8.54	66	2.86			95	
		All treatments	1	0.39	7	2.17	24	7.50	69	2.55			101	
		Treatment												

(CONTINUED)

Display WAB.3 Number of patients with/without Weight Increase AEs by demographics

			RACE									
					Other		Black		White		Total	
			n	%	n	%	n	%	n	%	n	
Weight increase AE	TRIAL DURATION	Treatment										
YES	SHORT-TERM	Haloperidol	1	1.79	1	0.99	4	6.25	3	0.61		9
		Olanzapine	-	-	3	7.14	11	14.47	28	8.48		42
		Other Neuroleptics	-	-	-	-	-	-	1	0.49		1
		Placebo	2	2.67	1	1.69	-	-	5	0.81		8
		Risperidone	1	0.27	11	2.07	21	2.92	41	1.11		74
		All treatments	4	0.69	16	2.16	36	3.66	78	1.46		134
		Treatment										
	Short + Long Term	Haloperidol	1	1.79	1	0.74	7	5.07	5	0.73		14
		Olanzapine	-	-	3	7.14	11	14.47	28	8.48		42
		Other Neuroleptics	-	-	-	-	-	-	2	0.48		2
		Placebo	2	2.67	1	1.69	-	-	5	0.81		8
		Risperidone	2	0.32	18	2.25	42	4.35	107	1.78		169
		All treatments	5	0.60	23	2.16	60	4.60	147	1.82		235
		Treatment										
Total	LONG-TERM	Treatment										
		Haloperidol	-	-	35	100.0	74	100.0	193	100.0		302
		Other Neuroleptics	2	100.0	20	100.0	-	-	212	100.0		234
		Risperidone	254	100.0	268	100.0	246	100.0	2304	100.0		3072
		All treatments	256	100.0	323	100.0	320	100.0	2709	100.0		3608
	SHORT-TERM	Treatment										
		Haloperidol	56	100.0	101	100.0	64	100.0	491	100.0		712
		Olanzapine	-	-	42	100.0	76	100.0	330	100.0		448
		Other Neuroleptics	72	100.0	7	100.0	8	100.0	206	100.0		293
		Placebo	75	100.0	59	100.0	116	100.0	618	100.0		868
Risperidone	377	100.0	532	100.0	720	100.0	3701	100.0		5330		

(CONTINUED)
Display WAE.3 Number of patients with/without Weight Increase AEs by demographics

			RACE										Total
					Other		Black		White		Total		
			n	%	n	%	n	%	n	%		n	
Total	TRIAL DURATION	All treatments											
	SHORT-TERM		580	100.0	741	100.0	984	100.0	5346	100.0	7651		
	Short + Long Term	Treatment											
		Haloperidol	56	100.0	136	100.0	138	100.0	684	100.0	1014		
		Olanzapine	-	-	42	100.0	76	100.0	330	100.0	448		
		Other Neuroleptics	74	100.0	27	100.0	8	100.0	418	100.0	527		
		Placebo	75	100.0	59	100.0	116	100.0	618	100.0	868		
		Risperidone	611	100.0	800	100.0	966	100.0	6005	100.0	8402		
	All treatments	836	100.0	1064	100.0	1304	100.0	8055	100.0	11259			

Display WAE:4 Number of patients with/without Weight Increase AEs by treatment and trial duration

	TRIAL DURATION																		Short + Long Term					
	LONG-TERM									SHORT-TERM														
	Treatment						Treatment						Treatment											
	Haloperidol		Other Neuroleptics		Risperidone		Haloperidol		Olanzapine		Other Neuroleptics		Placebo		Risperidone		Haloperidol		Olanzapine		Other Neuroleptics			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%		
Weight increase AE																								
NO	297	98.34	233	99.57	2977	96.91	703	98.74	406	90.63	292	99.66	860	99.08	5256	98.61	1000	98.62	406	90.63	525	99.62		
YES	5	1.66	1	0.43	95	3.09	9	1.26	42	9.38	1	0.34	8	0.92	74	1.39	14	1.38	42	9.38	2	0.38		
Total	302	100.00	234	100.00	3072	100.00	712	100.00	448	100.00	293	100.00	868	100.00	5330	100.00	1014	100.00	448	100.00	527	100.00		

(CONTINUED)

	Short + Long Term				
	Treatment				Total
	Placebo	Risperidone	Placebo	Risperidone	
	n	%	n	%	n
Weight increase AE					
NO	860	99.08	8233	97.99	11024
YES	8	0.92	169	2.01	235
Total	868	100.00	8402	100.00	11259

Display NAB.5 Number of patients with Weight Increase AEs by Mode Dose

	AGE GROUP																								Total																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																										
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	MISSING				<4 mg/day				4-6 mg/day				>6 mg/day				MISSING				<0.03 mg/kg/day					0.03-0.04 mg/kg/day				>0.04 mg/kg/day				MISSING				<0.75 mg/day				0.75-1.5 mg/day				>1.5 mg/day																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																					
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Display WAB.6 Number of patients with/without Weight Increase AEs by BMI at baseline

		Treatment										Total
		Haloperidol		Olanzapine		Other Neurolepti- cs		Placebo		Risperidone		
		n	%	n	%	n	%	n	%	n	%	
BMI Category	Weight increase AE											
BMI<23	NO	341	99.13	107	91.45	210	99.53	347	98.86	2329	97.24	3334
	YES	3	0.87	10	8.55	1	0.47	4	1.14	66	2.76	84
23<BMI<=27	NO	297	99.00	115	88.46	166	100.0	169	99.41	1806	98.10	2553
	YES	3	1.00	15	11.54	-	-	1	0.59	35	1.90	54
BMI>27	NO	284	97.59	181	91.41	137	99.28	122	99.19	1695	97.47	2419
	YES	7	2.41	17	8.59	1	0.72	1	0.81	44	2.53	70
Total		935	100.0	445	100.0	515	100.0	644	100.0	5975	100.0	8514

Display WAB.7 Total Exposure of Risperidone Patients and Weight Increase AEs

OBS	TRIAL ID.	Treatment	Patients in Trial	Patient Years of Exposure	Patients who had AEs
1	BEL-5	Haloperidol	22	4.31	0
2	BEL-7	Haloperidol	32	0.81	1
3	FRA-3	Haloperidol	20	1.38	0
4	INT-2	Haloperidol	226	29.66	0
5	INT-24	Haloperidol	115	22.15	0
6	INT-3	Haloperidol	87	8.27	0
7	INT-6	Haloperidol	99	49.87	0
8	KOR-1	Haloperidol	19	2.95	0
9	USA-1	Haloperidol	53	3.93	0
10	USA-102	Haloperidol	53	2.36	4
11	USA-79	Haloperidol	203	153.88	5
12	INT-45	Olanzapine	242	31.58	22
13	USA-112	Olanzapine	205	27.56	20
14	AUT-1	Other Neuro	33	3.11	0
15	FIN-1	Other Neuro	50	4.18	0
16	FRA-3	Other Neuro	21	1.41	0
17	GER-5	Other Neuro	20	1.30	0
18	INT-7	Other Neuro	52	6.67	0
19	INT-9	Other Neuro	74	6.89	0
20	SUI-1	Other Neuro	43	5.68	1
21	CAN-19	Placebo	57	5.65	0
22	GBR-28	Placebo	13	0.89	0
23	INT-24	Placebo	114	21.10	0
24	INT-3	Placebo	88	7.22	0
25	INT-39	Placebo	25	1.79	1
26	INT-46	Placebo	75	3.02	2
27	USA-063	Placebo	163	30.97	0
28	USA-1	Placebo	54	3.58	0
29	USA-102	Placebo	51	2.08	0
30	USA-72	Placebo	83	5.06	2
31	USA-93	Placebo	63	6.13	0
32	AUT-1	Risperidone	34	3.35	0
33	BEL-17	Risperidone	115	73.92	0
34	BEL-21	Risperidone	6	0.02	0
35	BEL-22	Risperidone	7	0.60	2
36	BEL-24	Risperidone	6	0.48	0
37	BEL-5	Risperidone	22	4.80	0
38	BEL-7	Risperidone	28	0.56	0
39	CAN-19	Risperidone	53	5.78	4
40	FIN-1	Risperidone	48	4.34	0
41	FRA-3	Risperidone	21	1.52	0
42	GER-28	Risperidone	10	0.70	0
43	GBR-29	Risperidone	19	13.53	3
44	GER-3	Risperidone	13	0.88	0
45	GER-5	Risperidone	39	2.28	0
46	INT-1	Risperidone	121	8.91	0
47	INT-10	Risperidone	211	21.20	2
48	INT-2	Risperidone	1136	153.13	3
49	INT-24	Risperidone	115	19.68	0
50	INT-3	Risperidone	348	38.00	1
51	INT-39	Risperidone	29	2.00	0
52	INT-4	Risperidone	384	311.01	3
53	INT-45	Risperidone	247	30.91	10
54	INT-46	Risperidone	75	9.04	1
55	INT-47	Risperidone	39	25.70	2
56	INT-6	Risperidone	91	56.35	5
57	INT-7	Risperidone	55	7.10	0
58	INT-8	Risperidone	109	67.67	0
59	INT-9	Risperidone	75	7.53	0
60	ITA-1	Risperidone	31	2.19	0
61	KOR-1	Risperidone	16	2.14	0
62	NED-2	Risperidone	40	16.05	1
63	NED-9	Risperidone	19	2.16	1
64	SUI-1	Risperidone	43	5.89	0
65	USA-063	Risperidone	462	84.91	3
66	USA-1	Risperidone	53	4.28	1

Display WAE.7 Total Exposure of Risperidone Patients and Weight Increase AEs

OBS	TRIAL ID.	Treatment	Patients in Trial	Patient Years of Exposure	Patients who had AEs
67	USA-102	Risperidone	52	14.90	4
68	USA-112	Risperidone	202	25.77	17
69	USA-34	Risperidone	22	4.88	0
70	USA-5	Risperidone	7	5.48	0
71	USA-6	Risperidone	265	133.35	2
72	USA-60	Risperidone	441	28.47	3
73	USA-64	Risperidone	103	20.23	3
74	USA-7	Risperidone	105	140.57	0
75	USA-70	Risperidone	330	208.19	5
76	USA-72	Risperidone	163	10.28	3
77	USA-79	Risperidone	192	182.20	6
78	USA-9	Risperidone	107	71.57	9
79	USA-93	Risperidone	55	5.43	8
80	USA-97	Risperidone	107	70.42	22

Display WAE.7 Total Exposure of Risperidone Patients and Weight Increase AEs

OBS	Treatment	Patients who had AEs	Total Patients	Patient Years of Exposure	Per Treatment Year (%)
1	Haloperidol	10	929	279.57	3.58
2	Olanzapine	42	447	59.14	71.02
3	Other Neuro	1	293	29.24	3.42
4	Placebo	6	786	87.49	6.86
5	Risperidone	124	6271	1900.35	6.53

DISPLAY WEI.1A: NUMBER OF RISPERIDONE PATIENTS WITH WEIGHT GAIN BY MODE DOSE

RISPERIDONE	AGE GROUP																		Total
	< 18						18 - 65						> 65						
	MODE DOSE RANGES						MODE DOSE RANGES						MODE DOSE RANGES						
	<0.03 mg/kg/day		0.03-0.04 mg/kg/day		>0.04 mg/kg/day		<4 mg/day		4-6 mg/day		>6 mg/day		<0.75 mg/day		0.75-1.5 mg/day		>1.5 mg/day		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
PCT GROUP																			
<7 %	28	49.12	16	50.00	61	41.78	485	88.18	1448	86.34	1467	83.21	400	84.21	195	91.55	226	90.40	4326
7-14 %	17	29.82	9	28.13	41	28.08	50	9.09	168	10.02	215	12.20	57	12.00	16	7.51	19	7.60	592
>14 %	12	21.05	7	21.88	44	30.14	15	2.73	61	3.64	81	4.59	18	3.79	2	0.94	5	2.00	245
Total	57	100.00	32	100.00	146	100.00	550	100.00	1677	100.00	1763	100.00	475	100.00	213	100.00	250	100.00	5163

DISPLAY WEI.1B: NUMBER OF HALOPERIDOL PATIENTS WITH WEIGHT GAIN

HALOPERIDOL	AGE GROUP				Total
	18 - 65		> 65		
	N	%	N	%	N
PCT GROUP					
<7 %	645	94.02	84	95.45	729
7-14 %	33	4.81	4	4.55	37
>14 %	8	1.17	-	-	8
Total	686	100.00	88	100.00	774

DISPLAY WEI.1C: NUMBER OF OLANZAPINE PATIENTS WITH WEIGHT GAIN

OLANZAPINE	AGE GROUP		Total
	18 - 65		
	N	%	N
PCT GROUP			
<7 %	296	73.27	296
7-14 %	87	21.53	87
>14 %	21	5.20	21
Total	404	100.00	404

DISPLAY WEI.1D: NUMBER OF OTHER NEUROLEPTICS PATIENTS WITH WEIGHT GAIN

OTHER NEUROLEPTICS	AGE GROUP		Total
	18 - 65		
	N	%	N
PCT GROUP			
<7 %	176	87.13	176
7-14 %	23	11.39	23
>14 %	3	1.49	3
Total	202	100.00	202

DISPLAY WEI.1E: NUMBER OF PLACEBO PATIENTS WITH WEIGHT GAIN

PLACEBO	AGE GROUP						Total
	< 18		18 - 65		> 65		
	N	%	N	%	N	%	
PCT GROUP							
<7 %	107	91.45	285	92.83	226	93.78	618
7-14 %	8	6.84	20	6.51	13	5.39	41
>14 %	2	1.71	2	0.65	2	0.83	6
Total	117	100.00	307	100.00	241	100.00	665

DISPLAY WEI.1F: NUMBER OF RISPERIDONE PATIENTS WITH WEIGHT GAIN

RISPERIDONE	AGE GROUP						Total
	< 18		18 - 65		> 65		
	N	%	N	%	N	%	
PCT GROUP							N
<7 %	105	44.68	3400	85.21	821	87.53	4326
7-14 %	67	28.51	433	10.85	92	9.81	592
>14 %	63	26.81	157	3.93	25	2.67	245
Total	235	100.00	3990	100.00	938	100.00	5163

DISPLAY WEI.2A: MEAN WEIGHT CHANGE OF RISPERIDONE PATIENTS BY MODE DOSE

RISPERIDONE		AGE GROUP								
		< 18			18 - 65			> 65		
		MODE DOSE RANGES			MODE DOSE RANGES			MODE DOSE RANGES		
		<0.03 mg/kg- /day	0.03- 0.04 mg/kg- /day	>0.04 mg/kg- /day	<4 mg/day	4-6 mg/day	>6 mg/day	<0.75 mg/day	0.75- 1.5 mg/day	>1.5 mg/day
WEIGHT CHANGE, Kg	MEAN	3.218	3.500	3.812	1.157	1.539	1.469	0.352	0.148	0.404
WEIGHT CHANGE, Kg	STD	3.666	2.886	3.888	3.947	4.327	4.531	4.120	3.089	3.246

DISPLAY WEI.2B: MEAN WEIGHT CHANGE OF HALOPERIDOL PATIENTS

HALOPERIDOL		AGE GROUP	
		18 - 65	> 65
WEIGHT CHANGE, Kg	MEAN	0.066	-1.168
WEIGHT CHANGE, Kg	STD	3.127	3.523

DISPLAY WEI.2C: MEAN WEIGHT CHANGE OF OLANZAPINE PATIENTS

OLANZAPINE		AGE GROUP
		18 - 65
WEIGHT CHANGE, Kg	MEAN	3.212
WEIGHT CHANGE, Kg	STD	4.447

DISPLAY WEI.2D: MEAN WEIGHT CHANGE OF OTHER NEUROLEPTICS PATIENTS

OTHER NEUROLEPTICS		AGE GROUP
		18 - 65
WEIGHT CHANGE, Kg	MEAN	0.958
WEIGHT CHANGE, Kg	STD	3.279

DISPLAY WEI.2E: MEAN WEIGHT CHANGE OF PLACEBO PATIENTS

PLACEBO		AGE GROUP		
		< 18	18 - 65	> 65
WEIGHT CHANGE, Kg	MEAN	0.574	0.173	-0.311
WEIGHT CHANGE, Kg	STD	1.666	3.763	3.353

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism
Evaluation of glucose metabolism with risperidone

DISPLAY WEI.3: NUMBER OF PATIENTS WITH WEIGHT GAIN BY TRIAL DURATION OF TREATMENT

PCT GROUP	TRIAL DURATION																		
	SHORT-TERM																		
	AGE GROUP																		
	< 18				18 - 65										> 65				
	RANDOMISATION GROUP				RANDOMISATION GROUP										RANDOMISATION GROUP				
	PLACEBO		RISPERIDONE		HALOPERIDOL		OLANZAPINE		OTHER NEUROLEPTI		PLACEBO		RISPERIDONE		HALOPERIDOL		PLACEBO		RISPERIDONE
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N
<7 %	107	91.45	79	60.77	373	92.10	296	73.27	176	87.13	285	92.83	2428	87.46	84	95.45	226	93.78	471
7-14 %	8	6.84	42	32.31	26	6.42	87	21.53	23	11.39	20	6.51	280	10.09	4	4.55	13	5.39	46
>14 %	2	1.71	9	6.92	6	1.48	21	5.20	3	1.49	2	0.65	68	2.45	-	-	2	0.83	10
Total	117	100.00	130	100.00	405	100.00	404	100.00	202	100.00	307	100.00	2776	100.00	88	100.00	241	100.00	527

(CONTINUED)

DISPLAY WEI.3: NUMBER OF PATIENTS WITH WEIGHT GAIN BY TRIAL DURATION OF TREATMENT

PCT GROUP	TRIAL DURATION										Total
	SHORT-TERM										
	AGE GROUP										
	> 65	LONG-TERM									
		AGE GROUP									
	RANDOMISATION GROUP	< 18		18 - 65				> 65			
		RANDOMISATION GROUP		RANDOMISATION GROUP				RANDOMISATION GROUP			
	RISPERIDONE	RISPERIDONE		HALOPERIDOL		RISPERIDONE		RISPERIDONE			
	%	N	%	N	%	N	%	N	%		
	<7 %	89.37	26	24.76	272	96.80	972	80.07	350	85.16	
7-14 %	8.73	25	23.81	7	2.49	153	12.60	46	11.19	780	
>14 %	1.90	54	51.43	2	0.71	89	7.33	15	3.65	283	
Total	100.00	105	100.00	281	100.00	1214	100.00	411	100.00	7208	

DISPLAY WEI.4A: NUMBER OF RISPERIDONE PATIENTS WITH WEIGHT GAIN BY SEX

RISPERIDONE	SEX				Total
	FEMALE		MALE		
	N	%	N	%	N
PCT GROUP					
<7 %	1566	84.83	2758	83.20	4324
7-14 %	213	11.54	379	11.43	592
>14 %	67	3.63	178	5.37	245
Total	1846	100.00	3315	100.00	5161

DISPLAY WEI.4B: NUMBER OF HALOPERIDOL PATIENTS WITH WEIGHT GAIN BY SEX

HALOPERIDOL	SEX				Total
	FEMALE		MALE		
	N	%	N	%	
PCT GROUP					
<7 %	257	94.49	472	94.02	729
7-14 %	12	4.41	25	4.98	37
>14 %	3	1.10	5	1.00	8
Total	272	100.00	502	100.00	774

DISPLAY WEI.4C: NUMBER OF OLANZAPINE PATIENTS WITH WEIGHT GAIN BY SEX

OLANZAPINE	SEX				Total
	FEMALE		MALE		
	N	%	N	%	
PCT GROUP	N	%	N	%	N
<7 %	87	71.31	209	74.11	296
7-14 %	29	23.77	58	20.57	87
>14 %	6	4.92	15	5.32	21
Total	122	100.00	282	100.00	404

DISPLAY WEI.4D: NUMBER OF OTHER NEUROLEPTICS PATIENTS WITH WEIGHT GAIN BY SEX

OTHER NEUROLEPTICS	SEX				Total
	FEMALE		MALE		
	N	%	N	%	
PCT GROUP					N
<7 %	55	88.71	121	86.43	176
7-14 %	5	8.06	18	12.86	23
>14 %	2	3.23	1	0.71	3
Total	62	100.00	140	100.00	202

DISPLAY WEI.4E: NUMBER OF PLACEBO PATIENTS WITH WEIGHT GAIN BY SEX

PLACEBO	SEX				Total
	FEMALE		MALE		
	N	%	N	%	
PCT GROUP					N
<7 %	261	92.23	357	93.46	618
7-14 %	18	6.36	23	6.02	41
>14 %	4	1.41	2	0.52	6
Total	283	100.00	382	100.00	665

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism
Evaluation of glucose metabolism with risperidone

DISPLAY WEI.5: NUMBER OF PATIENTS WITH WEIGHT GAIN BY RACE

PCT GROUP	RACE																			
	BLACK										CAUCASIAN									
	RANDOMISATION GROUP										RANDOMISATION GROUP									
	HALOPERIDOL		OLANZAPINE		OTHER NEUROLEPTI		PLACEBO		RISPERIDONE		HALOPERIDOL		OLANZAPINE		OTHER NEUROLEPTI		PLACEBO		RISPERIDONE	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
<7 %	104	96.30	45	69.23	7	100.00	93	93.94	513	81.69	499	94.51	218	73.15	107	84.92	478	93.00	3125	
7-14 %	3	2.78	15	23.08	-	-	5	5.05	78	12.42	23	4.36	67	22.48	16	12.70	31	6.03	398	
>14 %	1	0.93	5	7.69	-	-	1	1.01	37	5.89	6	1.14	13	4.36	3	2.38	5	0.97	161	
Total	108	100.00	65	100.00	7	100.00	99	100.00	628	100.00	528	100.00	298	100.00	126	100.00	514	100.00	3684	

(CONTINUED)

PCT GROUP	RACE												Total
	CANCA- SIAN	RANDOMISATION GROUP											
		RAN- DO- NISAT- ION GROUP	OTHER										
			RANDOMISATION GROUP										
			RISPE- RIDONE	HALOPERIDOL		OLANZAPINE		OTHER NEUROLEPTI		PLACEBO		RISPERIDONE	
%	N	%	N	%	N	%	N	%	N	%	N		
<7 %	84.83	100	90.91	33	80.49	6	100.00	47	90.38	487	79.19	5862	
7-14 %	10.80	9	8.18	5	12.20	-	-	5	9.62	89	14.47	744	
>14 %	4.37	1	0.91	3	7.32	-	-	-	-	39	6.34	275	

(CONTINUED)

DISPLAY WEI.5: NUMBER OF PATIENTS WITH WEIGHT GAIN BY RACE

RANDOMISATION GROUP	RACE											
	CAUCASIAN											
	OTHER											
	RANDOMISATION GROUP											
	RISPERIDONE	HALOPERIDOL		OLANZAPINE		OTHER NEUROLEPTI		PLACEBO		RISPERIDONE		Total
	%	N	%	N	%	N	%	N	%	N	%	N
Total	100.00	110	100.00	41	100.00	6	100.00	52	100.00	615	100.00	6881

DISPLAY WEL.6A: NUMBER OF RISPERIDONE PATIENTS WITH WEIGHT GAIN BY BMI GROUP

RISPERIDONE	AGE GROUP																			Total
	< 18						18 - 65						> 65							
	BMI GROUP						BMI GROUP						BMI GROUP							
	BMI<23		23<BMI<=27		BMI>27		BMI<23		23<BMI<=27		BMI>27		BMI<23		23<BMI<=27		BMI>27			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%		
PCT GROUP																			N	
<7 %	82	43.85	15	53.57	7	46.67	932	77.22	1031	87.23	1171	92.13	396	84.26	247	92.86	149	88.69	4030	
7-14 %	52	27.81	7	25.00	6	40.00	187	15.49	114	9.64	82	6.45	55	11.70	16	6.02	16	9.52	535	
>14 %	53	28.34	6	21.43	2	13.33	88	7.29	37	3.13	18	1.42	19	4.04	3	1.13	3	1.79	229	
Total	187	100.00	28	100.00	15	100.00	1207	100.00	1182	100.00	1271	100.00	470	100.00	266	100.00	168	100.00	4794	

DISPLAY WEI.6B: NUMBER OF HALOPERIDOL PATIENTS WITH WEIGHT GAIN BY BMI GROUP

HALOPERIDOL	AGE GROUP													Total
	18 - 65						> 65							
	BMI GROUP						BMI GROUP							
	BMI<23		23<BMI<=27		BMI>27		BMI<23		23<BMI<=27		BMI>27			
	N	%	N	%	N	%	N	%	N	%	N	%	N	
PCT GROUP														
<7 %	182	91.00	202	93.95	234	96.69	34	97.14	26	92.86	16	100.00	694	
7-14 %	15	7.50	8	3.72	8	3.31	1	2.86	2	7.14	-	-	34	
>14 %	3	1.50	5	2.33	-	-	-	-	-	-	-	-	8	
Total	200	100.00	215	100.00	242	100.00	35	100.00	28	100.00	16	100.00	736	

DISPLAY WEI.6C: NUMBER OF OLANZAPINE PATIENTS WITH WEIGHT GAIN BY BMI GROUP

OLANZAPINE	AGE GROUP								Total
	18 - 65								
	BMI GROUP								
	BMI<23		23<BMI<=27		BMI>27		N		
	N	%	N	%	N	%			
PCT GROUP									
<7 %	63	60.58	84	71.79	149	82.32	296		
7-14 %	33	31.73	24	20.51	28	15.47	85		
>14 %	8	7.69	9	7.69	4	2.21	21		
Total	104	100.00	117	100.00	181	100.00	402		

DISPLAY WBI.6D: NUMBER OF OTHER NEUROLEPTICS PATIENTS WITH WEIGHT GAIN BY BMI GROUP

OTHER NEUROLEPTICS	AGE GROUP						
	18 - 65						
	BMI GROUP						
	BMI<23		23<BMI<=27		BMI>27		Total
	N	%	N	%	N	%	N
PCT GROUP							
<7 %	56	83.58	68	86.08	50	92.59	174
7-14 %	9	13.43	11	13.92	3	5.56	23
>14 %	2	2.99	-	-	1	1.85	3
Total	67	100.00	79	100.00	54	100.00	200

DISPLAY WRI.6B: NUMBER OF PLACEBO PATIENTS WITH WEIGHT GAIN BY BMI GROUP

PLACEBO	AGE GROUP																		Total
	< 18						18 - 65						> 65						
	BMI GROUP						BMI GROUP						BMI GROUP						
	BMI<23		23<BMI<=27		BMI>27		BMI<23		23<BMI<=27		BMI>27		BMI<23		23<BMI<=27		BMI>27		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
PCT GROUP																			
<7 %	92	91.09	10	100.00	2	100.00	49	94.23	58	96.67	60	98.36	119	91.54	63	96.92	36	94.74	489
7-14 %	7	6.93	-	-	-	-	3	5.77	2	3.33	1	1.64	10	7.69	1	1.54	2	5.26	26
>14 %	2	1.98	-	-	-	-	-	-	-	-	-	-	1	0.77	1	1.54	-	-	4
Total	101	100.00	10	100.00	2	100.00	52	100.00	60	100.00	61	100.00	130	100.00	65	100.00	38	100.00	519

DISPLAY WEI.7A: MEAN WEIGHT CHANGE OF RISPERIDONE PATIENTS BY BMI GROUP

RISPERIDONE		AGE GROUP								
		< 18			18 - 65			> 65		
		BMI GROUP			BMI GROUP			BMI GROUP		
		BMI<23	23<BM- I<=27	BMI>27	BMI<23	23<BM- I<=27	BMI>27	BMI<23	23<BM- I<=27	BMI>27
WEIGHT CHANGE, Kg	MEAN	3.271	4.629	5.713	2.208	1.438	0.623	0.745	-0.415	0.265
WEIGHT CHANGE, Kg	STD	3.249	4.557	5.252	4.296	4.335	4.377	3.400	3.691	4.278

Volume I/Page 158

JJRPprev 00380035
Confidential/Produced in Litigation Pursuant to Protective Order
D807.173

R. 6071

DISPLAY WEI.7B: MEAN WEIGHT CHANGE OF HALOPERIDOL PATIENTS BY BMI GROUP

HALOPERIDOL		AGE GROUP					
		18 - 65			> 65		
		BMI GROUP			BMI GROUP		
		BMI<23	23<BMI- I<=27	BMI>27	BMI<23	23<BMI- I<=27	BMI>27
WEIGHT CHANGE, Kg	MEAN	0.424	0.533	-0.551	-0.943	-0.532	-2.775
WEIGHT CHANGE, Kg	STD	2.815	3.159	3.175	3.011	3.466	3.661

DISPLAY WEI.7C: MEAN WEIGHT CHANGE OF OLANZAPINE PATIENTS BY BMI GROUP

OLANZAPINE		AGE GROUP		
		18 - 65		
		BMI GROUP		
		BMI<23	23<BMI<=27	BMI>27
WEIGHT CHANGE, Kg	MEAN	3.777	3.254	2.841
WEIGHT CHANGE, Kg	STD	3.636	4.930	4.548

DISPLAY WEI.7D: MEAN WEIGHT CHANGE OF OTHER NEUROLEPTICS PATIENTS BY BMI GROUP

OTHER NEUROLEPTICS		AGE GROUP		
		18 - 65		
		BMI GROUP		
		BMI<23	23<BMI<=27	BMI>27
WEIGHT CHANGE, Kg	MEAN	1.543	0.885	0.328
WEIGHT CHANGE, Kg	STD	2.803	3.329	3.720

DISPLAY WEI.7E: MEAN WEIGHT CHANGE OF PLACEBO PATIENTS BY BMI GROUP

PLACEBO	AGE GROUP								
	< 18			18 - 65			> 65		
	BMI GROUP			BMI GROUP			BMI GROUP		
	BMI<23	23<BM- I<=27	BMI>27	BMI<23	23<BM- I<=27	BMI>27	BMI<23	23<BM- I<=27	BMI>27
WEIGHT CHANGE, Kg MEAN	0.494	1.170	1.150	-0.384	-0.441	-0.410	0.202	-1.205	-0.474
WEIGHT CHANGE, Kg STD	1.740	0.897	1.626	3.406	3.453	3.919	2.928	4.157	3.194

DISPLAY WEI.8: MEAN WEIGHT CHANGE OF TREATMENT BY TRIAL DURATION OF TREATMENT

		TRIAL DURATION												
		SHORT-TERM										LONG-TERM		
		AGE GROUP										AGE GROUP		
		< 18		18 - 65					> 65			< 18	18 - 65	> 65
		RANDOMISATION GROUP		RANDOMISATION GROUP					RANDOMISATION GROUP			RANDOMISATION GROUP	RANDOMISATION GROUP	RANDOMISATION GROUP
		PLACE-BO	RISPE-RIDONE	HALOP-ERIDOL	OLANZ-APINE	OTHER-NEURO-LEPTI	PLACE-BO	RISPE-RIDONE	HALOP-ERIDOL	PLACE-BO	RISPE-RIDONE	RISPE-RIDONE	HALOP-ERIDOL	RISPE-RIDONE
WEIGHT CHANGE, Kg	MEAN	0.574	2.128	0.073	3.212	0.958	0.173	1.323	-1.168	-0.311	0.371	5.478	0.055	1.759
WEIGHT CHANGE, Kg	STD	1.666	1.869	3.543	4.447	3.279	3.763	3.659	3.523	3.353	3.081	4.510	2.409	5.659

6.2. Annexes

Annex 1A: Patient listing of demographics and glucose-related adverse events in Phase1-3 trials

CRF ID	TRIAL ID	Adverse event preferred term	Sex	Race	Age years	Weight kg	Height cm	Treatment	Trial phase	Onset dose (mg)	Treatment duration	Action taken	SAE	Outcome	Duration in phase days
PHASE 2-3															
A03142	GBR-29	Glycosuria	Male	Caucasian	38	85.5	168	Risperidone	Treatment					Recovered	
267	INT-10	Hypoglycemia	Female	Oriental	44	64	161	Risperidone	Double-blind	8				Recovered	1
1069	INT-2	Hyperglycaemia	Female	Caucasian	66	73.2	165	Placebo	Single-blind	0 mg				Recovered	1
A00118	INT-23	Diabetes mellitus	Female	Caucasian	73	44	134	Risperidone	Open				yes	Recovered	
A00367	INT-23	Hypoglycaemia	Male	Caucasian	74	44	159	Risperidone	Open				yes	Died	
165	INT-24	Hyperglycaemia	Male	Caucasian	82	53.3	165	Haloperidol		1.75	43+ days		no	Not recovered	1
450	INT-24	Hyperglycaemia	Female	Caucasian	80	52.9		Risperidone		0.25	43+ days		no	Recovered	1
170	INT-24	Hypoglycaemia	Female	Caucasian	84	75		Placebo		1.5	43+ days		no	Recovered	6
A00469	INT-26	Hyperglycaemia	Male	Caucasian	82	64	163	Risperidone	Follow-up				no	Recovered	
25	INT-4	Diabetes	Male	Caucasian	51	68	171	Risperidone	Follow-up	6 mg			no	Not recovered	194
252	INT-4	Diabetes	Male	Asian	44	77.5	166	Risperidone	Follow-up	12 mg			no	Not recovered	50
365	INT-4	Diabetes	Male	Hispanic	25	102	172	Risperidone	Follow-up	4 mg			no	Recovered	
A30577	INT-45	Diabetes mellitus	Female	Caucasian	53	99	176	Olanzapine	Treatment				no	Not recovered	
A30094	INT-45	Hyperglycaemia	Female	Caucasian	59	62	160	Risperidone	Treatment				no	Not recovered	
A30142	INT-45	Hyperglycaemia	Male	Caucasian	50	52	154	Risperidone	Treatment				yes	Recovered	
A30142	INT-45	Hypoglycaemia	Male	Caucasian	50	52	154	Risperidone	Treatment				yes	Recovered	
429	INT-6	Acidosis	Male	Caucasian	37	85.2	175.2	Risperidone	Double-blind	15 mg			no	Recovered	1
146	INT-9	Diabetes mellitus	Male	Caucasian	43	95	177	Remoxiprid	Double-blind	600 mg			no	Not recovered	9
119202	USA-054	Blood sugar increased	Male	Black	52	93							no	Recovered	
124501	USA-054	Blood sugar increased	Male	Black	52	105							no	Recovered	
1204	USA-063	Coma diabetic	Male	Black	85	67.6	177.8	Risperidone	Treatment	0.5	1-42 days	DC	no	Died	1
1204	USA-063	Coma diabetic	Male	Black	85	67.6	177.8	None	Post-trial		1-42 days	DC	no	Died	2

CRF ID	TRIAL ID	Adverse event preferred term	Sex	Race	Age years	Weight kg	Height cm	Treatment	Trial phase	Onset dose (mg)	Treatment duration	Action taken	SAE	Outcome	Duration in phase days
106	USA-063	Diabetes mellitus	Female	Black	76	47.2	154.9	Risperidone	Treatment	1	43+ days		no	Not recovered	57
4014	USA-063	Diabetes mellitus	Female	Caucasian	94	61.7	157.5	Risperidone	Treatment	0.5	1-42 days		yes	Recovered	10
1212	USA-063	Diabetes mellitus aggravated	Male	Caucasian	67	63.6	172.7	Risperidone	Treatment	2	43+ days		no	Recovered	20
2201	USA-063	Diabetes mellitus aggravated	Female	Black	69	67.2	162.6	Risperidone	Treatment	2	43+ days		no	Recovered	1
210	USA-063	Hyperglycaemia	Male	Caucasian	90	68.1	167.6	None	Pre-trial	--	43+ days		no	Not recovered	1
210	USA-063	Hyperglycaemia	Male	Caucasian	90	68.1	167.6	Placebo	Run-in		43+ days		no	Not recovered	7
210	USA-063	Hyperglycaemia	Male	Caucasian	90	68.1	167.6	Placebo	Treatment		43+ days		no	Not recovered	84
911	USA-063	Hyperglycaemia	Male	Caucasian	70	72.6	160	Placebo	Treatment	0.25	43+ days		yes	Recovered	3
1007	USA-063	Hyperglycaemia	Male	Caucasian	76	73.1	172.7	Placebo	Treatment	0.5	43+ days		no	Recovered	19
1204	USA-063	Hyperglycaemia	Male	Black	85	67.6	177.8	Risperidone	Treatment	0.5	1-42 days	DC	yes	Died	1
1204	USA-063	Hyperglycaemia	Male	Black	85	67.6	177.8	None	Post-trial		1-42 days	DC	yes	Died	2
1712	USA-063	Hyperglycaemia	Male	Black	70	75.4	198.1	Risperidone	Treatment	1	43+ days		no	Recovered	23
2216	USA-063	Hyperglycaemia	Female	Black	80	48.6	165.1	Risperidone	Treatment	1	43+ days		no	Recovered	76
2613	USA-063	Hyperglycaemia	Female	Caucasian	83	44.5	152.4	Risperidone	Treatment	2	1-42 days	DC	yes	Not recovered	9
3513	USA-063	Hyperglycaemia	Female	Caucasian	87	39	157.5	Risperidone	Treatment	1	43+ days		no	Not recovered	13
3903	USA-063	Hyperglycaemia	Male	Caucasian	73	65.4	177.8	Risperidone	Treatment	2	43+ days		no	Recovered	21
3903	USA-063	Hyperglycaemia	Male	Caucasian	73	65.4	177.8	None	Post-trial		43+ days		no	Recovered	78
3909	USA-063	Hyperglycaemia	Male	Caucasian	76	79	167.6	Risperidone	Treatment	2	43+ days		no	Not recovered	31
4013	USA-063	Hyperglycaemia	Male	Caucasian	86	93.5	172.7	Risperidone	Treatment	0.5	43+ days		yes	Recovered	3
4113	USA-063	Hyperglycaemia	Female	Caucasian	95		172.7	Placebo	Treatment	0.25	1-42 days	DC	yes	Died	1
115	USA-063	Hypoglycaemia	Female	Black	79	49	170.2	Risperidone	Treatment	1	43+ days		yes	Recovered	4
115	USA-063	Hypoglycaemia	Female	Black	79	49	170.2	None	Post-trial		43+ days		yes	Recovered	1
3906	USA-063	Hypoglycaemia	Male	Caucasian	73	70.4	182.9	Risperidone	Treatment	1	43+ days		no	Recovered	1
1712	USA-063	Plasma osmolality increased	Male	Black	70	75.4	198.1	Risperidone	Treatment	1	43+ days		no	Recovered	23
A30030	USA-102	Diabetes mellitus	Male	Caucasian	64	78.9	188	Placebo	DB	0			yes	Recovered	4
A30030	USA-102	Diabetes mellitus	Male	Caucasian	64	78.9	188	None	Post trial				yes	Recovered	5
A30053	USA-102	Hyperglycaemia	Male	Caucasian	38	175.1	185.4	Risperidone	Open	0			no	Not recovered	1

CRFID	TRIAL ID	Adverse event preferred term	Sex	Race	Age years	Weight kg	Height cm	Treatment	Trial phase	Onset dose (mg)	Treatment duration	Action taken	SAE	Outcome	Duration in phase days
A30065	USA-102	Hyperglycaemia	Female	Black	46	117.5	172.7	Haloperidol	DB	2			no	Not recovered	1
A30065	USA-102	Hyperglycaemia	Female	Black	46	117.5	172.7	None	Post trial				no	Not recovered	4
A30226	USA-102	Hyperglycaemia	Male	Hispanic	47	87.1	182.9	Placebo	DB	0			no	Not recovered	1
A30374	USA-112	Diabetes mellitus	Male	Caucasian	39	105.2	180.3	None	Pre trial	--			no	Not recovered	4
A30374	USA-112	Diabetes mellitus	Male	Caucasian	39	105.2	180.3	Risperidone	Treatment				no	Not recovered	57
A30251	USA-112	Glycosuria	Male	Black	42	95.7	182.9	Olanzapine	Treatment	0			no	Not recovered	1
A30167	USA-112	Hyperglycaemia	Male	Caucasian	36	110.2	175.3	Risperidone	Treatment	4			no	Recovered	2
A30191	USA-112	Hyperglycaemia	Male	Caucasian	57	89.4	172.7	Risperidone	Treatment	2			no	Not recovered	1
A30192	USA-112	Hyperglycaemia	Female	Black	60	76.2	162.6	Risperidone	Treatment	4			no	Not recovered	2
A30195	USA-112	Hyperglycaemia	Male	Hispanic	62	84.8	162.6	None	Pre trial	--			no	Not recovered	8
A30195	USA-112	Hyperglycaemia	Male	Hispanic	62	84.8	162.6	Olanzapine	Treatment				no	Not recovered	54
A30217	USA-112	Hyperglycaemia	Female	Black	36	88.9	167.6	Risperidone	Treatment	4			no	Recovered	43
A30217	USA-112	Hyperglycaemia	Female	Black	36	88.9	167.6	Risperidone	Treatment	4			no	Not recovered	14
A30251	USA-112	Hyperglycaemia	Male	Black	42	95.7	182.9	Olanzapine	Treatment	0			no	Not recovered	1
A30350	USA-112	Hyperglycaemia	Male	Black	39	59	170.2	None	Pre trial	--			no	Not recovered	1
A30350	USA-112	Hyperglycaemia	Male	Black	39	59	170.2	Olanzapine	Treatment				no	Not recovered	58
A30419	USA-112	Hyperglycaemia	Male	Caucasian	46	59	154.9	Risperidone	Treatment	4			no	Recovered	17
A30394	USA-112	Hypoglycaemia	Female	Black	52	117	167.6	Risperidone	Treatment	6			no	Recovered	1
118	USA-34	Diabetes mellitus	Male	White	67	74.5	162.56	Risperidone	Open II				no	Not recovered	101
118	USA-34	Diabetes mellitus	Male	White	67	74.5	162.56	None	Post trial	0			no	Not recovered	101
113	USA-34	Hyperglycaemia	Male	White	80	79.5	175.26	Risperidone	Open II				no	Not recovered	79
113	USA-34	Hyperglycaemia	Male	White	80	79.5	175.26	None	Post trial	0			no	Not recovered	86
201	USA-5/USA-7	Hyperglycaemia	Male	Black	29	87.3	149.86	Risperidone	Open	6			no	Recovered	141
254	USA-6	Hypoglycaemia	Male	White	19	82.3	178	Risperidone	Open	12			no	Recovered	1
254	USA-6	Hypoglycaemia	Male	White	19	82.3	178	No drug	Post-treatment				no	Recovered	1
263	USA-6/USA-7	Diabetes mellitus	Male	Black	42	108.2	178	Risperidone	Open	4			no	Not recovered	
293	USA-6/USA-7	Diabetes mellitus	Female	White	49	93.6	170	Risperidone	Open	4			no	Not recovered	

CRF ID	TRIAL ID	Adverse event preferred term	Sex	Race	Age years	Weight kg	Height cm	Treatment	Trial phase	Onset date (mg)	Treatment duration	Action taken	SAB	Outcome	Duration in phase days
293	USA-6/USA-7	Diabetes mellitus	Female	White	49	93.6	170	Risperidone	Open				no	Not recovered	.
293	USA-6/USA-7	Diabetes mellitus	Female	White	49	93.6	170	No drug	Pre-treatment				no	Not recovered	.
626	USA-6/USA-7	Diabetes mellitus	Male	White	39	90.5	170.2	Risperidone	Open	4			no	Not recovered	.
626	USA-6/USA-7	Diabetes mellitus	Male	White	39	90.5	170.2	Risperidone	Open	4			no	Not recovered	.
712	USA-6/USA-7	Diabetes mellitus	Male	Black	37	90.7	173	Risperidone	Open	16			no	Not recovered	.
263	USA-6/USA-7	Hypoglycaemia	Male	Black	42	108.2	178	Risperidone	Open				no	Not recovered	.
263	USA-6/USA-7	Hypoglycaemia	Male	Black	42	108.2	178	No drug	Pre-treatment				no	Not recovered	.
810	USA-60	Diabetes mellitus	Female	Black	62	129.8	170.18	None	Pre trial				no	Not recovered	3
810	USA-60	Diabetes mellitus	Female	Black	62	129.8	170.18	Risperidone	Double-blind				no	Not recovered	28
810	USA-60	Hyperglycaemia	Female	Black	62	129.8	170.18	Risperidone	Pre trial				no	Not recovered	3
810	USA-60	Hyperglycaemia	Female	Black	62	129.8	170.18	Risperidone	Double-blind				no	Not recovered	28
902	USA-60	Hypoglycaemia	Female	White	41	57.7	165.1	Risperidone	Double-blind	6			no	Recovered	8
4011	USA-60	Hypoglycaemia	Male	Black	52	70.8		Risperidone	Double-blind	6			no	Recovered	3
A014	USA-64	Hyperglycaemia	Female	Black	68	61.7	147.32	Risperidone	Open	1			no	Not recovered	58
A080	USA-64	Hyperglycaemia	Female	Black	77	94.4	162.56	Risperidone	Open	1			no	Recovered	11
2916	USA-70	Diabetes mellitus	Female	Black	82	64	157.5	Risperidone	Open	0.25			yes	Recovered	5
210	USA-70	Hyperglycaemia	Male	Caucasian	90	53.6	167.6	None	Pre trial	--			no	Not recovered	92
210	USA-70	Hyperglycaemia	Male	Caucasian	90	53.6	167.6	Risperidone	Open				no	Not recovered	343
304	USA-70	Hyperglycaemia	Male	Caucasian	79	76.7	180.3	Risperidone	Open	0.25			no	Not recovered	16
808	USA-70	Hyperglycaemia	Female	Caucasian	78	59.5	160	Risperidone	Open	0.25			no	Recovered	5
904	USA-70	Hyperglycaemia	Female	Caucasian	87	47.7	154.9	Risperidone	Open	0.25			no	Recovered	6
904	USA-70	Hyperglycaemia	Female	Caucasian	87	47.7	154.9	Risperidone	Open	0.25			no	Not recovered	205
1101	USA-70	Hyperglycaemia	Female	Caucasian	92	58.6	149.9	Risperidone	Open	0.25			no	Not recovered	31
1219	USA-70	Hyperglycaemia	Male	Caucasian	60	79.5	172.7	Risperidone	Open	0.25			no	Not recovered	43
2004	USA-70	Hyperglycaemia	Female	Black	86	76.3	157.5	Risperidone	Open	0.25			no	Not recovered	88

CRF ID	TRIAL ID	Adverse event	Sex	Race	Age	Weight	Height	Treatment	Trial phase	Onset dose	Treatment	Action	SAB	Outcome	Duration in
RIS-		preferred term			years	kg	cm			(mg)	duration	taken			phase days
3307	USA-70	Hyperglycaemia	Male	Polynesian/ east	76	48.1	175.3	None	Post trial	0			no	Recovered	3
3309	USA-70	Hyperglycaemia	Female	Oriental	99	45.9	157.5	Risperidone	Open	0.25			no	Not recovered	121
3606	USA-70	Hyperglycaemia	Female	Black	82	82.6	165.1	Risperidone	Open	0.25			no	Not recovered	45
3909	USA-70	Hyperglycaemia	Male	Caucasian	76	79	167.6	None	Pre trial	-			no	Recovered	45
3909	USA-70	Hyperglycaemia	Male	Caucasian	76	79	167.6	Risperidone	Open				no	Recovered	130
4118	USA-70	Hyperglycaemia	Female	Caucasian	93	62.2	144.8	Risperidone	Open	0.25		DC	yes	Not recovered	3
4206	USA-70	Hyperglycaemia	Female	Caucasian	86	49.9	172.7	Risperidone	Open	0			yes	Not recovered	1
4220	USA-70	Hyperglycaemia	Male	Caucasian	82	83.5	182.9	Risperidone	Open	0.25			no	Recovered	1
2718	USA-70	Hypoglycaemia	Female	Caucasian	68	53.6	152.4	Risperidone	Open	0			no	Recovered	1
4210	USA-70	Hypoglycaemia	Female	Caucasian	80	44	160	Risperidone	Open	0.25			no	Recovered	9
253	USA-72	Hyperglycaemia	Male	Hispanic	27	85.8		Risperidone	Double-blind	8			no	Recovered	3
253	USA-72	Hyperglycaemia	Male	Hispanic	27	85.8		None	Post trial				yes	Recovered	10
253	USA-72	Ketosis	Male	Hispanic	27	85.8		Risperidone	Double-blind	8			no	Recovered	3
253	USA-72	Ketosis	Male	Hispanic	27	85.8		None	Post trial				no	Recovered	10
48	USA-79	Diabetes mellitus	Female	Black	35	94.4	165.1	Risperidone	Double-blind	4			no	Not recovered	261
54	USA-79	Diabetes mellitus	Male	White	36	109	177.8	Risperidone	Double-blind	4			yes	Not recovered	532
54	USA-79	Diabetes mellitus	Male	White	36	109	177.8	None	Post trial				yes	Not recovered	1
66	USA-79	Diabetes mellitus	Female	Black	41	96.7	165.1	Haloperidol	Double-blind	5			no	Not recovered	184
84	USA-79	Diabetes mellitus	Female	Hispanic	56	122.6	157.48	Haloperidol	Double-blind	20			yes	Recovered	33
302	USA-79	Diabetes mellitus	Male	Hispanic	46	103.5	177.8	Haloperidol	Double-blind	0			yes	Not recovered	114
302	USA-79	Diabetes mellitus	Male	Hispanic	46	103.5	177.8	None	Post trial				yes	Not recovered	1
468	USA-79	Diabetes mellitus	Male	American indian	37	129.4	182.88	Haloperidol	Double-blind	10			no	Not recovered	559
468	USA-79	Diabetes mellitus	Male	American indian	37	129.4	182.88	None	Post trial				no	Not recovered	1
555	USA-79	Diabetes mellitus	Female	White	30	98.5	162.56	Risperidone	Double-blind	4			no	Not recovered	167
555	USA-79	Diabetes mellitus	Female	White	30	98.5	162.56	None	Post trial				no	Not recovered	1
561	USA-79	Diabetes mellitus	Male	Hispanic	31	136.2	187.96	Haloperidol	Double-blind	2			no	Not recovered	1
561	USA-79	Diabetes mellitus	Male	Hispanic	31	136.2	187.96	Haloperidol	Double-blind				no	Not recovered	283
561	USA-79	Diabetes mellitus	Male	Hispanic	31	136.2	187.96	None	Post trial				no	Not recovered	1

CRFID	TRIAL ID	Adverse event	Sex	Race	Age	Weight	Height	Treatment	Trial phase	Onset dose	Treatment	Action	SAE	Outcome	Duration in
	RIS-	preferred term			years	kg	cm			(mg)	duration	taken			phase days
601	USA-79	Diabetes mellitus	Male	White	62	89.9	175.26	Risperidone	Double-blind	0			yes	Recovered	6
601	USA-79	Diabetes mellitus	Male	White	62	89.9	175.26	Risperidone	Double-blind	4			yes	Recovered	1
601	USA-79	Diabetes mellitus	Male	White	62	89.9	175.26	None	Post trial				yes	Recovered	14
174	USA-79	Glycosuria	Male	Hispanic	46	81.3	167.64	Risperidone	Double-blind	4			no	Recovered	13
73	USA-79	Hyperglycaemia	Male	Hispanic	35	81.7	167.64	Risperidone	Double-blind	6			no	Recovered	171
76	USA-79	Hyperglycaemia	Male	White	45	112.6	187.96	Haloperidol	Double-blind	15			no	Recovered	36
76	USA-79	Hyperglycaemia	Male	White	45	112.6	187.96	None	Post trial				no	Recovered	34
153	USA-79	Hyperglycaemia	Female	White	48	107.6	170.18	Risperidone	Double-blind	6			no	Recovered	35
174	USA-79	Hyperglycaemia	Male	Hispanic	46	81.3	167.64	Risperidone	Double-blind	4			no	Recovered	13
215	USA-79	Hyperglycaemia	Female	Black	58	79.9	170.18	Haloperidol	Double-blind	20			no	Recovered	15
215	USA-79	Hyperglycaemia	Female	Black	58	79.9	170.18	Haloperidol	Double-blind	20			no	Recovered	43
215	USA-79	Hyperglycaemia	Female	Black	58	79.9	170.18	Haloperidol	Double-blind	20			no	Recovered	8
295	USA-79	Hyperglycaemia	Male	Hispanic	44	72.6	167.64	None	Post trial	0			no	Recovered	22
295	USA-79	Hyperglycaemia	Male	Hispanic	44	72.6	167.64	None	Post trial	0			no	Not recovered	1
299	USA-79	Hyperglycaemia	Female	Hispanic	39	105.8	162.56	Risperidone	Double-blind	8			no	Not recovered	33
349	USA-79	Hyperglycaemia	Female	White	63	69.9	147.32	None	Post trial	0		DC	yes	Not recovered	1
366	USA-79	Hyperglycaemia	Male	White	41	77.2	175.26	Haloperidol	Double-blind	10			no	Recovered	29
380	USA-79	Hyperglycaemia	Male	White	39	88.1	175.26	Risperidone	Double-blind	4			no	Not recovered	202
380	USA-79	Hyperglycaemia	Male	White	39	88.1	175.26	None	Post trial				no	Not recovered	6
468	USA-79	Hyperglycaemia	Male	American indian	37	129.4	182.88		Pre trial				no	Recovered	6
468	USA-79	Hyperglycaemia	Male	American indian	37	129.4	182.88	Haloperidol	Double-blind				no	Recovered	1
468	USA-79	Hyperglycaemia	Male	American indian	37	129.4	182.88	Haloperidol	Double-blind				no	Recovered	197
555	USA-79	Hyperglycaemia	Female	White	30	98.5	162.56	Risperidone	Double-blind	4			no	Not recovered	194
555	USA-79	Hyperglycaemia	Female	White	30	98.5	162.56	None	Post trial				no	Not recovered	1
84	USA-79	Hypoglycaemia	Female	Hispanic	56	122.6	157.48	None	Post trial	0			no	Recovered	13
A3066	USA-97	Ketosis	Male	Caucasian	5	16	99.1	Risperidone	Open label	0.0719			no	Recovered	100

PHASE

Volume 1/Page 169

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D807.184

R. 6082

CRF ID	TRIAL ID	Adverse event preferred term	Sex	Race	Age years	Weight kg	Height cm	Treatment	Trial phase	Onset dose (mg)	Treatment duration	Action taken	SAB	Outcome	Duration in phase days
1															
A300030	INT-54	Glycosuria	Female	Caucasian	42	89.0	166	Risperidone	Treatment				no	na	

NB: Patients 4113 and 1204 in trial USA-63 died of non-glucose related adverse events. Patient #254 in trial USA-6 was hospitalized for a glucose-related adverse event but was recorded in the clinical database as having a serious adverse event. Patient #76 in trial USA-79 discontinued due the glucose-related adverse event of elevated glucose laboratory value but was not entered as discontinued in the clinical database. A narrative is provided for all patients who died and had a glucose-related adverse event, had a serious glucose-related adverse event, or discontinued treatment due to a glucose-related adverse event regardless of whether they were indicated as such in the electronic clinical database.

In the text, racial groups include the following types, Black= black; white= white and Caucasian; other= Asian, Oriental, Polynesian, American Indian, Hispanic, mixed, and other. DB = double-blind

Annex 1B: Patient listing of demographics and weight-increased adverse events in Phase 1 trials

Listing of patients with Weight Increase AEs

Trial ID	Adverse Event Preferred Term	CRF ID	Sex	Race	Age, Years	Weight, kg	Height, cm	Treatment	Randomisation Group	Trial Onset Phase	Dose	Duration of Treatment	AE Action Taken	AE Outcome	Duration in Phase
INT-54	GLYCOBURIA	A30003	FEMALE	CAUCASIAN	42	89.0	166	RISPERIDONE RIS25MG/RIS50MG	OPEN2				NONE	NOT YET RECOVERED	
INT-54	WEIGHT INCREASE	A30008	FEMALE	CAUCASIAN	38	90.0	175	RISPERIDONE RIS25MG/RIS50MG	OPEN1				NONE	NOT YET RECOVERED	
INT-54	WEIGHT INCREASE	A30011	MALE	CAUCASIAN	36	79.0	177	RISPERIDONE RIS25MG/RIS50MG	OPEN1				NONE	NOT YET RECOVERED	
INT-54	WEIGHT INCREASE	A30012	MALE	CAUCASIAN	49	79.0	170	RISPERIDONE RIS25MG/RIS50MG	OPEN1				NONE	NOT YET RECOVERED	
INT-54	WEIGHT INCREASE	A30023	FEMALE	CAUCASIAN	41	80.0	175	RISPERIDONE RIS25MG/RIS50MG	OPEN1				NONE	NOT YET RECOVERED	
INT-54	WEIGHT INCREASE	A30023	FEMALE	CAUCASIAN	41	80.0	175	RISPERIDONE RIS25MG/RIS50MG	OPEN2				NONE	NOT YET RECOVERED	
INT-54	WEIGHT INCREASE	A30028	MALE	CAUCASIAN	30	100.0	176	RISPERIDONE RIS25MG/RIS50MG	OPEN1				NONE	NOT YET RECOVERED	
INT-54	WEIGHT INCREASE	A30030	MALE	CAUCASIAN	35	103.0	192	RISPERIDONE RIS25MG/RIS50MG	OPEN1				NONE	NOT YET RECOVERED	
INT-54	WEIGHT INCREASE	A30032	MALE	CAUCASIAN	30	90.0	153	RISPERIDONE RIS25MG/RIS50MG	OPEN1				NONE	NOT YET RECOVERED	

Volume I/Page 171

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Annex 2A: Patient listing of concomitant medication and previous and concomitant disorders

CRF ID.	Trials	Who-preferred term	Adverse event (verbatim)	Phase	Drug	US TRIALS		Concomitant medication started before the date of the glucose-related adverse event	Cardio-vascular disorder history	Cardio-vascular disorder active	Endocrine disorder history	Endocrine disorder active
						Daily Dose at Onset (mg)	Days to onset					
48 ^{PC}	USA-79	Diabetes mellitus	Diabetes (new onset)	DB	Risperidone	4	85	robatussin, cough drops (cold, sore throat); tylenol (headache); albuterol (asthma); micronase (diabetes); amoxicillin (gum infection); iodine (gum pain)	no	na	no	na
54 ^{CV}	USA-79	Diabetes mellitus	Diabetes mellitus	DB	Risperidone	4	253	atenolol (htn); clonidine (htn); aspirin (headache); zestrin (htn)	yes	na	no	na
54	USA-79	Diabetes mellitus	Diabetes mellitus	POST	None							
66	USA-79	Diabetes mellitus	Diabetes	DB	Haloperidol	5	611	augmentin (tooth abscess); tylenol (lumbosacral pain); amaryl, norvasc started day of AE	no	na	no	na
73	USA-79	Hyperglycaemia	Increased blood sugar	DB	Risperidone	6	31	advil (headache)	no	na	no	na
76 ^{CV}	USA-79	Hyperglycaemia	Elevated glucose	DB	Haloperidol	15	365	none	yes	na	no	na
76	USA-79	Hyperglycaemia	Elevated glucose	POST	None							
84 ^{PC, CV}	USA-79	Diabetes mellitus	Diabetes	DB	Haloperidol	20	369	NPH insulin (diabetes); vasotec (htn); prempo (hormone suppl); ex-lax (constipation); tylenol (headache); glucophage (diabetes); amoxicillin (prophylaxis); hydrocodone (tooth pain); humulin insulin (diabetes); lipitor (cholest. prophylaxis); rezulin same day as AE	yes	na	yes	na
84	USA-79	Hypoglycaemia	Hospitalization for hypoglycemia	POST	None	0	442					
106	USA-63	Diabetes	Diabetes	TMT	Risperidone	1	28	multivitamin; docusate (constipation);	no	na	no	na

US TRIALS												
CRF ID.	Trials	Who-preferred term	Adverse event (verbatim)	Phase	Drug	Daily Dose at Onset (mg)	Days to onset	Concomitant medication started before the date of the glucose-related adverse event	Cardio-vascular disorder history	Cardio-vascular disorder active	Endocrine disorder history	Endocrine disorder active
		mellitus	mellitus					peridex rinse (oral hygiene)				
113 ^{PC,CV}	USA-34	Hyperglycaemia	Hyperglycemia	OPEN	Risperidone			hydrocortisone (dermatitis)	yes	na	yes	na
113	USA-34	Hyperglycaemia	Hyperglycemia	POST	None	0	28					
115 ^{PC,CV}	USA-63	Hypoglycaemia	Hypoglycemic episode	TMT < >	< Risperidone >	< 1 >	80	aspirin (stroke prevention); vasotec (htn); digoxin (CHF); propylthiouracil (hyperthyroid); chronulac (constipation); vit B12 (deficiency); duoderm, tolnaflate powder (sacral decubitus); sepra (UT); multivitamin; tylenol (pain); insulin (diabetes); dulcolax, fleets, MOM, pericelace, neoloid (constipation); synalar cream (decubitus)	yes	na	yes	na
115	USA-63	Hypoglycaemia	Hypoglycemic episode	POST	None							
118	USA-34	Diabetes mellitus	Diabetes (hyperglycemia)	OPEN	Risperidone			ipratropium, albuterol (COPD); acetaminophen (cellulitis); ascorbic acid (suppl); multivitamin; B complex; amoxicillin, epsom salts (skin infection)	no	na	no	na
118	USA-34	Diabetes mellitus	Diabetes (hyperglycemia)	POST	None	0	14					
153	USA-79	Hyperglycaemia	Hyperglycemia	DB	Risperidone	6	275	premarin, provera (ERT); cefzil (pharyngitis); ibuprofen (headache); zocor (hyperlipidemia), prilosec started day of AB	no	na	no	na
174	USA-79	Glycosuria	Glucose in urine	DB	Risperidone	4	531	iac-hydrin lotion (dry skin)	no	na	no	na
174	USA-79	Hyperglycaemia	Increase blood glucose	DB	Risperidone	4	531					
210	USA-63	Hyperglycaemia	Elevated glucose	PRE-	None	-	-8	verapamil (atrial fibrillation); lasix (diuretic); K-dur (suppl)				
210	USA-70	Hyperglycaemia	Elevated glucose	RUN	Placebo			verapamil (atrial fibrillation); lasix (diuretic); K-dur (suppl)	na	na	na	na

US TRIALS												
CRF ID.	Trials	Who-preferred term	Adverse event (verbatim)	Phase	Drug	Daily Dose at Onset (mg)	Days to onset	Concomitant medication started before the date of the glucose-related adverse event	Cardio-vascular disorder history	Cardio-vascular disorder active	Endocrine disorder history	Endocrine disorder active
210 ^{CV}	USA-70	Hyperglycaemia	Elevated glucose	TMT	Placebo							
210	USA-70	Hyperglycaemia	Elevated glucose	PRE	None	-	-92					
210	USA-70	Hyperglycaemia	Elevated glucose	OPEN	Risperidone							
215 ^{FC}	USA-79	Hyperglycaemia	Elevated glucose	DB	Haloperidol	20	253	norflex (arthritis pain); glipizide (diabetes); diclofenac (arthritis); pravachol (hyperlipidemia); lorabid (respiratory infection); naprelan (arthritis); bactrim, nystatin (lip infection); zocor (hyperlipidemia)	no	na	yes	na
215	USA-79	Hyperglycaemia	Elevated glucose	DB	Haloperidol	20	454					
215	USA-79	Hyperglycaemia	Elevated glucose	DB	Haloperidol	20	706					
253	USA-72	Hyperglycaemia	Increased blood sugar	DB<->	<Risperidone >	<8>	30	cogentin (EPS, akathisia); ativan (anxiety); nicorette (nicotine craving); mylanta (dyspepsia); prolixin (psychotic symptoms)	na	na	no	na
253	USA-72	Hyperglycaemia	Increased blood sugar	POST	None							
253	USA-72	Ketosis	Acetonaemia	DB<->	<Risperidone >	<8>	30					
253	USA-72	Ketosis	Acetonaemia	POST	None							
254	USA-6	Hypoglycaemia	Hospitalized hypoglycemia	OPEN	Risperidone	12	223	cogentin (EPS); ativan (anxiety); chloral hydrate (anxiety)	na	na	na	na
254	USA-6	Hypoglycaemia	Hospitalized hypoglycemia	POST	No drug							

CRF ID.	Trials	Who-preferred term	Adverse event (verbatim)	Phase	Drug	US TRIALS							
						Daily Dose at Onset (mg)	Days to onset	Concomitant medication started before the date of the glucose-related adverse event	Cardio-vascular disorder history	Cardio-vascular disorder active	Endocrine disorder history	Endocrine disorder active	
263	USA-6/USA-7	Diabetes mellitus	Hypoglycemia type II diabetes mellitus	OPEN	Risperidone	4	253	cogentin (stiffness)	na	na	na	na	
293 ^{CV}	USA-6/USA-7	Diabetes mellitus	(diabetes) NIDDM	OPEN	Risperidone	4	167	vasotec (htn edema); potassium chloride (replacement); digoxin (heart condition); lasix (edema); klonopin (agitation); ativan (agitation); chloral hydrate (insomnia)	na	na	na	na	
295 ^{FC}	USA-79	Hyperglycaemia	Increased glucose	POST	None	0	590	glucotrol (diabetes); maalox (stomach virus); pravachol (diabetes); erythromycin (pneumonia); glucophage (diabetes); baby aspirin (viral infection); ambien (sleep).	no	na	no	na	
295	USA-79	Hyperglycaemia	Increased glucose	POST	None	0	673						
299	USA-79	Hyperglycaemia	Increased glucose	DB	Risperidone	8	511	lao-hydrin lotion (dry skin)	no	na	no	na	
302	USA-79	Diabetes mellitus	Onset of diabetes	DB	Haloperidol	0	248	none	no	na	no	na	
302	USA-79	Diabetes mellitus	Onset of diabetes	POST	None								
304 ^{FC,CV}	USA-70	Hyperglycaemia	Increased blood sugar	OPEN	Risperidone	0.25	139	tylenol (pain); metoprolol, lasix (CAD); NPH insulin (diabetes); glycerine supp. (constipation); propulsid (upset stomach); isorbid (CAD); reg. Insulin (diabetes); lansoprazole (GI distress); MOM (constipation); maalox (upset stomach); dilacor, ASA (CAD); silvadene (skin ulcer); nitro (GI distress); paxil (depression); riopan, axid (upset stomach);	na	na	na	na	

US TRIALS												
CRF ID,	Trials	Who-preferred term	Adverse event (verbatim)	Phase	Drug	Daily Dose at Onset (mg)	Days to onset	Concomitant medication started before the date of the glucose-related adverse event	Cardio-vascular disorder history	Cardio-vascular disorder active	Endocrine disorder history	Endocrine disorder active
								omeprazole (GI distress); bacitracin (cellulitis); diabetic tussin (URI)				
349 ^{PC,CV}	USA-79	Hyperglycaemia	Pt lethargic hyperglycemia	POST	None	0	23	procardia (htn); glucophage, (diabetes), humulin (diabetes mellitus); vancomycin (rhinitis); mycelex (candidiasis); clindamycin, erythromycin, lotrimin, dopamine, heparin, dopamine, 0.9 nS, DSW started day of AE.	yes	na	yes	na
366 ^{PC}	USA-79	Hyperglycaemia	Elevated glucose	DB	Haloperidol	10	28	glyburide (Type II DM)	no	na	yes	na
380 ^{PC}	USA-79	Hyperglycaemia	Episodic hyperglycemia	DB	Risperidone	4	58	zantac (esophageal reflux); multivitamin; Vitamin B; phenergan (nausea/vomiting); percocet, darvocet, tylenol (post-surgical pain)	no	na	yes	na
380	USA-79	Hyperglycaemia	Episodic hyperglycemia	POST	None							
468 ^{CV}	USA-79	Diabetes mellitus	Diabetes	DB	Haloperidol	10	63	atenolol (high BP); lipid (high cholesterol); adalat, mevacor, glucotrol XL started on day of AE	yes	na	no	na
468	USA-79	Diabetes mellitus	Diabetes	POST	None							
468	USA-79	Hyperglycaemia	Clinically significant	PRE			-6					
468	USA-79	Hyperglycaemia	Glucose level	DB	Haloperidol							
468	USA-79	Hyperglycaemia	Glucose level	DB	Haloperidol							
555 ^{CV, a}	USA-79	Diabetes mellitus	Diabetes mellitus	DB	Risperidone	4	222	sulfatrin (infection); cephalaxin (folliculitis); pepto-bismol (nausea, vomiting, diarrhea); aspirin (pain); lipitor (increased cholesterol); dep-provera, micronor (hypothalamic depression);	yes	na	yes	na

US TRIALS												
CRF ID.	Trials	Who-preferred term	Adverse event (verbatim)	Phase	Drug	Daily Dose at Onset (mg)	Days to onset event	Concomitant medication started before the date of the glucose-related adverse event	Cardio-vascular disorder history	Cardio-vascular disorder active	Endocrine disorder history	Endocrine disorder active
								terazol (yeast infection); tussin, robatussin (cough)				
555	USA-79	Diabetes mellitus	Diabetes mellitus	POST	None							
555	USA-79	Hyperglycaemia	Increased glucose	DB	Risperidone	4	195					
555	USA-79	Hyperglycaemia	Increased glucose	POST	None							
561	USA-79	Diabetes mellitus	Diabetes	DB	Haloperidol	2	1	none	no	na	no	na
561	USA-79	Diabetes mellitus	Diabetes	DB	Haloperidol							
561	USA-79	Diabetes mellitus	Diabetes	POST	None							
601 ^{PC,CV}	USA-79	Diabetes mellitus	Uncontrolled diabetes mellitus	DB	Risperidone	0	123	insulin (DM); procordia (htn); actigal (gall stones)	yes	na	yes	na
601	USA-79	Diabetes mellitus	Uncontrolled diabetes mellitus	DB	Risperidone	4	364					
601	USA-79	Diabetes mellitus	Mellitus	POST	None							
626	USA-6/USA-7	Diabetes mellitus	Diabetes mellitus	OPEN	Risperidone	4	357	cimetidine (hernia reflux); tums, maalox (reflux); alupent, theodur, aminosyn (asthma); chloral hydrate (insomnia); afrin, dimetapp (nasal congestion); cold tablets (cough); doxycycline (sore throat); comtrex (cold)	na	na	na	na

US TRIALS												
CRF ID.	Trials	Who-preferred term	Adverse event (verbatim)	Phase	Drug	Daily Dose at Onset (mg)	Days to onset	Concomitant medication started before the date of the glucose-related adverse event	Cardio-vascular disorder history	Cardio-vascular disorder active	Endocrine disorder history	Endocrine disorder active
808 ^{PC,CV}	USA-70	Hyperglycaemia	Hyperglycemia	OPEN	Risperidone	0.25	125	ASA (vascular insufficiency); synthroid (hypothyroid); tylenol (pain); MOM (constipation); darvocet (pain); chloral hydrate (insomnia); insulin, glyburide (diabetes); levothyroxine (hypothyroid); flu shot; bacitracin (scrape)	na	na	na	na
810	USA-60	Diabetes mellitus	NIDDM (nerv onset)	PRE	None	.	-3	none	yes	na	no	na
810 ^{PC,CV}	USA-60	Diabetes mellitus	NIDDM (nerv onset)	DB	Risperidone							
810	USA-60	Hyperglycaemia	Increased glucose	PRE	Risperidone	.	-3					
810	USA-60	Hyperglycaemia	Increased glucose	DB	Risperidone							
902 ^a	USA-60	Hypoglycaemia	Hypoglycemia (low serum glucose)	DB	Risperidone	6	14	lorazepam (anxiety/insomnia); habitrol (nicotine replacement); loxoxyl (thyroid replacement); tylenol (menstrual cramps); zantac (nausea); fibercon (diarrhea); Kaopectate, imodium (loose stools);	no	na	yes	na
90 ^{CV}	USA-70	Hyperglycaemia	Hyperglycemia (249)	OPEN	Risperidone	0.25	136	Kaopectate (diarrhea); bisacodyl, MOM (constipation); tylenol (pain/fever); potassium (replacement); coumadin (aortic valve replaced); lasix (htn); axid (peptic ulcer disease); O2 (hypoxia); fibercon (constipation); procardia (htn); vantin (pneumonia); fleets (constipation); biacin, ceftin (pneumonia); tobrex (eye infection); rocephin (pneumonia)	na	na	na	na
904	USA-70	Hyperglycaemia	Hyperglycemia (198) NIDDM	OPEN	Risperidone	0.25	162					

US TRIALS												
CRF ID.	Trials	Who-preferred term	Adverse event (verbatim)	Phase	Drug	Daily Dose at Onset (mg)	Days to onset	Concomitant medication started before the date of the glucose-related adverse event	Cardio-vascular disorder history	Cardio-vascular disorder active	Endocrine disorder history	Endocrine disorder active
911 ^{PC,CV}	USA-63	Hyperglycaemia	Hyperglycemia	TMT	Placebo	0.25	5	catapress, lopressor (htn); surfak (constipation); digoxin (CHF); multivitamin, vitamin C (suppl); humulin R (IDDM); propulsid (gastritis); ASA (CAD); nitropatch (htn); micro-K (suppl); econopred (eye infection); cardura (htn)	yes	na	yes	na
1007 ^{CV}	USA-63	Hyperglycaemia	Increased blood sugars (>200) intermitte	TMT	Placebo	0.5	66	docusate (stool softener); metipronellil (glaucoma); hydrocortisone cream, zinc oxide (rash); chloral hydrate (sleep); acetaminophen (pain/fever); multivitamin; benazepril (htn); bacitracin; novahistine (cough)	yes	na	no	na
1101 ^{CV}	USA-70	Hyperglycaemia	Incr abn glucose	OPEN	Risperidone	0.25	167	tylenol (pain); ASA (S/P.CVA); dioctyl, fleet, MOM, metamucil (constipation); vicodin (pain)	na	na	na	na
1204 ^{PC}	USA-63	Coma diabetic	Diabetic coma	TMT	Risperidone	0.5	13	lactulose; fleets; kaexalate (hyperkalemia); insulin (diabetes)	no	na	yes	na
1204	USA-63	Coma diabetic	Diabetic coma	POST	None							
1204	USA-63	Hyperglycaemia	Hyperglycemia -hospitalized	TMT	Risperidone	0.5	13					
1204	USA-63	Hyperglycaemia	Hyperglycemia -hospitalized	POST	None							
1212 ^{PC,CV}	USA-63	Diabetes mellitus aggravated	Fluctnating blood sugars	TMT	Risperidone	2	61	enteric aspirin (prophylaxis); clotrimazole (rash); ranitidine (stomach distress); tylenol (pain); insulin (diabetes); senna (constipation)	yes	na	yes	na

US TRIALS												
CRF ID.	Trials	Who-preferred term	Adverse event (verbatim)	Phase	Drug	Daily Dose at Onset (mg)	Days to onset	Concomitant medication started before the date of the glucose-related adverse event	Cardio-vascular disorder history	Cardio-vascular disorder active	Endocrine disorder history	Endocrine disorder active
1219 ^{PC,CV}	USA-70	Hyperglycaemia	Fluctuating blood sugar	OPEN	Risperidone	0.25	140	lasix (CHF); insulin (IDDM); quinapril (CAD); polysporin, collagenase, zinc ointment, neosporin, Carrington's gel, A&D ointment (healing); semma, colace, Fleet's (constipation); tylenol (pain); coumadin (impaired hemodynamics); dicloxacillin (cellulitis); salsalate (pain); potassium chloride (replacement); percocet (pain);	na	na	na	na
1712 ^{CV,*}	USA-63	Hyperglycaemia	Hyperglycemia	TMT	Risperidone	1	6	petrolatum (car protection); monistat powder (skin irritation); tapazole (hyperthyroid); zantac (erosive esophagus); PPD (diagnostic)	yes	na	yes	na
1712	USA-63	Plasma osmolality increased	Increase serum osmolality	TMT	Risperidone	1	6					
2004 ^{CV}	USA-70	Hyperglycaemia	Increased blood sugar	OPEN	Risperidone	0.25	86	zantac (prevent GI bleed); aspirin (prophylaxis); docusate (constipation); digoxin (atrial fibrillation); enteric aspirin (prevent MI); furosemide (CHF); ferrous sulfate (anemia); tylenol (pain)	na	na	na	na
2201 ^{PC,CV}	USA-63	Diabetes mellitus aggravated	Physician noted diabetes worse	TMT	Risperidone	2	62		yes	na	yes	na
2201	USA-63	Hyperglycaemia	Increased glucose	OPEN	Risperidone	6	324					
2216 ^{PC}	USA-63	Hyperglycaemia	Elevated blood sugar	TMT	Risperidone	1	9	sulfa-trimethaprin (UTI); bisacodyl, docusate, MOM (constipation); acetaminophen (pain); Greer's goo, lubriderm (fragile skin); calcium carbonate, glyburide (diabetes)	no	na	yes	na

Response to FDA Request for Information : Evaluation of the Effect of Risperidone on Glucose Metabolism
Evaluation of glucose metabolism with risperidone

US TRIALS												
CRF ID.	Trials	Who-preferred term	Adverse event (verbatim)	Phase	Drug	Daily Dose at Onset (mg)	Days to onset	Concomitant medication started before the date of the glucose-related adverse event	Cardio-vascular disorder history	Cardio-vascular disorder active	Endocrine disorder history	Endocrine disorder active
2613 ^{PC,CV}	USA-63	Hyperglycaemia	Increased blood glucose	TMT	Risperidone	2	29	pepcid (ulcer); tylenol (headache/fever); diabeta (diabetes); cytotec, Motrin (pain); eliminite (scabies);	yes	na	yes	na
2718	USA-70	Hypoglycaemia	One-time fbs of 59 etiology unknown	OPEN	Risperidone	0	36	MOM, bisacodyl, senokot (constipation); acetaminophen (pain); amoxicillin (UTI); multivitamin; betagen (glaucoma)	na	na	na	na
2916 ^{PC}	USA-70	Diabetes mellitus	Diabetes mellitus	OPEN	Risperidone	0.25	15	humulin (insulin)	na	na	na	na
3307 ^{CV}	USA-70	Hyperglycaemia	Elevated glucose	POST	None	0	443	docusate, dulcolax (constipation); adalat (htn); tagamet (GI bleeding); ensure, probalance (suppl); proscar, hytrin (BPH); tylenol (fever); O2 (shortness of breath); clindamycin, rocephin (pneumonia); capoten (htn); kaopectate (diarrhea); robatussin (cough); benadryl (insomnia); flu vaccine; resinol (excoriation); duoderm (redness)	na	na	na	na
3309	USA-70	Hyperglycaemia	Elevated serum glucose	OPEN	Risperidone	0.25	240	antifungal, lotrisone (perineal rash); Fleet's enema, MOM (constipation); ensure (suppl); duoderm (open area)	na	na	na	na
3513 ^{CV}	USA-63	Hyperglycaemia	Elevated blood sugar	TMT	Risperidone	1	54	niacalcin, calcium carbonate (osteoporosis); multivitamin; bacitracin (skin tears); robatussin (pneumonia); tylenol (pain); senna (constipation); ferrous sulfate (anemia); baby aspirin (valvular h.d.); augmentin (pneumonia)	yes	NA	no	na
3606	USA-70	Hyperglycaemia	Increased blood sugar	OPEN	Risperidone	0.25	292	multivitamin; acetaminophen (pain); erythromycin (tooth extraction); novocaine, carbocaine (pain tooth	na	na	na	na

Response to FDA Request for Information : Evaluation of the Effect of Risperidone on Glucose Metabolism
Evaluation of glucose metabolism with risperidone

US TRIALS													
CRF ID.	Trials	Who-preferred term	Adverse event (verbatim)	Phase	Drug	Daily Dose at Onset (mg)	Days to onset	Concomitant medication started before the date of the glucose-related adverse event	Cardio-vascular disorder history	Cardio-vascular disorder active	Endocrine disorder history	Endocrine disorder active	
								extraction); acetaminophen (pain)					
3903 ^{CV}	USA-63	Hyperglycaemia	Elevated glucose	TMT	Risperidone	2	64	docusate, cascara, magnesium sulfate (constipation); tylenol (pain); maalox (indigestion); flu vaccine same day as AE	yes	na	no	na	
3903	USA-63	Hyperglycaemia	Elevated glucose	POST	None								
3906 ^{CV}	USA-63	Hypoglycaemia	Low blood glucose	TMT	Risperidone	1	29	lovastatin (hyperlipidemia); furosemide (rales); dipivefrin, betaxolol (glaucoma); ensure (suppl); docusate (constipation); potassium chloride (rales); tylenol (pain)	yes	na	no	na	
3909	USA-70	Hyperglycaemia	Elevated blood glucose	TMT	Risperidone	2	63	docusate, psyllium, sorbitol (constipation); tylenol (pain/fever)	na	na	na	na	
3909 ^{CV}	USA-63	Hyperglycaemia	Elevated blood glucose	PRE	None	--	-45	[docusate, psyllium, sorbitol] ciprofloxacin, clotrimazole (UTI)	yes	na	no	na	
3909	USA-63	Hyperglycaemia	Elevated blood glucose	OPEN	Risperidone								
4011 ^{CV}	USA-60	Hypoglycaemia	Low serum glucose	DB	Risperidone	6	4	ativan (agitation); tylenol (headache)	yes	na	no	na	
4013 ^{PCCV}	USA-63	Hyperglycaemia	Increased blood sugar dx diabetes	TMT	Risperidone	0.5	3	tylenol (pain/fever); MOM (constipation); Micro-K (suppl); cardizen (hta); natural tears (dry eyes); imodium (loose stools); levisen (nausea/vomiting); nitrostat (chest pain); acetefed (rhinids); excedrin PM (pain); vitamin B12 (anemia); docusate (constipation); zantac (epigastric pain); ASA (pain)	yes	na	yes	na	
4014 ^{PCCV}	USA-63	Diabetes mellitus	Diabetes out of control	TMT	Risperidone	0.5	3	humulin (insulin); nitrobid (angina); micro-K (potassium); lasix (diuretic); dipyridamole (ITBP); ASA (blood	yes	na	yes	na	

US TRIALS												
CRF ID.	Trials	Who-preferred term	Adverse event (verbatim)	Phase	Drug	Daily Dose at Onset (mg)	Days to onset	Concomitant medication started before the date of the glucose-related adverse event	Cardio-vascular disorder history	Cardio-vascular disorder active	Endocrine disorder history	Endocrine disorder active
								thinner); micronase (diabetes); propranolol (HBP)				
4113 ^{CV,PC}	USA-63	Hyperglycaemia	Hyperglycemia	TMT<	<Placebo>	<0.25>	9	centrum, ferrous sulfate (suppl); darvocet (pain); synthroid (hypothyroid); debrox (ear wax impaction)	yes	na	yes	na
4118 ^{CV}	USA-7	Hyperglycaemia	Hyperglycemia	OPEN	Risperidone	0.25	282	lanoxin (proximal atrial fibrillation); oxidstat (fungal); triamcinolone (rash); aspirin (prophylaxis); metrogel (erythema); teargen, refresh (dry eyes); pepcid (peptic ulcer disease); ocular vitamins, K-dur (na); MOM (constipation); tetracycline (psoriasis); nizoral (seborrhea); flu shot; zantac (peptic ulcer disease); tylenol (fever); neosporin (skin tears); lasix (edema); aclovate (erythema); septri (UTI)	na	na	na	na
4206	USA-7	Hyperglycaemia	Hyperglycemia (hospitalized)	OPEN<	<Risperidone	<0>	101	multivitamin; natural tears (dry eyes); relafen (antacid)	na	na	na	na
4210 ^{CV}	USA-7	Hypoglycaemia	Low blood sugar of 48	OPEN	Risperidone	0.25	2	digoxin (heart disease); alamag (indigestion); MOM (constipation); acetaminophen (pain/fever)	na	na	na	na
4220 ^{PC,CV}	USA-7	Hyperglycaemia	Elevated glucose	OPEN	Risperidone	0.25	1	aspirin (coronary atherosclerosis); triamcinolone (rash); doxycycline (skin disorder); cod liver oil (Alzheimer's disease); diabeta (DM)	na	na	na	na
5263 ^{PC}	USA-7	Hypoglycaemia	Hypoglycemia (type II diabetes mellitus)	PRE-	No drug		0	insulin (hypoglycemia)	na	na	na	na
5263	USA-7	Hypoglycaemia	Hypoglycemia (type II diabetes)	OPEN	Risperidone							

CRF ID.	Trials	Who-preferred term	Adverse event (verbatim)	Phase	Drug	US TRIALS							
						Daily Dose at Onset (mg)	Days to onset	Concomitant medication started before the date of the glucose-related adverse event	Cardio-vascular disorder history	Cardio-vascular disorder active	Endocrine disorder history	Endocrine disorder active	
5293 ^{FC,CV}	USA-7	Diabetes mellitus	mellitus) NIDDM (diabetes)	PRE-	No drug		0	potassium (potassium replacement); digoxin (heart condition); lasix (edema); ativan (agitation); glucotrol (diabetes)	na	na	na	na	
5293	USA-7	Diabetes mellitus	NIDDM (diabetes)	OPEN	Risperidone								
5626	USA-7	Diabetes mellitus	Diabetes mellitus (adult onset)	OPEN	Risperidone	4	13	none	na	na	na	na	
5712	USA-7	Diabetes mellitus	Diabetes mellitus	OPEN	Risperidone	16	667	colace (constipation); maalox (heartburn); cortisporin (ear infection); bleph-10 (eye infection); vasocon (eye infection)	na	na	na	na	
119202	USA-54	Blood sugar increased	Increased blood sugar					NA					
124501	USA-54	Blood sugar increased	Blood sugar increase 300					NA					
A014	USA-64	Hyperglycaemia	Increase blood glucose	OPEN	Risperidone	1	28	thioridazine (psychosis); tylenol (pain); propine (glaucoma); truspot (glaucoma); levobunolol (glaucoma); benadryl (bradykinesia)	no	na	no	na	
A080 ^{FC,CV}	USA-64	Hyperglycaemia	High blood sugar	OPEN	Risperidone	1	1	glucotrol (diabetes); vasotec (htn); procordia, insulin day of AE	yes	na	yes	na	
A30030 ^{FC,CV}	USA-102	Diabetes mellitus	Uncontrolled diabetes	TMT1	Placebo	0	11	procordia (htn); lasix (htn); pepcid (gastritis); vasotec (htn); clonidine (htn); colace (constipation); cogenin (EPS)	yes	yes	yes	yes	
A30030	USA-102	Diabetes mellitus	Uncontrolled diabetes	POST	None								
A30053	USA-102	Hyperglycaemia	Increased glucose level	TMT3	Risperidone	0	93	lorazepam (agitation/insomnia);	no	no	no	no	
A30065 ^{CV}	USA-102	Hyperglycaemia	Hyperglycemia	TMT1	Haloperidol	2	21	ferrous sulfate (anemia); tobramycin (eye	yes	no	no	no	

US TRIALS												
CRF ID.	Trials	Who-preferred term	Adverse event (verbatim)	Phase	Drug	Daily Dose at Onset (mg)	Days to onset	Concomitant medication started before the date of the glucose-related adverse event	Cardio-vascular disorder history	Cardio-vascular disorder active	Endocrine disorder history	Endocrine disorder active
								infection); chloral hydrate (insomnia); simethicone (dyspepsia); magnesium citrate (constipation)				
A30065	USA-102	Hyperglycaemia	Hyperglycemia	POST	None							
A30167 ^{FC}	USA-112	Hyperglycaemia	Elevated blood sugar	TMT	Risperidone	4	6	cogentin (EPS); acetaminophen (pain); alivan (agitation/anxiety); glucotrol (NIDDM); wellbutrin (depression)	no	no	yes	yes
A30191 ^{FC,CV}	USA-112	Hyperglycaemia	Inc glycohemoglobin a1c	TMT	Risperidone	2	58	dulcolax (constipation); multivitamin (anemia); mycellex ointment (dermatitis); hytrin (BPH); lac-hytrin (dermatitis)	yes	no	yes	no
A30192 ^{FC,CV}	USA-112	Hyperglycaemia	Hyperglycemia	TMT	Risperidone	4	58	nitro-dur (ASHD); lasix (hta); glucotrol XL (DM)	yes	yes	yes	yes
A30195 ^{FC}	USA-112	Hyperglycaemia	Hyperglycemia	PRE	None	--	-8	cogentin (EPS); glucotrol (DM); lopid (hypercholesterolemia)	no	no	yes	yes
A30195	USA-112	Hyperglycaemia	Hyperglycemia	TMT	Olanzapine							
A30217 ^{FC}	USA-112	Hyperglycaemia	Elevated blood sugar	TMT	Risperidone	4	1	ferrous sulfate (hospital requirement); micronase (diabetes)	no	no	yes	yes
A30226 ^{FC}	USA-102	Hyperglycaemia	Elevated glucose	TMT	Placbo	0	5	insulin (diabetes); tylenol (pain); multivitamin (suppl); lorazepam (agitation)	no	no	yes	yes
A30251 ^{FC}	USA-112	Glycosuria	Elevated urine glucose	TMT	Olanzapine	0	43	SMZ-TMP (chest congestion); glucotrol (diabetes); pseudoephedrine guaifensin (chest congestion)	no	no	yes	yes
A30251	USA-112	Hyperglycaemia	Elevated glycohemoglobin	TMT	Olanzapine	0	43					
A30350	USA-112	Hyperglycaemia	Elevated glycohemoglobin	PRE	None	--	-1	none	no	no	no	no
A30350	USA-112	Hyperglycaemia	Elevated	TMT	Olanzapine							

Response to FDA Request for Information: Evaluation of the Effect of Risperidone on Glucose Metabolism
Evaluation of glucose metabolism with risperidone

US TRIALS												
CRF ID.	Trials	Who-preferred term	Adverse event (verbatim)	Phase	Drug	Daily Dose at Onset (mg)	Days to onset	Concomitant medication started before the date of the glucose-related adverse event	Cardio-vascular disorder history	Cardio-vascular disorder active	Endocrine diorder history	Endocrine diorder active
			glycohemoglobin									
A30374 ^{PC, CV}	USA-112	Diabetes mellitus	Diabetes mellitus	PRE	None	—	4	benadryl (sleep); aspirin (prophylaxis); levothyroxine (hypothyroid); metformin (NIDDM); vitamin E (antioxidant); glyburide (NIDDM); flurazepam (sleepless); lorazepam (anxiety); clonazepam (agitation); simvastatin (hyperlipidemia)	yes	yes	yes	yes
A30374	USA-112	Diabetes mellitus	Diabetes mellitus	TMT	Risperidone							
A30394 ^{PC, CV}	USA-112	Hypoglycaemia	Hypoglycaemia	TMT	Risperidone	6	19	insulin (diabetes); procordia (htn)	yes	yes	yes	yes
A30419 ^{PC}	USA-112	Hyperglycaemia	High blood sugar for 2 weeks	TMT	Risperidone	4	14	ASA (prophylaxis); glucophage, insulin (diabetes); zocor (lower cholesterol); roxulin (diabetes)	no	no	yes; diabetes	yes
A3066	USA-97	Ketosis	Ketonuria	OPEN	Risperidone	0.071	190	ritalin (ADHD); vistaril (sleep initiation difficulty)	na	na	na	na
2201	USA-5/USA-7	Hyperglycaemia	Elevated blood sugar	TMT	Risperidone	4	44					

PC = pre-existing condition of diabetes as indicated by history of glucose-related or unspecified endocrine disorder and/or by use of concomitant medication for glucose-related condition prior to onset of the first glucose-related adverse event, CV = pre-existing cardiovascular condition.

na=not available, htn=hypertension, hx=medical history, BPH=benign prostatic hyperplasia, CHF=congestive heart failure, UTI=urinary tract infection, ERT=estrogen replacement therapy, AE=adverse event, K-DUR=potassium supplement, EPS=extrapyramidal symptoms, CAD=coronary arterial disease, NPH=type of insulin medication, GI=gastrointestinal, MOM=Milk of Magnesia, URI=upper respiratory infection, DM=diabetes mellitus, IDDM=insulin-dependent diabetes mellitus, CVA=cardiovascular disease, HBP=high blood pressure, ASHD=arteriosclerotic heart disease, ADHD=attention deficit/hyperactivity disorder.

a: Patient had a history of endocrine disorder, unspecified, and concomitant medication suggested an endocrine condition other than glucose abnormalities.

Annex 2B: Patient listing of concomitant medication and previous and concomitant disorders

NON-US TRIALS									
CRF ID	Trial ID	Adverse event preferred term	Adverse event (verbatim)	Phase	Treatment	Daily Dose at Onset (mg)	Days to onset	Concomitant medications (disorder) at any time	Concomitant disease or history
A03142 ^{PC}	GBR-29	Glycosuria	--	--	Risperidone			lithium carbonate (anti-manic mood stabilizer); fluoxetine hydrochloride (depressive episode); cetirizine hydrochloride (hayfever); canesten-HC (fungal rash); cimetidine-octapressin (tooth extraction); fluvirina (influenza vaccine); sudocrem (sore nose); paracetamol (pain from dental treatment)	Concomitant hypertension, glycogen synthetase deficiency, short of breath on exertion, obesity
267	INT-10	Hypoglycaemia	Hypoglycaemia	DB	Risperidone	8		Akineton (extrapyramidal symptoms); lepticur (extrapyramidal symptoms); lutenyl (menorrhagia) rivotril (anxiety)	History of hyponatremia, leucocytosis, scarlatina, tachycardia
1069 ^{PC, CV}	INT-2	Hyperglycaemia	--	--	Placebo	0 mg		Aspirin (fever); ASS and embolism (thrombosis risk); dydile and furesis (heart dis. congestive); glibenclamide (diabetes mellitus); insulin (hyperglycaemia); lorazepam (insomnia and restlessness); nifedipin (hypertension); pentoxifylline (PVD); reparyl (hypertension)	History of diabetes mellitus type II B, cardiac insufficiency oedema and peripheral circulatory disorder
A00118 ^{PC, CV}	INT-23	Diabetes mellitus	Hospitalized due to diabetes mellitus	Open	Risperidone			Isosorbide monon., digiloxin, acetylsalicylic acid and felodipine (cardiac insufficiency); isosorbide dinit. (coronary heart disease); pizotifen (lack of appetite); haloperidol (schizophrenia); insulin intern. act., acarbose and glibenclamide (diabetes mellitus);	Concomitant cardiac insufficiency, diabetes mellitus IIb; history of recurrent retroauricular exanthema
A00367	INT-23	Hypoglycaemia	Hypoglycaemia	Open	Risperidone			Orphenadrine (EPS); haloperidol (schizophrenia); povidone-iodine and sulfadiazine silver (first degree burn on nose); silicon and tetracycline (self-inflicted scratches); nitrazepam (insomnia); oxazepam (agitation); bisacodyl (constipation); paracetamol (headache);	Concomitant BHP, arteriosclerotic chr. vertebro cerebellar insufficiency, constipation, enlargement of right thyroid lobe, intermittent headache, s/p gastrectomy (subtotal) due to duodenal ulcer, s/p prostatectomy, scoliosis; history of bronchopneumonia, iron deficiency anaemia, TBC of lungs
165 ^{CV}	INT-24	Hyperglycaemia	Increased glucose	Treatment	Haloperidol	1.75	43+ days	Temesta (anxiety); nitrong (angina pectoris); propavan (insomnia); trombyl (prophylaxis); blocadren (glaucoma); behepan (B 12 decrease); lactulose (constipation)	Concomitant constipation, angina pectoris, B 12 decrease substitution, glaucoma

NON-US TRIALS									
CRF ID	Trial ID	Adverse event preferred term	Adverse event (verbatim)	Phase	Treatment	Daily Dose at Onset (mg)	Days to onset	Concomitant medications (disorder) at any time	Concomitant disease or history
450	INT-24	Hyperglycaemia	Hyperglycemia	Treatment	Risperidone	0.25	43+ days	Fluzone (flu prophylaxis)	None
170	INT-24	Hypoglycaemia	Low level of glucose	Treatment	Placebo	1.5	43+ days	Selexid (urinary tract infection); waran (autoimmune haemolytic anemia lung emboli); folacin (folic acid decrease); levaxin (hypothyroidism); prednisolone (autoimmune haemolytic anemia lung emboli); zantac (duodenal ulcer)	Concomitant hypothyroidism, duodenal ulcer, lung emboli, urinary tract infection, haemolytic anemia (autoimmune)
A00469 ^{PC}	INT-26	Hyperglycaemia	High blood glucose	Follow up	Risperidone			Erythromycin stearate (aspiration pneumonia); chloramphenicol (eye irritation and redness); betamethasone (scalp irritation); folic acid (low serum folate); ferrous gluconate (low haemoglobin, iron); lorazepam (agitation and/or aggression); glucagon (hypoglycaemia); metformin (diabetes); glibenclamide (high blood sugar); sodium phosphates (constipation); erythromycin (left lower lobe pneumonia); paracetamol (breakthrough discomfort, osteoarthritis); acetylsalicylic acid (osteoarthritis); polyvinyl alcohol (eye irritation); amoxicillin (aspiration pneumonia/urin; influenza vaccine (flu prevention)	Concomitant blind left eye, 2nd chronic process, p/ catar, Sx, cataract R eye, non-insulin dependent diabetes, osteoarthritis, tardive dyskinesia; history of prostate cancer (surgery in 1990)
25	INT-4	Diabetes	Diabetes	Follow up	Risperidone	6 mg		None	None
252	INT-4	Diabetes	Hyperglycaemia	Follow up	Risperidone	12 mg		Daonil (diabetes mellitus)	None
365	INT-4	Diabetes	Diabetes	Follow up	Risperidone	4 mg		Euglycon and glibenclamide (hyperglycaemia);	None
A30577 ^{PC}	INT-45	Diabetes mellitus	--	--	Olanzapine			Zopiclone (insomnia); paracetamol (headache, sore throat, common cold); bisacodyl (constipation)	Concomitant insomnia; history of hyperglycaemia, post menopausal bleeding
A30094 ^{PC,CV}	INT-45	Hyperglycaemia	--	--	Risperidone			Oxazepam (anxiety); thioridazine hydrochloride (schizophrenia); acetylsalicylic acid (thrombosis cerebral); insulin human injection, insulin isophane (diabetes mellitus); tetrazoline hydrochloride (conjunctivitis); sodium picosulfate (constipation); ferrous sulfate and multi-kalkki (general health)	Concomitant diabetes mellitus (stable) and conjunctivitis intermittent; history of anaemia, spinal stenosis operated '83, thrombosis cerebral '93, dysarthria dyspraxia

NON-US TRIALS									
CRF ID	Trial ID	Adverse event preferred term	Adverse event (verbatim)	Phase	Treatment	Daily Dose at Onset (mg)	Days to onset	Concomitant medications (disorder) at any time	Concomitant disease or history
A30142 PC,CV	INT-45	Hyperglycaemia	--	--	Risperidone			Insulin, insulin isophane (diabetes mellitus); Lisinopril (hypertonia); temazepam (insomnia); perphenazine (schizophrenia); redol comp. (cough); clobutanol hydrochloride (cough); propranolol (tachycardia); paracetamol (fever); cefcroxime sodium (pneumonia); pentoxifyverine citrate (cough); lactulose (constipation); furosemide (Insul. cordis due to pneumonia); miconazole nitrate (tinea pedis); cefalexin monohydrate (pneumonia); sodium picosulfate (constipation)	Concomitant diabetes, retinopathy, diabetica, hypertension and bronchitis cough; history of abscessus perianalis and pyelonephritis URI
429 ^{PC}	INT-6	Acidosis	Stomach acidity	DBPG	Risperidone	15 mg		Loperamide (diarrhoea); norfloxacin (urinary tract infection); chloral hydrate (insomnia, anxiety); metformin (diabetes); glibenclamide (diabetes); bisacodyl (constipation); docusate sodium (constipation); diclofenac (back pain); phenoxymethylpenicillin (tooth infection)	Concomitant diabetes, infection
146	INT-9	Diabetes mellitus	--	--	Remoxipride	600 mg		Disipal (akathisia and stiffness); euglucon (diabetes); nitrazepam (insomnia)	History of commotio (concussion) at the age of 14
A30003	INT-54	Glycosuria	Elevated urine glucose	--	Risperidone	50 mg (depot)		Praxiten (anxiety); olicard (angina pectoris); fluphenazine (schizophrenia)	Not available

PC: Pre-existing condition of diabetes or abnormality of glucose-metabolism. CV: pre-existing cardiovascular condition. Those concomitant medications listed are for disorders that occurred at anytime. The disorders indicated in bold type are those treated before the occurrence of the glucose-related adverse event. Cardiovascular diseases treated with concomitant medications are also indicated in bold type.

Annex 3: Patient listing of abnormal laboratory glucose values under fasting conditions in Phase 1 trials

TRIAL=BEI-34 Patient=5 Laboratory test=Glucose

	VISIT	Measurement	Unit of measurement	Lower limit	Upper limit	ABNORMALITY CODE
2	1	102	mg/dl	75	115	B
	3	24	mg/dl	75	115	
	4	78	mg/dl	75	115	
	5	103	mg/dl	75	115	

TRIAL=BEI-34 Patient=6 Laboratory test=Glucose

	VISIT	Measurement	Unit of measurement	Lower limit	Upper limit	ABNORMALITY CODE
	1	65	mg/dl	76	110	B
	2	87	mg/dl	76	110	
	3	97	mg/dl	76	110	
	4	97	mg/dl	76	110	
	5	93	mg/dl	76	110	

TRIAL=INT-25 Patient=1 Laboratory test=Glucose

	VISIT	Measurement	Unit of measurement	Lower limit	Upper limit	ABNORMALITY CODE
	1	138	mg/dl	75	105	A
	8	131	mg/dl	75	105	
	10	126	mg/dl	75	105	
	12	113	mg/dl	75	105	
	14	128	mg/dl	75	105	
	16	107	mg/dl	75	105	

Volume I/Page 195

JJRP/rev 00380072

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D807.210

R. 6108

TRIAL=INT-25 Patient=7 Laboratory test=Glucose

VISIT	Measurement	Unit of measurement	Lower limit	Upper limit	ABNORMALITY CODE
1	59	mg/dl	76	110	B
8	80	mg/dl	76	110	
10	118	mg/dl	76	110	A
12	129	mg/dl	76	110	A
14	125	mg/dl	76	110	A
16	69	mg/dl	76	110	B

TRIAL=INT-25 Patient=9 Laboratory test=Glucose

VISIT	Measurement	Unit of measurement	Lower limit	Upper limit	ABNORMALITY CODE
1	80	mg/dl	76	110	
8	79	mg/dl	76	110	
10	77	mg/dl	76	110	
12	77	mg/dl	76	110	
14	74	mg/dl	76	110	B
16	72	mg/dl	76	110	B

JRF--TRIAL RIS-USA-111

LISTING: SERUM GLUCOSE RESULTS NORMAL AT BASELINE AND ABNORMAL AT FOLLOWUP

POPULATION: ALL SUBJECTS

INVESTIGATOR: POTKIN S. , UNITED STATES OF AMERICA

CRF ID: A30001 RACE: CAUCASIAN

SEX: MALE AGE, years: 36

WEIGHT, kg: 84.8

RANDOMIZATION GROUP: RISPERIDONE

	INTERVAL:	SCREENING	DAY 7	DAY 14	DAY 28	DAY 42	DAY 56
	STUDY PHASE:	OPEN	OPEN	OPEN	OPEN	OPEN	OPEN
	TREATMENT:		RISPERIDONE	RISPERIDONE	RISPERIDONE	RISPERIDONE	RISPERIDONE
	DATE OF SAMPLING:	27JUN97	14JUL97	21JUL97	05AUG97	18AUG97	29AUG97
	ONSET DOSE:		0 MG	0 MG	0 MG	0 MG	0 MG
	DAYS ON DOSE ONSET:		6	13	28	41	52
	NO. OF DAYS IN PHASE:	-10	7	14	29	42	53
LABORATORY TEST	NORMAL RANGE						
CLINICAL CHEMISTRY							
GLUCOSE	70-115 mg/dl	102	105	96	181 AA	91	91

AA/BB : VALUE ABOVE/BELOW PATHOLOGICAL LIMITS

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PAGE 2

JRF--TRIAL RIS-USA-111

LISTING: SERUM GLUCOSE RESULTS NORMAL AT BASELINE AND ABNORMAL AT FOLLOWUP (CONTINUED)

POPULATION: ALL SUBJECTS								
INVESTIGATOR: POTKIN S. , UNITED STATES OF AMERICA								
CRF ID: A30006 RACE: CAUCASIAN								
SEX: MALE AGE, years: 48 WEIGHT, kg:146.1								
RANDOMIZATION GROUP: RISPERIDONE								
INTERVAL:		SCREENING	DAY 7	DAY 14	DAY 28	DAY 42	DAY 56	
STUDY PHASE:		OPEN	OPEN	OPEN	OPEN	OPEN	OPEN	
TREATMENT:		RISPERIDONE	RISPERIDONE	RISPERIDONE	RISPERIDONE	RISPERIDONE	RISPERIDONE	
DATE OF SAMPLING:		03JUL97	14JUL97	21JUL97	04AUG97	18AUG97	29AUG97	
ONSET DOSE:		0 MG	0 MG	0 MG	0 MG	0 MG	0 MG	
DAYS ON DOSE ONSET:		6	13	27	41	52	52	
NO. OF DAYS IN PHASE:		-4	7	14	28	42	53	
LABORATORY TEST		NORMAL RANGE						
CLINICAL CHEMISTRY		-----						
GLUCOSE		70-115 mg/dl	102	171 AA	181 AA	192 AA	147 AA	205 AA

AA/BB : VALUE ABOVE/BELOW PATHOLOGICAL LIMITS

PAGE 3

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JRF--TRIAL RIS-USA-111

LISTING: SERUM GLUCOSE RESULTS NORMAL AT BASELINE AND ABNORMAL AT FOLLOWUP (CONTINUED)

POPULATION: ALL SUBJECTS
INVESTIGATOR: POTKIN S. , UNITED STATES OF AMERICA
CRF ID: A30008 RACE: CAUCASIAN
SEX: MALE AGE, years: 42 WEIGHT, kg: 76.2
RANDOMIZATION GROUP: RISPERIDONE

	INTERVAL:	SCREENING	DAY 7	DAY 14	DAY 28	DAY 42	DAY 56
	STUDY PHASE:	OPEN	OPEN	OPEN	OPEN	OPEN	OPEN
	TREATMENT:		RISPERIDONE	RISPERIDONE	RISPERIDONE	RISPERIDONE	RISPERIDONE
	DATE OF SAMPLING:	05JUL97	14JUL97	21JUL97	04AUG97	18AUG97	29AUG97
	ONSET DOSE:		0 MG	0 MG	0 MG	0 MG	0 MG
	DAYS ON DOSE ONSET:		5	13	27	41	52
	NO. OF DAYS IN PHASE:	-2	7	14	28	42	53
LABORATORY TEST	NORMAL RANGE						
CLINICAL CHEMISTRY							
GLUCOSE	70-115 mg/dl	88	72	97	122 AA	93	77

AA/BB : VALUE ABOVE/BELOW PATHOLOGICAL LIMITS

PAGE 4 (LAST PAGE)

16JUN00 12:16

Volume 1/Page 199

JJRPprev 00380076
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R. 6112

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JRF--TRIAL, RIS-USA-111

LISTING: SERUM GLUCOSE RESULTS NORMAL AT BASELINE AND ABNORMAL AT FOLLOWUP (CONTINUED)

POPULATION: ALL SUBJECTS

INVESTIGATOR: POTKIN S. , UNITED STATES OF AMERICA

CRF ID: A30009 RACE: HISPANIC

SEX: MALE AGE, years: 39 WEIGHT, kg: 86.2

RANDOMIZATION GROUP: RISPERIDONE

	INTERVAL:	SCREENING	DAY 7	DAY 14	DAY 28	DAY 42	DAY 56
	STUDY PHASE:	OPEN	OPEN	OPEN	OPEN	OPEN	OPEN
	TREATMENT:		RISPERIDONE	RISPERIDONE	RISPERIDONE	RISPERIDONE	RISPERIDONE
	DATE OF SAMPLING:	10JUL97	17JUL97	24JUL97	07AUG97	28AUG97	04SEP97
	ONSET DOSE:		0 MG	0 MG	0 MG	0 MG	0 MG
	DAYS ON DOSE ONSET:		6	13	27	48	55
	NO. OF DAYS IN PHASE:	0	7	14	28	49	56
LABORATORY TEST	NORMAL RANGE						
CLINICAL CHEMISTRY							
GLUCOSE	70-115 mg/dl	83	93	92	99	160 AA	135 AA

AA/BB : VALUE ABOVE/BELOW PATHOLOGICAL LIMITS

Volume 1/ Page 200

JJRPrev 00380077
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R. 6113

Annex 4A: Narratives for deaths, other serious adverse events and adverse events leading to discontinuation due to glucose-related adverse events**CROSS-REFERENCE KEY FOR PATIENT NARRATIVES**

Glucose-related Adverse Events

Trial no. Patient no.	Treatment group	Adverse event (WHO preferred term)	DC due to AE	SAE	Death
ADULTS (18-65 years)					
USA-79 (Double-blind)					
0054	RIS	Diabetes mellitus		X	
0601 ^a	RIS	Diabetes mellitus		X	
0076	HAL	Elevated glucose/labs	X ^c		
0084 ^a	HAL	Diabetes mellitus			
		Hypoglycemia		X	
0302	HAL	Diabetes mellitus		X	
0349 ^a	HAL	Hyperglycemia	X	X	
INT-45 (Double-blind)					
A30142 ^a	RIS	Hyperglycemia			
		Hypoglycemia		X	
USA-102 (Double-blind)					
A30030 ^a	PLA	Uncontrolled diabetes		X	
USA-6					
0254	RIS	Hypoglycemia		X ^b	
GERIATRICS (>65 years)					
USA-63 (Double-blind)					
0911 ^a	PLA	Hyperglycemia		X	
4113 ^{a,e}	PLA	Hyperglycemia	X	X	(X ^d)
0115 ^a	RIS	Hypoglycemia		X	
1204 ^a	RIS	Diabetic coma	X	X	X
2613 ^a	RIS	Hyperglycemia	X		
4013 ^a	RIS	Hyperglycemia		X	
4014 ^a	RIS	Diabetes mellitus		X	
INT-23 (Open-label)					
A00118 ^a	RIS	Diabetes mellitus		X	
A00367	RIS	Hypoglycemia		X	(X ^d)
USA-70 (Open-label)					
2916 ^a	RIS	Diabetes mellitus		X	
4118	RIS	Hyperglycemia	X	X	
4206	RIS	Hyperglycemia		X	
TOTAL			6	19	1^f

DC: Discontinuation; SAE: Serious adverse event; PLA: placebo; HAL: haloperidol; RIS: risperidone

A patient narrative is provided in Annex 4 for all patients listed in this table.

a: Patient had a pre-existing condition of diabetes either reported during screening or based on disorder treated with concomitant medication before the onset of the glucose-related adverse event.

b: This patient was not included in the clinical database listing in Annex 1 as having a serious adverse event that was glucose-related although the patient was hospitalized for hypoglycemia.

c: This patient was not included in the clinical database listing in Annex 1 as having discontinued treatment because of elevated glucose laboratory values.

d: This patient died but death was not due to a glucose-related adverse event. A narrative is provided in Annex 4 for completeness.

e: Patient had an endocrine disorder that was unspecified.

f: Only one patient is indicated because only one patient died of a glucose related adverse event. The additional patients surrounded by parenthesis in this column did not die from glucose-related causes but are shown for completeness.

Janssen Research Foundation

NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism
Evaluation of glucose metabolism with risperidone

39

Some death narratives contain addenda with additional information that was not available when the original narratives were written. Thus the attached may include both the original and updated narratives, which have not been made concordant.

Volume 1/Page 202

JJRPrev 00380079
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R. 6115

CROSS-REFERENCE KEY FOR PATIENT NARRATIVES
Glucose-related adverse events

Trial no. Patient no.	Treatment group	Adverse event (WHO preferred term)	DC due to AE	SAE	Death
ADULTS (18-65 years)					
USA-79 (Double-blind)					
0054	RIS	Diabetes mellitus		X	
0601	RIS	Diabetes mellitus		X	
0076	HAL	Elevated glucose/labs	X		
0084	HAL	Diabetes mellitus			
		Hypoglycemia		X	
0302	HAL	Diabetes mellitus		X	
0349	HAL	Hyperglycemia	X	X	
INT-45 (Double-blind)					
A30142	RIS	Hyperglycemia		X	
		Hypoglycemia			
USA-102 (Double-blind)					
A30030	PLA	Uncontrolled diabetes		X	
USA-6 (Open-label)					
0254	RIS	Hypoglycemia		X	
GERIATRICS (≥65 years)					
USA-63 (Double-blind)					
0911	PLA	Hyperglycemia		X	
4113	PLA	Hyperglycemia	X	X	X
0115	RIS	Hypoglycemia		X	
1204	RIS	Diabetic coma	X	X	X
2613	RIS	Hyperglycemia	X		
4013	RIS	Hyperglycemia		X	
4014	RIS	Diabetes mellitus		X	
INT-23 (Open-label)					
A00118	RIS	Diabetes mellitus		X	
A00367	RIS	Hypoglycemia		X	X
USA-70 (Open-label)					
2916	RIS	Diabetes mellitus		X	
4118	RIS	Hyperglycemia	X	X	
4206	RIS	Hyperglycemia		X	

DC: Discontinuation; SAE: Serious adverse event

Janssen Research Foundation

NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

Evaluation of glucose metabolism with risperidone

41

Risperidone—RIS-USA-79
Serious Adverse Event Summary

Subject:	A30054 RED	Investigator:	Nakra, R. (Site # 26)		
Date of birth:	25MAR60	Trial medication:	Risperidone		
Race:	Caucasian	Treatment duration:	784 days		
Sex:	Male	Treatment start:	25JUN96		
Country:	USA	Treatment stop:	17AUG98		

Date of serious adverse event:	04MAR97			
Serious adverse event (verbatim):	Severity	Relation to study med	Start	End
Diabetes mellitus	moderate	none	04MAR97	not specified

Baseline subject data:

-Diagnosis: Schizoaffective disorder – depressive type
-Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score = 57 at baseline
-Clinical Global Impression (CGI) = "mild" at baseline
-Medical history: Hypertension, well controlled; mild obesity
-Physical examination: No abnormal findings; ECG within normal limits

Psychiatric history:

Date of most recent discharge from psychiatric hospital:	15NOV93
Age at onset of psychotic symptoms:	24 years of age
Age at time of first psychiatric hospitalization:	24 years of age
Age at first pharmacologic treatment:	24 years of age
Number of previous psychiatric hospitalizations:	03
Number of suicide attempts:	00
Date of most recent suicide attempt:	N/A
Number of courses of ECT:	00
Date of most recent treatment:	N/A
Treatment of substance abuse:	No

Study drug administration:

-Start of treatment: 25JUN96
-Regimen: 25JUN96 – 25JUN96: 1.0 mg/day
 26JUN96 – 26JUN96: 2.0 mg/day
 27JUN96 – 17AUG98: 4.0 mg/day

Clinical narrative:

The patient, a 36-year-old man, entered the study on June 25, 1996. On March 4, 1997, after 278 days of study medication treatment, the patient was hospitalized for diabetes mellitus. The patient stabilized and was discharged on March 6, 1997, and started treatment with glipizide (10 mg daily) on March 13, 1997. He continued on study medication without interruption during his hospitalization. The patient completed the course of the study on August 17, 1998 after 784 days of study medication treatment. The investigator considered diabetes mellitus to be unrelated to study medication.

The reported ECG rates and intervals are within normal limits. This patient developed poorly controlled diabetes, was hospitalized for stabilization, and was prescribed glipizide. Elevated glucose levels have been reported infrequently (0.9%) with risperidone. In this patient, a relationship of elevated glucose to study medication is possible, but less likely given that the diabetic condition was present at study entry and improved while on study medication. Serum sodium was decreased at Days 29 and 190. This may be related to risperidone as hyponatremia has been reported in 1.2% of patients receiving the drug. The increase in prolactin levels since entry into the study is most likely related to risperidone. The borderline increases in WBC and decrease in potassium are of unclear significance or relationship to study medication.

Volume 1/Page 204

JJRPprev 00380081
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R. 6117

Patient: A30054/RED (continued)

ECG data:

Date	Timepoint	Vent rate (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTc (ms)
17JUN96	SCREEN	69	160	100	380	405
31DEC96	WEEK 28	74	160	100	380	417
24JUN97	WEEK 52	74	150	80	350	387
09DEC97	WEEK 76	90	150	90	330	403
26MAY98	WEEK 100	75	134	84	354	395

Concomitant medication:Psychotropic medication:

Haloperidol

Dosage*

10mg QD

Start

15DEC92

End

24JUN96

Other concurrent medication:

Atenolol

not recorded

prior to study

not recorded

Clonidine

not recorded

prior to study

not recorded

Aspirin

PRN

06SEP96

ongoing

Lisinopril, hydrochlorothiazide

not recorded

17DEC96

not recorded

Glipizide

not recorded

13MAR97

ongoing

Quinapril

not recorded

13MAR97

ongoing

Metformin HCl

not recorded

12AUG97

ongoing

Hydrochlorothiazide

not recorded

05DEC97

ongoing

*Since the case report form did not specifically request dosage, some dosages were not recorded.

Other adverse events (verbatim):

Headache (intermittent)

Severity

mild

Relation to study med

none

Start

06SEP96

End

14OCT96

Tooth extraction

mild

none

04MAR97

04MAR97

Scapular cyst

mild

none

24JUN97

still present

Haloneus melanocytic nevus

mild

none

24JUN97

still present

Clinical laboratory tests:Abnormal laboratory values:

Laboratory test:	Reference range	(Day 0)					
		Baseline	Day 29	Day 190	Day 302	Day 365	Day 533
WBC	3.2 - 11 m/cumm	11.24					
Sodium	135 - 148 mEq/L	138	132	131			
Potassium	3.5 - 5.5 mEq/L	3.5	3.4				
Serum glucose	60 - 115 mg/dL	107	131	372		180	143
GGT	0 - 65 U/L	55				68	
Prolactin	1 - 20 ng/mL	18.91	30.51	32.24	21.66	28.87	28.3

Risperidone—RIS-USA-79
Serious Adverse Event Summary

Subject:	A30601 RED	Investigator:	Brenner, R. (Site #2)
Date of birth:	07JUN35	Trial medication:	Risperidone
Race:	Caucasian	Treatment duration:	364 days
Sex:	Male	Treatment start:	26AUG97
Country:	USA	Treatment stop:	24AUG98

Date of serious adverse event:	26DEC97			
Serious adverse event (verbatim):	Severity	Relation to study med	Start	End
Uncontrolled diabetes mellitus	moderate	none	26DEC97	31DEC97

Baseline subject data:

-Diagnosis: Schizophrenia, paranoid type
 -Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score = 61 at baseline
 -Clinical Global Impression (CGI) = "moderate" at baseline
 -Medical history: Exploratory laparotomy 1964; IDDM
 -Physical examination: Abdomen: old surgical scar; ECG abnormal but not clinically significant (QRS contour abnormal - consistent with anteroseptal infarct, age undetermined)

Psychiatric history:

Date of most recent discharge from psychiatric hospital: 12NOV96
 Age at onset of psychotic symptoms: 24 years of age
 Age at time of first psychiatric hospitalization: 24 years of age
 Age at first pharmacologic treatment: 24 years of age
 Number of previous psychiatric hospitalizations: 04
 Number of suicide attempts: 00
 Date of most recent suicide attempt: N/A
 Number of courses of ECT: 00
 Date of most recent treatment: N/A
 Treatment of substance abuse: No

Study drug administration:

-Start of treatment: 26AUG97
 -Regimen: 26AUG97 - 26AUG97: 1.0 mg/day
 27AUG97 - 27AUG97: 2.0 mg/day
 28AUG97 - 25DEC97: 4.0 mg/day
 26DEC97 - 31DEC97: 0.0 mg/day
 01JAN98 - 24AUG98: 4.0 mg/day

Clinical narrative:

The patient, a 62-year-old man, began study medication treatment on August 26, 1997. On December 26, 1997, he was hospitalized for exacerbation of his diabetes mellitus. His blood sugar was 572 mg/dL. He also complained of gastritis, polyuria, and polydipsia. Study medication was temporarily discontinued and the patient was treated with IV fluids, insulin, and famotidine. He stabilized and was discharged on December 31, 1997. The patient went on to complete the study on August 24, 1998, after 364 days on study medication. At study completion, PANSS score was 52 (61 at baseline). The CGI was "mild" and unchanged relative to baseline CGI. The investigator considered exacerbation of diabetes mellitus to be not related to study medication.

Screening results reported borderline QTc and QRS contour abnormality consistent with anteroseptal infarct age undetermined; this was judged by the site as not clinically significant. Week 28 ECG results reported QRS (T) contour abnormality and prolonged QT interval judged by the site as not significantly different from screening ECG. Week 52 ECG results were reported as within normal limits with a borderline QTc. This patient with a history of IDDM, S/P exploratory laparotomy, and ECG evidence of anterior myocardial infarction was hospitalized for diabetic control in the setting of gastritis responsive to hydration and insulin. Risperidone is rarely associated with diabetes and infrequently associated with gastritis. This episode occurred after 120 days on study medication and did not recur in the 240 days following resumption of study medication, indicating an unlikely relationship of this event to study medication. This event was more likely due to a gastrointestinal infection triggering a diabetic exacerbation. The ongoing elevation of serum and urine glucose reflects poor control of the pre-existing diabetic condition. A relationship between risperidone and decreased diabetic control is possible given that the baseline glucose was within normal range and

Patient: A30601 **RED** (continued)

glucose level was markedly improved at 14 days after study discontinuation. Additional information on dosing and management would be required to support this association. The increase in prolactin from baseline and hyperprolactinemia is expected with medications such as risperidone (pre-study anti-psychotic) that antagonize dopamine D2 receptors. Although no adverse event was reported, the laboratory abnormalities present at Day 364 (study completion) suggest a second undiagnosed diabetic exacerbation (serum glucose of 591 mg/dL with urine glucose positive) with possible infection (leukocytosis with leftward shift and lymphopenia). The ECG abnormalities reported at screening are consistent with this patient's history. The reported concomitant medications and laboratory results do not explain the prolonged QT interval at Week 52; another potential explanation is ischemia since this patient has a history of myocardial infarction.

ECG data:

Date	Timepoint	Heart rate (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTc (ms)
18AUG97	SCREEN	95	162	70	354	448
10MAR98	WEEK 28	88	134	96	392	478
24AUG98	WEEK 52	90	154	76	360	444

Concomitant medication:Psychotropic medication:

Chlorpromazine HCl

Dosage*StartEndOther concurrent medication:

Insulin

not recorded

prior

ongoing

Nifedipine

not recorded

prior

ongoing

Ursodeoxycholic acid

not recorded

prior

ongoing

Famotidine

not recorded

27DEC97

not specified

Normal saline

not recorded

27DEC97

not specified

*Since the case report form did not specifically request dosage, some dosages were not recorded.

Other adverse events (verbatim):

Gastritis

Severity
mildRelation to study med
noneStart
27DEC97End
31DEC97Clinical laboratory tests:Abnormal laboratory values:Laboratory test:Reference range

		(Day 0)							
		Baseline	Day 28	Day 197	Day 364	Day 364+(2)*	Day 364+(14)*		
WBC	3.2-11 m/cumm	8.44			12.21				
Seg neutrophils	40-75%	59.8		82.5	79.9				
Lymphocytes	15-47%	28.5		11.6	11.8				
Sodium	135-148 mEq/L	140			130				
Calcium	8.5-10.6 mg/dL	8.2							
Serum glucose	60-115 mg/dL	105	324	273	591	347		189	
Prolactin	1-20 ng/mL	8.34	27.84	31.2	25.93				
Urine glucose	--	Neg		Trace	++		+	++	
Urine ketones	--	Neg						Trace	
Urine WBC	--	-		1-3					

* X+(Y) indicates number of days treated plus number of days post therapy when specimen was drawn.

Risperidone—RIS-USA-79
Premature Discontinuation Summary

Subject:	A30076RED	Investigator:	DePriest, M. (Site # 7)
Date of birth:	05MAR51	Trial medication:	Haloperidol
Race:	Caucasian	Treatment duration:	400 days
Sex:	Male	Treatment start:	18JUL96
Country:	USA	Treatment stop:	21AUG97

Date of discontinuation:	28AUG97			
Reason for discontinuation:	Abnormal lab result - elevated lab values			
<u>Adverse event (verbatim):</u>	<u>Severity</u>	<u>Relation to study med</u>	<u>Start</u>	<u>End</u>
Elevated glucose	mild	possible	17JUL97	Subseq
Elevated uric acid	mild	possible	28AUG97	not specified
Elevated alkaline phosphate	mild	possible	17JUL97	01AUG97
Elevated alkaline phosphate	mild	possible	28AUG97	not specified
Elevated AST	mild	possible	17JUL97	Subseq
Elevated ALT	mild	possible	17JUL97	Subseq
Increased MCV	mild	possible	17JUL97	Subseq
Elevated GGT	mild	possible	17JUL97	Subseq

Baseline subject data:

-Diagnosis: Schizophrenia, undifferentiated type

-Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score = 63 at baseline

-Clinical Global Impression (CGI) = "moderate" at baseline

-Medical history: History of hypertension; fracture of right collar bone and right arm

-Physical examination: No abnormalities noted; ECG within normal limits

Psychiatric history:

Date of most recent discharge from psychiatric hospital: 22AUG95

Age at onset of psychotic symptoms: 33 years of age

Age at time of first psychiatric hospitalization: 33 years of age

Age at first pharmacologic treatment: 33 years of age

Number of previous psychiatric hospitalizations: 05

Number of suicide attempts: 00

 Date of most recent suicide attempt: N/A

Number of courses of ECT: 00

 Date of most recent treatment: N/A

Treatment of substance abuse: No

Study drug administration:

-Start of treatment: 18JUL96

-Regimen:

18JUL96 – 18JUL96: 2.0 mg/day

19JUL96 – 19JUL96: 5.0 mg/day

20JUL96 – 24JUL96: 10.0 mg/day

25JUL96 – 30JUL96: 15.0 mg/day

31JUL96 – 06AUG96: 15.0 mg/day

07AUG96 – 13AUG96: 15.0 mg/day

14AUG96 – 10SEP96: 15.0 mg/day

11SEP96 – 08OCT96: 15.0 mg/day

09OCT96 – 03NOV96: 15.0 mg/day

04NOV96 – 02DEC96: 15.0 mg/day

03DEC96 – 02JAN97: 15.0 mg/day

03JAN97 – 30JAN97: 15.0 mg/day

31JAN97 – 25FEB97: 15.0 mg/day

26FEB97 – 25MAR97: 15.0 mg/day

26MAR97 – 22APR97: 15.0 mg/day

23APR97 – 21MAY97: 15.0 mg/day

22MAY97 – 19JUN97: 15.0 mg/day

20JUN97 – 16JUL97: 15.0 mg/day

17JUL97 – 12AUG97: 15.0 mg/day

13AUG97 – 21AUG97: 15.0 mg/day

Patient: A30076[REDACTED] (continued)

Clinical narrative:

The patient, a 60-year-old woman, began study medication treatment on May 12, 1997. On February 19, 1998, after approximately 9 months on study medication, the patient attended the clinic for a scheduled study visit. At this time, she reported that she had experiencing neck and trunk stiffness for approximately one month (which she did not report to the clinic before this visit). The patient was discontinued because of this adverse event and the fact that the patient had stopped taking medication for longer than 7 days (she admitted that she had stopped taking study medication on January 29, 1998). She completed final visit assessments on February 19, 1998. Physical examination results were normal relative to screening examination. The PANSS score was 82 (85 at baseline) and the CGI was "moderate" and unchanged relative to baseline. The CGI of severity subscale of the EPRS for parkinsonism was between "very mild" and "mild," and the CGI for dyskinesia fluctuated between "absent" and "very mild" throughout the study. The investigator considered neck and trunk stiffness to be possibly related to study medication.

All ECG results (at Screening, Week 28, and final visit) reported sinus bradycardia and were judged by the site to be within normal limits. This patient was discontinued because of extrapyramidal symptoms and failure to take study medication for greater than seven days. Extrapyramidal symptoms are expected with haloperidol and this is the most likely explanation for this patient's symptoms. There was an isolated increase in the glucose at Day 198. Hyperglycemia is expected with haloperidol; this abnormality may be related to study medication, a non-fasting condition, or occult diabetes. There was an isolated increase in the HCO₃ at Day 284 of dubious clinical significance. Elevated prolactin is expected with haloperidol. However, the sporadic increases in prolactin at Days 0 and 198 interposed, with low normal levels at the other 2 laboratory assessments, raises the question of noncompliance to study medication.

ECG data:

Date	Timepoint	Heart rate (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTc (ms)
25APR97	SCREEN	51	140	60	460	420
25NOV97	WEEK 28	55	150	70	430	410
19FEB98	WEEK 52	52	150	70	440	410

Concomitant medication:Psychotropic medication:

Fluphenazine HCl

Dosage*:

5 mg q day

Start

15FEB98

End

not specified

Other concurrent medication:

Benzotropine mesylate

not recorded

19FEB98

ongoing

*Since the case report form did not specifically request dosage, some dosages were not recorded.

Other adverse events (verbatim):

None

SeverityRelation to study medStartEndClinical laboratory tests:

Abnormal laboratory values:

Laboratory test:	Reference range	(Day 0) Baseline Day 29	Day 198	Day 284
Serum glucose	60 - 115 mg/dL	111	117	
BUN	7 - 26 mg/dL	6		
Prolactin	1 - 25 ng/mL	30.88	43.78	
HCO ₃	20 - 30 mEq/L	23.8		31.1

Risperidone—RIS-USA-79
Serious Adverse Event/Premature Discontinuation Summary

Subject:	A30084-RED	Investigator:	Cohn, C. (Site # 8)		
Date of birth:	02AUG39	Trial medication:	Haloperidol		
Race:	Hispanic	Treatment duration:	417 days		
Sex:	Female	Treatment start:	05JUL96		
Country:	USA	Treatment stop:	25AUG97		

Date of discontinuation:	29AUG97				
Reason for discontinuation:	Relapse				
<u>Serious adverse event (verbatim):</u>	<u>Severity</u>	<u>Relation to study med</u>	<u>Start</u>	<u>End</u>	
Exacerbation of psychosis violent behavior	severe	none	24AUG97	29AUG97	
Hospitalization for hypoglycemia	severe	none	19SEP97	01OCT97	
Exacerbation of psychosis	severe	none	24AUG97	29AUG97	
Hosp for exacerbation of schizophrenia	severe	none	23SEP97	01OCT97	
Hospitalization for syncope	moderate	none	19SEP97	01OCT97	

Baseline subject data:

-Diagnosis: Schizophrenia, paranoid type

-Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score = 58 at baseline

-Clinical Global Impression (CGI) = "moderate" at baseline

-Medical history: Hypertension – controlled with med.; obesity; mild TD left arm and leg (past history); insulin dependent diabetic

-Physical examination: Very obese; right ear canal mildly impacted; ECG abnormal – not clinically significant (sinus tachycardia, possible inferior infarct, age indeterminate)

Psychiatric history:

Date of most recent discharge from psychiatric hospital:	10OCT95
Age at onset of psychotic symptoms:	28 years of age
Age at time of first psychiatric hospitalization:	28 years of age
Age at first pharmacologic treatment:	28 years of age
Number of previous psychiatric hospitalizations:	05
Number of suicide attempts:	00
Date of most recent suicide attempt:	N/A
Number of courses of ECT:	00
Date of most recent treatment:	N/A
Treatment of substance abuse:	No

Study drug administration:

-Start of treatment: 05JUL96

-Regimen:

05JUL96 – 05JUL96: 2.0 mg/day

06JUL96 – 06JUL96: 5.0 mg/day

07JUL96 – 10JUL96: 10.0 mg/day

11JUL96 – 11JUL96: 5.0 mg/day

12JUL96 – 26JUL96: 15.0 mg/day

27JUL96 – 27JUL96: 20.0 mg/day

28JUL96 – 28JUL96: 15.0 mg/day

29JUL96 – 15NOV96: 20.0 mg/day

16NOV96 – 17NOV96: 0.0 mg/day

18NOV96 – 25NOV96: 20.0 mg/day

26NOV96 – 29NOV96: 0.0 mg/day

30NOV96 – 30NOV96: 20.0 mg/day

01DEC96 – 02DEC96: 0.0 mg/day

03DEC96 – 19JAN97: 20.0 mg/day

20JAN97 – 20JAN97: 5.0 mg/day

21JAN97 – 12JUL97: 20.0 mg/day

13JUL97 – 13JUL97: 0.0 mg/day

14JUL97 – 25AUG97: 20.0 mg/day

Patient: A30083-RED (continued)

Clinical narrative:

The patient, a 56-year-old woman, began study medication treatment on July 5, 1996. On August 24, 1997, after 417 days on study medication, the patient was hospitalized after reportedly exhibiting verbally and physically abusive behavior toward her family. On admission she was noted to be agitated. Her PANSS score had increased by over 25% relative to baseline (121 compared to 58 at baseline). Study medication was permanently discontinued on August 25, 1997 due to relapse and the patient was treated with olanzapine (15 mg/day) and chlorpromazine (25 mg PRN). She stabilized and was discharged on August 29, 1997, and completed final visit assessments on that same day. Physical examination results were normal except for obesity (as noted at screening). The PANSS score was 127 (58 at baseline) and the Clinical Global Impression was "marked" and "much worse" when compared to baseline ("moderate"). On September 19, 1997, the patient was again hospitalized after presenting at the emergency room with disorientation, confusion, and dizziness. She also exhibited agitation and violent behavior with apparent hallucinations and delusions. She was diagnosed with hypoglycemia, syncope, and exacerbation of psychosis. She was treated with risperidone (2 mg/day), lisinopril (20 mg/day), insulin (70/30, 34 units/day), amlodipine (2.5 mg/day), and Vitamin E (400 units daily). She recovered from all events and was discharged in stable condition on October 1, 1997. During the time period that the patient experienced tremors of the hands and feet (July 9, 1997 to August 4, 1997), the CGI subscale of the ESRS for parkinsonism worsened from "mild" to "moderate" and the CGI of dyskinesia worsened from "borderline" to "very mild." The investigator considered hypoglycemia, syncope, and all episodes of exacerbation of psychosis to be not related to study medication.

At Screening, Week 28, and Week 52, ECG results reported by the site indicated sinus tachycardia, possible inferior infarct, age indeterminate. At Weeks 28 and 100, a borderline abnormal QTc was noted. Final visit ECG also indicated sinus tachycardia. All ECG abnormalities were judged by the site to be not clinically significant. Psychotic exacerbation is expected with the underlying disease state. Three weeks after discontinuation, the patient presented with a complex that included disorientation, confusion, and dizziness. Assessment in the emergency room led to the diagnosis of hypoglycemia, syncope, and psychotic exacerbation. Given that these events occurred three weeks after discontinuation from the study, a relationship to study medication is unlikely. The reported ECG results included sinus tachycardia and possible inferior infarct. These abnormalities precede study entry and are likely related to a pre-existing condition and not to study medication. In addition, the reported QTc was in the borderline prolongation range for women; anti-psychotic medications including haloperidol can cause QTc prolongation. Hyperglycemia was evident on all laboratory assessments. Hyperglycemia is expected with haloperidol. In this patient, haloperidol may have contributed to the hyperglycemia; however, the presence at Screening suggests a pre-existing diabetic condition. Hyperprolactinemia was present on all laboratory assessments; anti-psychotic medications such as haloperidol block dopamine D2 receptors and can lead to increased prolactin.

ECG data:

Date	Timepoint	Vent rate (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTc (ms)
28JUN96	SCREEN	108	160	80	320	430
20JAN97	WEEK 28	118	160	80	330	460
09JUL97	WEEK 52	120	150	80	310	440
29AUG97	WEEK 100	120	160	80	320	450

Concomitant medication:Psychotropic medication:

	Dosage*	Start	End
Lorazepam	1 mg q day	29MAR93	22NOV96
Risperidone	3 mg BID	27SEP95	04JUL96
Risperidone	3 mg q day	29JUL96	01AUG96
Thorazine	50 mg q day	02AUG96	25AUG97
Lorazepam	1 mg QID	19DEC96	19DEC96
Lorazepam	1 mg q day	20 DEC96	25AUG97
Thorazine	25 mg PRN	26JUL97	not specified
Zyprexa	10 mg q day	26JUL97	27AUG97
Zyprexa	15 mg q day	28AUG97	28AUG97
Risperidone	2 mg BID	29AUG97	not specified

Patient: A30083RED (continued)

<u>Other concurrent medication:</u>	<u>Dosage*</u>	<u>Start</u>	<u>End</u>
NPH insulin	not recorded	prior	not specified
Enalapril maleate	not recorded	prior	ongoing
Conjugated estrogens	not recorded	prior	ongoing
Phenolphthalein	not recorded	08JUL96	not specified
Acetaminophen	not recorded	01JUL96	ongoing
Metformin	not recorded	09AUG96	not specified
Amoxicillin	not recorded	11NOV96	not specified
Hydrocodone bitartrate	not recorded	01NOV96	not specified
Insulin	not recorded	21MAR97	not specified
Atorvastatin calcium	not recorded	02JUL97	ongoing
Insulin	not recorded	27AUG97	ongoing
Troglitazone	not recorded	08JUL97	not specified
Sodium levothyroxine	not recorded	27AUG97	not specified
Levofloxacin	not recorded	28AUG97	not specified
Glipizide	not recorded	27AUG97	not specified

*Since the case report form did not specifically request dosage, some dosages were not recorded.

<u>Other adverse events (verbatim):</u>	<u>Severity</u>	<u>Relation to study med</u>	<u>Start</u>	<u>End</u>
Abdominal pain	moderate	none	27AUG97	29AUG97
Occasional stomach cramps	moderate	possible	27JUL96	13AUG97
Stomach cramps	moderate	possible	26JUL96	26JUL96
Increased agitation	moderate	possible	27JUL96	12AUG96
Anxiety	moderate	none	19DEC96	11MAY97
Constipation	moderate	yes	08JUL96	08JUL96
Leg cramps	moderate	possible	14JUL96	14JUL96
Diabetes	moderate	none	08JUL96	09AUG97
Intermittent diarrhea	mild	none	23SEP96	23DEC96
Fatigue	mild	possible	24DEC96	11MAY97
Increased audio hallucinations	moderate	none	27JUL96	16AUG96
Headache	moderate	none	prior	01JUL96
Headache	moderate	possible	14JUL96	14JUL96
Headache	mild	possible	26JUL96	26JUL96
Intermittent headaches	moderate	possible	23SEP96	11MAY97
Occasional headaches	mild	possible	27JUL96	22SEP96
Hypothyroidism	moderate	none	27AUG97	not specified
Tooth extraction advanced cavity	severe	none	01NOV96	01NOV96
Tremor (hands and feet)	mild	possible	09JUL97	04AUG97
Urinary tract infection	mild	none	28AUG97	Subseq

Clinical laboratory tests:

<u>Abnormal laboratory values:</u>		<u>(Day 0)</u>				
<u>Laboratory test:</u>	<u>Reference range</u>	<u>Baseline</u>	<u>Day 29</u>	<u>Day 200</u>	<u>Day 370</u>	<u>Day 417+(4)*</u>
Serum glucose	60 – 115 mg/dL	236	279	280	212	311
Prolactin	1 – 25 ng/mL	93.77	68.61	49.63	49.38	

* X+(Y) indicates number of days treated plus number of days post therapy when specimen was drawn.

Risperidone—RIS-USA-79
Serious Adverse Event Summary

Subject:	A30302 RED	Investigator:	Klegon, D. (Site # 12)
Date of birth:	26OCT50	Trial medication:	Haloperidol
Race:	Hispanic	Treatment duration:	355 days
Sex:	Male	Treatment start:	15AUG97
Country:	USA	Treatment stop:	10AUG98

Date of serious adverse event:	19APR98			
Serious adverse event (verbatim):	Severity	Relation to study med	Start	End
Onset of diabetes	severe	possible	19APR98	not specified
Syncope	severe	possible	19APR98	26APR98

Baseline subject data:

- Diagnosis: Schizophrenia, undifferentiated type
- Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score = 63 at baseline
- Clinical Global Impression (CGI) = "moderate" at baseline
- Medical history: Numbness fingers - R hand
- Physical examination: No teeth - wears artificial; smokes 1 pack of cigarettes over course of 3 days; ECG within normal limits

Psychiatric history:

- Date of most recent discharge from psychiatric hospital: 14OCT95
- Age at onset of psychotic symptoms: 16 years of age
- Age at time of first psychiatric hospitalization: 16 years of age
- Age at first pharmacologic treatment: 16 years of age
- Number of previous psychiatric hospitalizations: 06
- Number of suicide attempts: 00
- Date of most recent suicide attempt: N/A
- Number of courses of ECT: 01
- Date of most recent treatment: 26OCT66
- Treatment of substance abuse: No

Study drug administration:

- Start of treatment: 15AUG97
- Regimen: 15AUG97—15AUG97: 2.0 mg day
- 16AUG97—20JAN98: 5.0 mg day
- 21JAN98—21JAN98: 0.0 mg day
- 22JAN98—18APR98: 5.0 mg day
- 19APR98—23APR98: 0.0 mg/day
- 24APR98—10AUG98: 5.0 mg day

Clinical narrative:

The patient, a 47-year-old man, began study medication treatment on 15AUG97. On April 19, 1998, after approximately 8 months on study medication, the patient experienced dizziness and syncope and subsequently collapsed. He was brought to a hospital and was admitted to the intensive care unit due to elevated blood sugar (>700 mg/dL) and he was diagnosed with late onset diabetes. Study medication was discontinued for 5 days and restarted on April 24, 1998. The patient went on to complete the study on August 11, 1998. At final visit, physical examination was normal. The PANSS score totaled 67 (63 at baseline). The CGI was "very mild" and "very much improved" relative to baseline. The investigator considered syncope and onset of diabetes to be possibly related to study medication.

All ECG results were judged by the site as within normal limits; the screening and Week 28 result indicated borderline QTc. This 47-year-old male smoker on haloperidol was hospitalized in Week 35 for dizziness and syncope culminating in the diagnosis of diabetes. Hyperglycemia is expected with haloperidol. However, this event was most likely due to an underlying, undiagnosed, comorbid condition. The glucose level was uncharacteristically high, resulting in diuresis with symptomatic hypovolemia that required urgent treatment. This is more consistent with diabetes than medication-induced hyperglycemia. The patient resumed study medication and completed the study without further episodes of symptomatic hyperglycemia and had reasonably controlled serum glucose levels although no concomitant medications for treatment of diabetes were reported. Hence, relationship to study medication is less likely. The mild and transient elevation in SGPT is of dubious significance without other reported abnormalities in liver function tests.

Janssen Research Foundation

NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

Evaluation of glucose metabolism with risperidone

51

Patient: A30297 **RED** (continued)

ECG data:

Date	Timepoint	Heart rate (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTc (ms)
11AUG97	SCREEN	98	200	70	337	432
02MAR98	WEEK 28	110	120	58	320	432
11AUG98	WEEK 52	76	200	66	337	378

<u>Concomitant medication:</u>	<u>Dosage</u>	<u>Start</u>	<u>End</u>
<u>Psychotropic medication:</u> Benzotropine mesylate	1 mg q day	24JUN97	not specified
<u>Other concurrent medication:</u> None			

<u>Other adverse events (verbatim):</u>	<u>Severity</u>	<u>Relation to study med</u>	<u>Start</u>	<u>End</u>
Plightheaded & fell down	mild	none	11JUN98	11JUN98
Dizziness	severe	possible	19APR98	26APR98
Rummy nose	mild	possible	20JAN98	25FEB98

Clinical laboratory tests:

<u>Abnormal laboratory values:</u>		<u>(Day 0)</u>		
<u>Laboratory test:</u>	<u>Reference range</u>	<u>Baseline</u>	<u>Day 33</u>	<u>Day 200</u>
Phosphorus	2.5—5 mg/dL	2.9	2.4	2.4
Serum glucose	60—115 mg/dL	102	143	234
SGPT	0—55 U/L	29		71

Volume 1/Page 214

JJRPrev 00380091
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R. 6127

Risperidone—RIS-USA-79
Serious Adverse Event/Premature Discontinuation Summary

Subject:	A30349	Investigator:	Brenner, R. (Site #2)	
Date of birth:	31DEC33	Trial medication:	Haloperidol	
Race:	Caucasian	Treatment duration:	22 days	
Sex:	Female	Treatment start:	23JUL97	
Country:	USA	Treatment stop:	13AUG97	
Date of discontinuation:	15AUG97			
Reason for discontinuation:	Lethargy/hyperglycemia, MI, bronchitis			
Serious adverse event (verbatim):	Severity	Relation to study med	Start	End
Pt lethargic hyperglycemia	moderate	none	14AUG97	not specified
MI myocardial infarction	severe	none	14AUG97	not specified
Bronchitis	mild	none	14AUG97	not specified

Baseline subject data:

-Diagnosis: Schizophrenia, undifferentiated type
 -Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score = 56 at baseline
 -Clinical Global Impression (CGI) = "mild" at baseline
 -Medical history: H/O HTN; H/O CHF; H/O pneumonia; candidiasis between toes; DM; seasonal allergy
 -Physical examination: No noted abnormalities; ECG abnormal, not clinically significant (sinus tachycardia, left atrial abn, abn right superior axis deviation, T abn in high lateral leads)

Psychiatric history:

Date of most recent discharge from psychiatric hospital: 14MAR97
 Age at onset of psychotic symptoms: 19 years of age
 Age at time of first psychiatric hospitalization: 19 years of age
 Age at first pharmacologic treatment: 19 years of age
 Number of previous psychiatric hospitalizations: 05
 Number of suicide attempts: 00
 Date of most recent suicide attempt: N/A
 Number of courses of ECT: 21
 Date of most recent treatment: 1981
 Treatment of substance abuse: No

Study drug administration:

-Start of treatment: 23JUL97
 -Regimen: 23JUL97 - 23JUL97: 2.0 mg/day
 24JUL97 - 24JUL97: 5.0 mg/day
 25JUL97 - 29JUL97: 10.0 mg/day
 30JUL97 - 13AUG97: 20.0 mg/day

Clinical narrative:

The patient, a 63-year-old woman, began study medication treatment on July 23, 1997. Her medical history was significant for hypertension, congestive heart failure and diabetes mellitus. On August 14, 1997, after 22 days on study medication, the patient was admitted to the hospital with lethargy and shortness of breath. She was diagnosed as having myocardial infarction, hyperglycemia, lethargy and bronchitis; she was treated with heparin, insulin, and antibiotic therapy. She was discontinued from the study on August 15, 1997. No final visit assessments were performed. The patient reportedly recovered from the events but no hospital discharge date was provided. The investigator considered all of the above events to be not related to study medication.

ECG results, obtained only at screening, reported sinus tachycardia, left atrial abnormality, borderline QTc, abnormal right superior axis deviation, and T abnormality in high lateral leads; results were judged by the site to be not clinically significant. This patient with diabetes, hypertension, and congestive heart failure was hospitalized 22 days after study entry for myocardial infarction complicated by dyspnea, lethargy, and hyperglycemia that may have been precipitated by bronchitis. Details of work-up and treatment are limited. Myocardial infarction is not expected with haloperidol and is most likely due to pre-existing coronary artery disease (suggested by the baseline ECG) from underlying atherosclerosis in this patient with numerous cardiac risk factors. The abnormal laboratories at baseline reflect pre-existing conditions. The increase in prolactin at baseline is expected with anti-psychotic medications that antagonize dopamine D2 receptors.

Patient: A30349/RED (continued)

ECG data:

Date	Timepoint	Vent rate (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTc (ms)
15JUL97	SCREEN	101	150	100	352	457

Concomitant medication:	Dosage*	Start	End
<u>Psychotropic medication:</u>			
Haloperidol	5mg QID	14MAR97	22JUL97
<u>Other concurrent medication:</u>			
Nifedipine	not recorded	prior	ongoing
Metformin HCl	not recorded	prior	not specified
Glyburide	not recorded	prior	not specified
Insulin	not recorded	prior	ongoing
Beclomethasone dipropionate	not recorded	prior	not specified
Clotrimazole	not recorded	prior	not specified
Clindamycin	not recorded	14AUG97	ongoing
Erythromycin	not recorded	14AUG97	ongoing
Clotrimazole	not recorded	14AUG97	ongoing
Heparin	not recorded	14AUG97	ongoing
Dopamine	not recorded	14AUG97	ongoing
Normal saline	not recorded	14AUG97	ongoing
Dextrose	not recorded	14AUG97	ongoing
Potassium chloride	not recorded	15AUG97	ongoing

*Since the case report form did not specifically request dosage, some dosages were not recorded.

Other adverse events (verbatim):	Severity	Relation to study med	Start	End
Dermatitis groins and under R breast	mild	none	14AUG97	not specified

Clinical laboratory tests:

Abnormal laboratory values:		(Day 0)
Laboratory test:	Reference range	Baseline
HCT	33-48%	50
Phosphorus	2.5-5 mg/dL	5.2
Serum glucose	60-115 mg/dL	127
Prolactin	1-25 ng/mL	54.02
HCO3	20-30 mEq/L	31.3

JRF--TRIAL RIS-INT-45
SERIOUS ADVERSE EVENT SUMMARY

Subject: RED #A30142	Investigator: RILHIKANGAS R., MD
Age: 50 years	Trial medication: RISPERIDONE
Race: Caucasian	Treatment duration: 49 days
Sex: male	Treatment start: August 13, 1998
Country: FINLAND	Treatment stop: September 30, 1998

Serious adverse event: hypoglycaemia, pneumonia

BASELINE SUBJECT DATA - TREATMENT

- Diagnosis: schizophrenia, undifferentiated
- Medical and surgical history: ears, nose, throat: abscessus periapicalis; genitourinary: pyelonephritis uri
- Concomitant disorders: cardiovascular: hypertension; endocrine: diabetes; eyes: retinopathia diabetica; respiratory: bronchitis cough
- Physical examination: chest and lungs: bronchitis; skin: rash on the legs (because of diabetes)
- Previous medications: perphenazine (po 8 mg x 1); perphenazine (po 8 mg x 2)

CLINICAL NARRATIVE

This patient had an active medical condition of diabetes. On 17 August 1998, after 5 days of treatment, the patient had hypoglycaemia (verbatim: hypoglycaemia) and was sent to the emergency unit. Hypoglycaemia lasted until 31 August, was moderate and not considered drug-related by the investigator. Hyperglycaemia (verbatim: hyperglycaemia) had been reported on 14 August as moderate and lasted until 23 September. In the emergency unit, pneumonia (verbatim: pneumonia) was diagnosed on 22 August, after 10 days of treatment with risperidone. It resolved on 6 September, was moderate, and not considered drug-related.

ECG DATA

Date	Time	HR (bpm)	QRS (ms)	QT (ms)	QTc (ms)	QTlc (ms)	PQ (ms)	RR (ms)
10AUG1998		84	80	340	402	384	160	714
05OCT1998		100	80	320	413	382	160	600

(A=Above normal B=Below normal *=Abnormal P=Pathological)

CONCOMITANT MEDICATION

Medication	Dosage	Start	End
insulin			
sc human 10+12+8 iu		before trial	13AUG1998
insulin isophane, human biosynthetic			
sc human 30 iu		before trial	22AUG1998
lisinopril			
po 20 mg		before trial	ongoing at end of trial
temazepam			
po 20 mg		before trial	ongoing at end of trial
perphenazine			
po 8 mg		12AUG1998	12AUG1998
redol comp.			
po 10 ml x 3		13AUG1998	18AUG1998

Volume 1/Page 217

JJRPrev 00380094
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D807.232

CONCOMITANT MEDICATION

Medication	Start	End
Dosage		
insulin		
sc human 10+12+8+4 iu	14AUG1998	14AUG1998
insulin		
sc human 10+18+12 iu	15AUG1998	15AUG1998
insulin		
sc human 10+18+10 iu	16AUG1998	16AUG1998
insulin		
sc human 10+12+8 iu	17AUG1998	21AUG1998
clobutinol hydrochloride		
po 10 ml x 2-3	19AUG1998	20AUG1998
propranolol		
po 20 mg	19AUG1998	ongoing at end of trial
paracetamol		
po 500 mg	21AUG1998	21AUG1998
cefuroxime sodium		
iv 4.5 g	22AUG1998	31AUG1998
insulin		
sc human 10+6+8 iu	22AUG1998	22AUG1998
pentoxyverine citrate		
po 15 ml	22AUG1998	23AUG1998
insulin		
sc human 10+12 iu	23AUG1998	23AUG1998
insulin isophane, human biosynthetic		
sc human 10+10 iu	23AUG1998	23AUG1998
lactulose		
po 20 ml	23AUG1998	23AUG1998
furosemide		
iv 20 mg	24AUG1998	24AUG1998
insulin		
sc human 12+8 iu	24AUG1998	24AUG1998
insulin isophane, human biosynthetic		
sc human 6 iu	24AUG1998	24AUG1998
furosemide		
po 40 mg	25AUG1998	22SEP1998
insulin		
sc human 6+6+6 iu	25AUG1998	26AUG1998
insulin isophane, human biosynthetic		
sc human 10+10 iu	25AUG1998	25AUG1998
insulin isophane, human biosynthetic		
sc human 10+6 iu	26AUG1998	26AUG1998
miconazole nitrate		
1 x 2	26AUG1998	31AUG1998
insulin		
sc human 8+8+4 iu	27AUG1998	27AUG1998
insulin isophane, human biosynthetic		
sc human 4+12 iu	27AUG1998	28AUG1998
insulin		
sc human 8+6+6 iu	28AUG1998	28AUG1998
insulin		
sc human 6+4+6 iu	29AUG1998	29AUG1998
insulin isophane, human biosynthetic		
sc human 4+8 iu	29AUG1998	29AUG1998
insulin		
sc human 6+6+4 iu	30AUG1998	30AUG1998
insulin isophane, human biosynthetic		
sc human 4+10 iu	30AUG1998	31AUG1998
insulin		
sc human 8+6+6 iu	31AUG1998	31AUG1998
cefalexin monohydrate		
po 500 mg x 3	01SEP1998	06SEP1998

Volume 1/Page 218

JJRPrev 00380095

Confidential/Produced in Litigation Pursuant to Protective Order

D807.233

CONCOMITANT MEDICATION

Medication Dosage	Start	End
insulin		
sc human 8+6+6 iu	01SEP1998	01SEP1998
insulin isophane, human biosynthetic		
sc human 4+10 iu	01SEP1998	09SEP1998
insulin		
sc human 10+8+6 iu	02SEP1998	11SEP1998
insulin isophane, human biosynthetic		
sc human 4+8 iu	10SEP1998	13SEP1998
clobutinol hydrochloride		
po 10 ml	12SEP1998	12SEP1998
insulin		
sc human 10+12+5 iu	12SEP1998	12SEP1998
insulin		
sc human 10+8+6 iu	13SEP1998	21SEP1998
clobutinol hydrochloride		
po 10 ml	14SEP1998	14SEP1998
insulin isophane, human biosynthetic		
sc human 6+8 iu	14SEP1998	ongoing at end of trial
sodium picosulfate		
po 23 gtt	15SEP1998	15SEP1998
insulin		
sc human 10+6+6 iu	22SEP1998	ongoing at end of trial
clobutinol hydrochloride		
po 10 ml	23SEP1998	23SEP1998

OTHER ADVERSE EVENTS

Adverse event	Severity	Related	Start	End
hyperglycaemia	moderate	not	14AUG1998	23SEP1998
tachycardia	mild	not	19AUG1998	25AUG1998
fever	moderate	not	21AUG1998	21AUG1998
constipation	mild	not	23AUG1998	15SEP1998
cardiac failure	moderate	not	24AUG1998	22SEP1998
anaemia	mild	not	25AUG1998	
leukocytosis	mild	not	25AUG1998	05OCT1998
dermatitis fungal	mild	not	26AUG1998	31AUG1998

CLINICAL LABORATORY TESTS

The following 'code-4' or 'code-5' important laboratory abnormalities were detected:

(definitions: see footnote under first narrative)

Test (pathological values, unit)

wbc (<2800 ; >11200 /mm3)

10000 at baseline 15900 at week 2 14800 at week 4 11500 at week 8

No important laboratory abnormalities were reported as adverse event by the investigator.

JRF--TRIAL RIS-USA-102
SERIOUS ADVERSE EVENT SUMMARY

Patient: RED #A30030	Investigator: Bernner R., MD
Age: 64 years	Trial medication: PLACEBO
Race: Caucasian	Treatment duration: 14 days
Sex: male	DB duration: 14 days
Country: USA	Treatment start: December 18, 1998
	Treatment stop: December 31, 1998

treatment1 = double-blind, treatment2 = transition, treatment3 = open label

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
*diabetes mellitus (uncontrolled diabetes)	moderate	not	28DEC98	05JAN99	treatment1	11

** days after start treatment1

BASELINE PATIENT DATA

- Diagnosis: bipolar disorder, manic episode
- Medical and surgical history: cardiovascular; gastrointestinal
- Concomitant disorders: cardiovascular; endocrine; gastrointestinal
- Physical examination: skin
- Previous medications: clonidine (0.1mg); docusate sodium (300mg); enalapril maleate (40mg); famotidine (40mg); furosemide (20mg); nifedipine (90mg)

TREATMENT DATA:

Trt. Phase	Treatment	Start	Stop	Daily Dose (mg)	Duration
TREATMENT1	PLACEBO	18DEC1998	19DEC1998	0	2
TREATMENT1	PLACEBO	20DEC1998	26DEC1998	0	7
TREATMENT1	PLACEBO	27DEC1998	27DEC1998	0	1
TREATMENT1	PLACEBO	28DEC1998	31DEC1998	0	4

CLINICAL NARRATIVE

A serious adverse event occurred after 11 days of double-blind placebo treatment, on December 28, 1998; the patient, with known diabetes mellitus at entry into the trial, was diagnosed with uncontrolled diabetes mellitus.

The patient experienced an episode of hyperglycemia (blood sugar 680, 684 mg/dl), he was confused and he also reported a fall (no injury). His blood pressure was 180/110, later 140/110, 130/80, 120/80. He was placed on an insulin coverage. He stabilized and was transferred to the psychiatric unit on January 5, 1999. No further falls or confusion were reported.

The serious AE of diabetes mellitus was reported as moderate and not drug-related. The AE ended on January 5, 1999; the patient recovered from this AE.

ECG DATA

Date	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcF (ms)
18DEC1998	DB	BASELINE	59	164	90	442	438 BL	440 BL
05JAN1999	POST	MONTH 1	70	148	134 *	452	488 PL	476 PL

(A = Above normal, B = Below normal, * = Abnormal, P = Pathological, BL = Borderline, PL = Prolonged)

RIS-USA-6

RISPERIDONE

SERIOUS ADVERSE EVENT SUMMARY

PROTOCOL NUMBER: 64,766/0205-03
INVESTIGATOR: CHARNEY, M.D.
PATIENT: RED #254
SERIOUS ADVERSE EVENT: HOSPITALIZED FOR
HYPOGLYCEMIA

RED a 19-year-old white male, entered Study 204 and completed the double-blind treatment. Upon completion of the study and finalization of the database, it was determined that the patient was receiving risperidone 16 mg/day. The patient entered open label Study 205 on January 17, 1991 and was titrated to 12 mg risperidone/day on February 1, 1991.

The patient prematurely discontinued the study on September 15, 1991 (289 days after entry) because of a worsening of psychotic symptoms. He had become uncooperative and had refused three doses of medication. His last dose of study medication was August 27, 1991, 280 days after entry into Study 205. He had received a mode daily dose of 12 mg risperidone for 226 days. On August 27, 1991, **RED** was hospitalized for one day due to hypoglycemia. The investigator assessed the severity as moderate and the hypoglycemia resolved without any residual effects. He was given IV dextrose 1 ampule PRN for the hypoglycemia on August 28, 1991. No action was taken relative to the test drug and the investigator indicated that there was no relationship to the study medication.

Other concomitant medications near the time of his hospitalization included 500 mg of chloral hydrate at night for anxiety on August 26, 1991. From August 26, 1991 to August 28, 1991, he received 1 mg oral Ativan PRN for anxiety and on August 28, 1991 he received 1 mg Ativan IM PRN for agitation. During the study, he also received Cogentin® 2-3 mg/day for EPS.

The results of the laboratory assessments taken on August 13, 1991 were within normal limits with the exception of a clinically insignificant elevation in potassium (5.7 meq/L; normal range: 3.4-5.4 meq/L) and the presence of trace levels of urine ketones. On September 4, 1991 (8 days off drug), he had a significant elevation in CPK (722 U/L, normal range: 22-198 U/L). The CPK returned to normal (77 U/L) at the follow-up serum chemistry on October 3, 1991 (37 days off drug).

Volume 1/Page 221

JJRPrev 00380098
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D807.236

R. 6134

JRF--RIS-USA-63

RISPERIDONE--RIS-USA-63
SERIOUS ADVERSE EVENT SUMMARY

COUNTRY:	USA
INVESTIGATOR:	J. T. Hutton, MD
PATIENT:	RED #0911
STUDY MEDICATION:	Placebo
SERIOUS ADVERSE EVENTS:	Hospitalization:
	Blackout Spell
	Hospitalization:
	Infection to Thumb
	Hospitalization:
	Urosepsis

RED a 70-year-old Caucasian male, with a 7-year history of vascular dementia with delirium, entered RIS-USA-63 on November 8, 1996. The patient's medical history included: diabetic retinopathy, sinusitis, nasal septal deformity, coronary artery disease, hyperlipidemia, myocardial infarction, hypertension, angioplasty, supraventricular tachycardia, congestive heart failure, orthostatic hypotension, pneumonia, hemoptysis, obesity, gastritis, cholecystectomy, impotence, rectal surgery, laminectomy, diabetic neuropathy, headaches, insulin-dependent diabetes mellitus, hypokalemia, allergic rhinitis, and seizure secondary to hypoglycemia. Physical examination at baseline revealed general abrasions on the left foot. The patient's neurological examination showed a Babinski's reflex on the right side. The baseline ECG revealed a left QRS axis deviation, an extensive anterior myocardial infarction (probably old), a possible inferior myocardial infarction (probably old), and a sinus rhythm.

The patient received placebo, 2 tablets per day, starting on November 8, 1996 through November 15, 1996 during the single-blind washout period. The patient then received placebo, 2 tablets per day, during the double-blind phase starting on November 16, 1996 through the end of the patient's participation in the study on February 6, 1997.

The study medication was temporarily stopped after 5 days of double-blind treatment with placebo, when the patient experienced a blackout spell and was hospitalized (November 20, 1996). This event was considered severe and serious, but unrelated to study medication. The patient missed three doses of study medication on November 20 and 21, 1996. Double-blind treatment resumed on November 22, 1996 and the patient then completed the full course of study medication.

The patient was hospitalized a second time on December 20, 1996 for a moderate infection to the right thumb (December 20, 1996 - January 9, 1997).

Volume 1/Page 222

JJRPprev 00380099
Confidential/Produced in Litigation Pursuant to Protective Order
D807.237

JRF-RIS-USA-63

that occurred subsequent to a mild fracture of the right thumb (November 19, 1996 - January 9, 1997). A third hospitalization occurred for urosepsis of moderate severity (January 16, 1997 - January 18, 1997). The patient experienced lethargy and anorexia prior to the hospitalization. Both hospitalizations were considered to be serious adverse events; however, neither was considered to be related to the study medication.

During the study, the patient was treated with the following concurrent medications that were started prior to entry into the study and were ongoing at the end of the study: clonidine, docusate calcium, aspirin, metoprolol, digoxin, multivitamin, cisapride, and insulin (injection). The patient also received the following concurrent medications that were started after study entry and were ongoing at the end of the study: propoxyphene napsylate/acetaminophen (started November 23, 1996), nifedipine (started November 24, 1996), acetaminophen (started November 24, 1996), magnesium hydroxide (started November 24, 1996), lactulose (started November 24, 1996), benazepril (started January 7, 1997), and clemastine fumarate (started January 15, 1997). In addition, the patient received the following concurrent medications that were discontinued before the end of the study: doxazosin mesylate (prior to study - end-date unknown), nitroglycerin (prior to study - end-date unknown), potassium chloride supplement (prior to study - end-date unknown), ascorbic acid supplement (prior to study - end-date unknown), prednisolone acetate ophthalmic (prior to study - end-date unknown), lisinopril (November 24, 1996 - end-date unknown; January 19, 1997 - end-date unknown), ciprofloxacin ophthalmic (December 11, 1996 - end-date unknown), ticarcillin (December 20, 1996 - end-date unknown), vancomycin (December 20, 1996 - end-date unknown), ceftriaxone (January 16, 1997 - end-date unknown), amoxicillin (January 15, 1997 - end-date unknown), and ofloxacin (January 18, 1997 - end-date unknown). The patient also received lorazepam (November 9, 1996 - November 12, 1996; November 14 and 19, 1996; January 9, 1997) and diazepam (November 29 and 30, 1996; December 5, 1996).

In addition to the events discussed above, the following adverse events were reported: cataract surgery (December 10, 1996), blackout spell (January 31, 1997), and two falls (February 6 and 7, 1997). The severity of the surgery and falls were categorized as mild, and the blackout spell was considered to be of moderate severity. The surgery and blackout spell were not believed to be related to the study medication, but both falls were considered to be possibly related to the study medication.

Volume 1/Page 223

JJRPrev 00380100
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D807.238

IRF-RIS-USA-63

RISPERIDONE-RIS-USA-63
SERIOUS ADVERSE EVENT/DEATH SUMMARY

COUNTRY:	USA
INVESTIGATOR:	S. R. Cohen, MD
PATIENT:	RED #4113
STUDY MEDICATION:	Placebo
SERIOUS ADVERSE EVENT:	Stopped Eating (Poor Oral Intake)
CAUSE OF DEATH:	Multiple Organ Failure

RED a 95-year-old Caucasian female with a history of late-onset dementia of the Alzheimer's type with delusions and depression, entered RIS-USA-63 on July 15, 1996. The patient's medical history included headaches, hearing loss, chest pain, cholecystostomy, incontinence, degenerative joint disease, basal cell cancer, anemia, hypothyroidism and allergies to sulfa and aspirin. Her physical examination showed her general appearance to be thin, her skin atrophic with tears and ecchymosis, and decreased hearing. She had a right upper quadrant scar on her abdomen, a systolic murmur, mild kyphosis, and no pulse in her feet. The results of the neurological examination showed that she was incontinent in both bowel and bladder functions, knee and ankle reflexes were absent, severe akathisia and sighing, and she displayed a right Babinski. Her ECG evaluation at baseline was within the normal limits.

During the single-blind washout period, the patient received 2 tablets of placebo per day from July 16, 1996 to July 22, 1996. She then received two tablets of double-blind study medication per day from July 23, 1996 to July 29, 1996; she received only 1 tablet of study medication on July 30, 1996. On July 29, 1996, the patient appeared slightly more withdrawn and lethargic and stopped eating (poor oral intake). Over the next 48 hours the lethargy and decreased intake progressed. The patient died on July 31, 1996 of multiple organ failure.

The patient discontinued the study medication on July 30, 1996 after 8 days of treatment because of her poor oral intake. This event was considered life threatening and so represents a serious adverse event; however, the poor intake and subsequent death were the result of an intercurrent condition and were considered not related to the study medication.

The patient was treated with the following medications that were started prior to the study and were ongoing at the end of the study: multivitamins, ferrous sulfate, and propoxyphene napsylate/acetaminophen. Other medications taken during the study included lorazepam (July 16, 1996 - July 23, 1996), levothyroxine (started prior to study - July 28, 1996) and carbamide peroxide ear drops (July 21, 1996 - July 25, 1996).

Volume 1/Page 224

JJRPrev 00380101
Confidential/Produced in Litigation Pursuant to Protective Order
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NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

Evaluation of glucose metabolism with risperidone

62

JRF-RIS-USA-63

The only other adverse event reported during the study was severe weight loss (18 lbs in six months) that was not related to the study medication.

Volume 1/Page 225

JJRPrev 00380102
Confidential/Produced in Litigation Pursuant to Protective Order
D807.240

R. 6138

Additional death info: RIS-USA-63 BDD response

Patient #4113

Treatment: Placebo

Cause of Death: Multiple Organ Failure

This 95-year-old woman began double-blind medication on July 23, 1996. One week later, on July 29, the attending physician noted that she appeared to be slightly more withdrawn and lethargic and that her oral intake was poor. She also displayed slightly less akathisia, which had previously been very severe. Study medication was discontinued after eight days of treatment on July 30, 1996. Over the next 48 hours, oral intake decreased further, as did the lethargy. On the morning of July 31, the patient did not speak or follow commands, and had only moderate spontaneous movement of all extremities. Her lungs were clear and her cardiac examination was normal. She appeared very dehydrated, with sunken eyes and dry mucous membrane; her weight had decreased by 18 pounds over the previous six months. The patient's laboratory results for July 31 were as follows: BUN: 144 mg/dl; creatinine: 3.4 mg/dl; sodium: 169 mmol/L; chloride: 138 mmol/L; glucose: 205 mg/dl. The patient's family refused her hospitalization or nasogastric hydration, and she expired on July 31, 1996. The investigator did not think the death was related to study treatment, but rather due to the aging process, along with the progression of dementia and her overall compromised nutritional status. The death certificate did not show cause of death, and no autopsy was performed.

Volume 1/Page 226

JJRPrev 00380103
Confidential/Produced in Litigation Pursuant to Protective Order
D807.241

JRF-RIS-USA-63

RISPERIDONE-RIS-USA-63
SERIOUS ADVERSE EVENT SUMMARY

COUNTRY:	USA
INVESTIGATOR:	B. J. Carroll, PhD
PATIENT:	RED#115
STUDY MEDICATION:	Risperidone 1.0 mg
SERIOUS ADVERSE EVENT:	Hospitalized: Hypoglycemia

RED a 79-year-old Black female with a 6-year history of vascular dementia with delusions, entered RIS-USA-63 on December 5, 1996. The patient's medical history included: right cataract, left cataract removal, atrial fibrillation, hypertension, congestive heart failure, chronic constipation, right hip fracture and repair, extrapyramidal symptoms, tardive dyskinesia, parkinsonian symptoms, hyperthyroidism, insulin-dependent diabetes mellitus, pernicious anemia, B₁₂ deficiency (treated), recurrent transient ischemic attacks, and peripheral vascular disease. Physical examination at baseline revealed confusion, scabs and sores on left lower extremity, edentulous, cataracts, grade II heart murmur with normal sinus rhythm, and flexion contracture of left foot. The patient's neurological examination showed bilateral upper extremity tremors, inability to stand, fecal and urinary incontinence, and extrapyramidal signs (tongue and mouth movement). The baseline ECG was within normal limits with a possible ectopic atrial rhythm.

The patient received placebo, 2 tablets per day, starting on December 6, 1996 through December 12, 1996 during the single-blind washout period. The patient then received double-blind study medication, 2 tablets per day, starting on December 13, 1996 until the end of the patient's participation in the study.

The patient was hospitalized after 80 days of treatment with study medication on March 2, 1997 because of a hypoglycemic episode (March 2, 1997 - March 6, 1997). She had a history of unstable blood sugar levels due to intermittent refusal of food and fluids. For several days preceding this event, the patient had been refusing some meals. On the morning of March 2, 1997, she was nonverbal and perspiring profusely with cool and clammy skin, and had a somnolent appearance, closed eyes, and a droop to the bottom lip. Glucometer readings were 24 to 27; the patient's normal range was 180 to 220. The patient was transferred from her home Geropsychiatry ward to the Medical Services Unit on March 2, 1997, where she remained until March 6, 1997. She improved and her blood sugar levels normalized after administration of intravenous saline and appropriate adjustments to insulin injections based on oral intake. The decrease in blood sugar was caused by the patient's refusal to eat, combined with continued insulin

Volume 1/Page 227

JJRPrev 00380104
Confidential/Produced in Litigation Pursuant to Protective Order
D807.242

JRF-RIS-USA-63

injections. This hypoglycemic episode was considered to be serious, of moderate severity, and not related to the study medication. No study medication was administered after the morning dose on March 2, 1997 because the study medication was inadvertently omitted from the medication orders on the Medical Services Unit. The patient became agitated and was administered lorazepam. Since the patient was scheduled to exit RIS-USA-63 on March 6, 1997, no additional study medication was administered under the double-blind protocol after March 2, 1997.

During the study, the patient was treated with the following concurrent medications that were started prior to entry into the study and were ongoing at the end of the study: aspirin, enalapril maleate, digoxin, propylthiouracil, vitamin B₁₂, acetaminophen, insulin, bisacodyl, magnesium hydroxide, sodium biphosphate/sodium phosphate enema, lactulose, and a multivitamin.

The patient also received trimethoprim/sulfamethoxazole (December 6, 1996 - ongoing), tolnaftate powder (December 26, 1996 - ongoing), flexible hydroactive wound dressing (December 18, 1996 - ongoing), and magnesium citrate (March 4, 1997 - ongoing). In addition, the patient received the following concurrent medications that were discontinued before the end of the study: docusate sodium/casanthranol (prior to study - end-date unknown), castor oil (December 9, 1996 - end-date unknown), and fluocinolone acetonide cream (December 11, 1996 - end-date unknown). The patient received lorazepam (December 4, 6, 26, 1996 and March 2, 1997 - March 6, 1997) and chloral hydrate (December 5, 1996, January 15, 21, 26, 1997, and February 13, 20, 28, 1997).

In addition to the hypoglycemia discussed above, the following adverse events were reported: moderate urinary tract infection (December 5, 1996 - December 16, 1996; December 30, 1996 - January 10, 1997), moderate sacral decubitus (December 18, 1996 - January 31, 1997), and mild urinary tract infection (March 2, 1997 - ongoing). The sacral decubitus was considered to be unrelated to the study medication, but the urinary tract infections were deemed to be possibly related to the study medication.

Volume 1/Page 228

JJRPrev 00380105
Confidential/Produced in Litigation Pursuant to Protective Order
D807.243

JRF--RIS-USA-63

RISPERIDONE--RIS-USA-63
SERIOUS ADVERSE EVENT/DEATH SUMMARY

COUNTRY:	USA
INVESTIGATOR:	L Katz, MD
PATIENT:	RED #1204
STUDY MEDICATION:	Risperidone 1.0 mg
SERIOUS ADVERSE EVENT:	Hospitalized: Hyperglycemia
CAUSE OF DEATH:	Pneumonia

RED an 85-year-old Black male, with a history of uncomplicated, late onset dementia of the Alzheimer's type, entered RIS-USA-63 on December 12, 1995. The patient's medical history included: insulin-dependent diabetes, anemia, hyperkalemia, hypertension, hematuria, chronic renal insufficiency, benign prostatic hyperplasia, hypothyroidism, partial thyroidectomy, lacunar infarcts/focal atrophy, pseudo-obstruction, gastritis, peptic ulcer disease, colon surgery for cancer in 1985, PPD conversion, intermittent constipation, depression, and falls with head injury. His physical examination at baseline showed an abdominal midline scar and no teeth. His neurological examination at baseline revealed an increased resistance to passive movement, bladder-bowel incontinence, increased tone when tested for extrapyramidal signs, and abnormal reflexes of palmar grasp and eye blink. His ECG evaluation at baseline showed a sinus rhythm with left anterior fascicular block, sinus tachycardia and an ST wave abnormality.

The patient received placebo, 2 tablets per day, from December 12, 1995 through December 17, 1995 during the single-blind washout phase. The patient then received double-blind study medication, 2 tablets per day, starting on December 18, 1995 until the end of the patient's participation in the study.

The patient discontinued the study prematurely after 13 days of treatment with study medication on December 30, 1995 because of an adverse event: he was hospitalized for hyperglycemia, hypocalcemia, and urinary tract infection which progressed to non-ketotic, hyperosmolarity syndrome with acute renal failure. He died of pneumonia on January 1, 1996. The patient's hospitalization represents a serious adverse event that occurred during the study; however, the hospitalization, medical decline and resulting death of the patient were the result of an intercurrent event and were not related to the study medication. No other adverse events were reported during the study.

Volume 1/Page 229

JJRPrev 00380106
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D807.244

Additional death info: RIS-USA-63 BDD response

Patient #1204

Treatment: Risperidone 1.0-mg

Cause of Death: Hyperglycemia; Pneumonia

This 85-year-old man discontinued study medication after 13 days of treatment because of hospitalization for hyperglycemia, hypocalcemia, and urinary tract infection. Blood work done at screening revealed glucose 181 (nl: 70-125) mg/dl, creatinine 1.9 (0.17-1.8) mg/dl, Na 150 (135-146) meq/l, RBC 3.4 (3.7-5.5) mm/cumm, Hg 11.1 (11.8-15.8) g/dl, and Hct 32.3 % (36-49). The patient began study medication on December 18, 1995. Routine assessment on December 26 was unremarkable. The nursing staff noted that on December 30, the patient was lethargic and somnolent in the early morning hours and a blood glucose drawn at 12:30 was 491 mg/dl. The patient was sent to the emergency room and blood work done at 14:50 revealed a blood glucose level of 836 mg/dl, Na of 146 meq/l, and potassium of 2.6 meq/l. Urine was positive for >100,000 Proteus. The patient progressed into nonketotic hyperosmolarity syndrome with acute renal failure (demonstrated by BUN/creatinine 95/4.9 and hypoxia (ABG pH 7.44/pCO₂ 36/pO₂ 46). The patient expired on January 1, 1996 of urinary sepsis and the death was considered unrelated to study medication. No death certificate was available and no autopsy was performed.

Volume 1/Page 230

JJRPrev 00380107
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D807.245

JRF-RIS-USA-63

RISPERIDONE-RIS-USA-63
PREMATURE DISCONTINUATION SUMMARY

COUNTRY:	USA
INVESTIGATOR:	K. Sakaiye, MD
PATIENT:	RED #2613
STUDY MEDICATION:	Risperidone 2.0 mg
REASON FOR DISCONTINUATION:	Abnormal Lab Results for Liver Function and Blood Glucose

RED an 83-year-old Caucasian female with a 2-year history of mixed dementia, entered RIS-USA-63 on August 13, 1996. The patient's medical history included: cataracts, arteriosclerotic cerebral vascular disease, hypertension, interstitial pulmonary fibrosis, gastritis, urinary incontinence, osteoporosis, contractures, increased muscle tone, decreased spontaneous movement in left arm and leg, cerebral atrophy, cerebral ischemia, multiple skin tears, diabetes, anemia, poor dentition, general bruising to arms and legs, wheel chair-bound, leg pain, and a history of depression and anxiety. Her physical examination at baseline revealed poor dentition. Her neurological examination at baseline revealed fecal and urinary incontinence, tremor of tongue, mild cogwheel rigidity on right arm, presence of an abnormal glabella tap reflex, mild rigidity with left side greater than right, hyperkinetic activity, profound paranoia with combative reactions, indications of increased tone, and decreased spontaneous movements in left arm and leg. The patient's ECG evaluation at baseline detected a low limb lead voltage, and was otherwise within normal limits.

The patient received placebo, 2 tablets per day, starting on August 14, 1996 through August 20, 1996 during the single-blind washout period. The patient then received double-blind study medication, 2 tablets per day, starting on August 21, 1996 until the end of the patient's participation in the study.

The patient stopped the study medication after 37 days of treatment with the study medication on September 26, 1996 because of abnormal lab test results for blood glucose and liver function, including an elevated transaminase and bilirubin value, and a mild drop in albumin. The abnormal liver function values were seen on September 18, 1996 and on September 25, 1996. The study medication was discontinued for safety reasons. The patient appeared asymptomatic, and at time of discontinuation showed a non-tender abdomen, no hepatomegaly and no jaundice. The abnormal lab results for liver function were possibly related to the study medication.

Volume 1/Page 231

JJRPrev 00380108
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D807.246

JRF-RIS-USA-63

RISPERIDONE-RIS-USA-63
SERIOUS ADVERSE EVENT SUMMARY

COUNTRY:	USA
INVESTIGATOR:	C. Herndon, MD
PATIENT:	RED #4013
STUDY MEDICATION:	Risperidone 1.0 mg
SERIOUS ADVERSE EVENT:	Late Adult Onset Diabetes

RED an 86-year-old Caucasian male with an 8-year history of late-onset dementia of the Alzheimer's type with depressed mood, entered RIS-USA-63 on February 22, 1996. The patient's medical history included allergic rhinitis, hypertension, congestive heart failure, angina, cholecystectomy, constipation, dry skin, hypothyroidism, and pernicious anemia. During the baseline physical examination it was noted that the patient was obese with no abdominal masses. With the exception of the external genitalia, pelvic and rectum areas, which could not be examined, the remaining systems were normal. The results of his neurological examination showed that all functions were normal. His ECG evaluation at baseline showed a sinus rhythm with a first degree atrioventricular block with occasional premature ventricular contractions, left axis deviation, and a left ventricular hypertrophy. It was also noted that septal M.I. could not be ruled out.

During the single-blind washout period, the patient received 2 tablets of placebo per day from February 22, 1996 through February 28, 1996. He then received two tablets of double-blind study medication per day from February 29, 1996 through March 1, 1996. On March 3, 1996, after three days of treatment, he was temporarily discontinued from study medication through March 5, 1996. During this interval the patient was diagnosed with adult onset diabetes. Administration of the study medication was resumed on a 1 tablet twice daily dosage schedule from March 6, 1996 to May 15, 1996 at which time the patient completed the study.

The patient was treated with the following medications that were started prior to the study and were ongoing at the end of the study: vitamin B₁₂, docusate sodium, aspirin, ranitidine, acetaminophen/diphenhydramine, milk of magnesia, diltiazem HCl, potassium chloride, chlorpheniramine, acetaminophen, nitroglycerine, l-hyoscyamine sulfate, loperamide HCl, and artificial tears.

Other than an increase in the patient's blood sugar level (March 2, 1996 - March 4, 1996), which was not related to the study medication, no other adverse effects were noted.

Volume 1/Page 232

JJRPrev 00380109
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D807.247

JRF-RIS-USA-63

During the study, the patient was treated with the following concurrent medications: lactulose (started prior to study - ongoing), NPH insulin (started prior to study - ongoing), sodium polystyrene sulfonate (started prior to study - ongoing), Fleet® enema (started prior to study - ongoing), ticarcillin/clavulanate potassium (December 30, 1995 - ongoing), gentamicin sulfate (December 30, 1995 - ongoing), erythromycin (December 30, 1995 - ongoing) albuterol sulfate (December 30, 1995 - ongoing), and ceftriaxone sodium (December 30, 1995 - ongoing).

Volume 1/Page 233

JJRPrev 00380110
Confidential/Produced in Litigation Pursuant to Protective Order
D807.248

R. 6146

IRF-RIS-USA-63

RISPERIDONE-RIS-USA-63
SERIOUS ADVERSE EVENT/DEATH SUMMARY

COUNTRY:	USA
INVESTIGATOR:	C. Herndon, MD
PATIENT:	RED #4014
STUDY MEDICATION:	Risperidone 0.5 mg
SERIOUS ADVERSE EVENT:	Pneumonia, Urinary Tract Infection, Diabetes
CAUSE OF DEATH:	Cardiorespiratory Arrest

RED a 94-year-old Caucasian female with an 9-year history of late-onset dementia of the Alzheimer's type with delusions, entered RIS-USA-63 on March 14, 1996. The patient's medical history included hypertension, occasional diarrhea and constipation, occasional urinary tract infection and incontinence, osteoarthritis, lipoma, and diabetes mellitus. While listening to her lungs during the baseline physical examination a few respiratory wheezes were noted. With the exception of the patient's breast, external genitalia, pelvic and rectum areas, which could not be examined, the remaining systems were normal. The results of the neurological examination showed that she was incontinent in both bowel and bladder functions; however, the remaining functions were normal. Her ECG evaluation at baseline showed a sinus arrhythmia with a moderate left axis deviation, low QRS voltage, and a long QT interval.

During the single-blind washout period, the patient received 2 tablets of placebo per day from March 14, 1996 to March 20, 1996. She then received two tablets of double-blind study medication daily from March 21, 1996 to March 24, 1996. After 3 days, she was temporarily discontinued from March 25 to March 29 due to hospitalization with pneumonia, a urinary tract infection, and diabetes out of control all of which resolved by April 11, 1996.

On March 30, 1996 study medication was resumed and given on a 2 tablets per day dosing schedule until April 9, 1996. The patient's hospitalization represents a serious adverse event that occurred during the study; however, the pneumonia, urinary tract infection, and diabetes were the result of intercurrent events and were considered not related to the study medication.

The patient was administratively discontinued from the study prematurely after a total of 20 days treatment on April 10, 1996. The nursing home withheld the study medication and failed to notify the sponsor. Her final visit occurred on April 24, 1996. The patient's pneumonia recurred on April 25, 1996 and the patient died April 26, 1996, 17-days after study medication was discontinued.

Volume 1/Page 234

JJRPrev 00380111
Confidential/Produced in Litigation Pursuant to Protective Order
D807.249

JRF-RIS-USA-63

The patient again developed severe pneumonia on April 24, 1996, was hospitalized on April 25, 1996, and died on April 26, 1996. The immediate cause of death was listed as cardiorespiratory arrest. The cause of death was not considered to be related to the study medication.

The patient was treated with the following medications that were started prior to the study and were ongoing at the end of the study: humulin insulin, aspirin, propranolol, glyburide, dipyridamole, nitroglycerine, furosemide, and potassium chloride.

No other adverse events were reported during the study.

Additional death info: RIS-USA-63 BDD response

Patient #4014

Treatment: Risperidone 0.5-mg

Cause of Death: Cardiorespiratory Arrest

This 94-year-old woman with a history of insulin-dependent diabetes mellitus, urinary tract infections, and hypertension, discontinued study treatment after three days because of hospitalization for double pneumonia, a urinary tract infection, and exacerbation of diabetes. Subsequently, her laboratory values were consistent with severe infection leading to pneumonia, hyperglycemia, and hyperosmolality (BUN: 67 mg/dl; Na: 165 meq/l; glucose: 429 mg/dl; WBC: 8.9 m/cumm with a left shift and 16% bands).

The patient then resumed study treatment for approximately ten days. Study treatment was discontinued again and two weeks later the patient developed a fatal pneumonia and expired. Death was not considered to be related to study treatment, which had been discontinued 16 days previously. The death certificate attributed cause to cardiopulmonary arrest due to congestive heart failure and coronary artery disease; no autopsy was performed.

Volume 1/Page 236

JJRPrev 00380113
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D807.251

R. 6149

JRF-RIS-INT-23

RISPERIDONE -- RIS-INT-23

COUNTRY :	Germany
INVESTIGATOR :	Rieger M.
PATIENT :	RED #118
TRIAL MEDICATION :	risperidone
SERIOUS ADVERSE EVENT:	hospitalisation for therapy adjustment

RED a 73-year old, Caucasian female patient entered the trial on 05/10/95. Her height was 134 cm and her weight was 44.0 kg. The DSM-IV diagnosis was Chronic Schizophrenia of the residual type. The patient was hospitalised for 11 years before trial start. She was 22 years old when he experienced his first onset of psychiatric symptoms and 25 years old at the time of his first hospitalisation. The patient was hospitalised once before. Medical history revealed left chronic heart failure, hypertension, diabetes mellitus Type II. Medication stopped at baseline included haloperidol 7.5 mg/day, melperone 50 mg/day, started on 12/09/95.

Other medications taken by this patient during the trial Elantan 50 mg/day started on 21/02/96, Isoket retard 2 x 60 mg/day started prior to the trial till 20/02/96; Minobal 5 mg/day started on 21/02/96, Mosegor 2 x 10 ml/day started prior to the trial till 28/02/96; haloperidol 10 mg/day (started prior to the trial) till 18/12/95, haloperidol 5 mg on 19/12/95, digitoxine 0.07 mg/day till 20/02/96; Euglucon 2 tablets/ day from 22/12/95 to 20/02/96; insulin interm. action 2 x 8IE/day on 27/12/95, glucobay 3 x 1/day from 04/01/96 to 07/01/96; insulin interm. action 28-0-14 IE/day from 18/02/96 on; acetylsalicylic acid 100 mg/day from 21/02/96 on.

The patient was hospitalized from 16/02/96 to 29/02/96 for a therapy adjustment of pre-existing diabetes mellitus. The patient continues the trial; the daily dose at month 3 was 4 mg.

Volume 1/Page 237

JJRPrev 00380114
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D807.252

JRF-RIS-INT-23

RISPERIDONE -- RIS-INT-23 DEATH SUMMARY	
COUNTRY:	Israel
INVESTIGATOR:	Selgenik I., MD
PATIENT:	█████ # 367
TRIAL MEDICATION:	risperidone
CAUSE OF DEATH:	hypoglycaemia pneumonia sepsis circulatory failure
SERIOUS ADVERSE EVENT:	hypoglycaemia pneumonia sepsis circulatory failure

RED a 74-year-old caucasian male patient entered the trial on June 16, 1996. The patient was 37 years at onset of the psychiatric symptoms. The patient was diagnosed with Residual Chronic Schizophrenia (295.62). Medical history showed bronchopneumonia, iron deficiency anemia, the of lungs. Physical examination showed back: kyphoscoliosis, general appearance : kyphoscoliosis. Previous medications included haloperidol (any other neuroleptic) 5 mg PO from 14/05/93 and bisacodyl (other) prn PO from 03/11/90 and nitrazepam (other) 5 mg PO from 22/09/93 and orphenadrine (other) 50 mg PO from 23/02/93 and oxazepam (other) 10 mg PO from 18/10/94 and paracetamol (other) prn PO from 30/04/95. Risperidone was dosed as follows : on 23JUN96 3 mg/day, on 30JUN96 2 mg/day, on 07JUL96 2 mg/day, on 14JUL96 2 mg/day, on 15AUG96 2 mg/day, on 16SEP96 2 mg/day, on 27NOV96 1 mg/day.

The patient dropped out of the trial on 27NOV96 because of insufficient response. Serious adverse events occurred: 16 days after the end of treatment, on December 13, 1996: hypoglycaemia (patient died) until 23DEC96, 16 days after the end of treatment, on December 13, 1996: circulatory failure (patient died) until 23DEC96, 23 days after the end of treatment, on December 20, 1996: pneumonia (patient died) until 23DEC96, 23 days after the end of treatment, on December 20, 1996: sepsis (patient died) until 23DEC96.

The patient died because of hypoglycaemia from 13DEC96 to 23DEC96, pneumonia from 20DEC96 to 23DEC96, sepsis from 20DEC96 to 23DEC96, circulatory failure from 13DEC96 to 23DEC96.

Other medications taken by this patient were

for EPS:
- orphenadrine (50 mg qd PO started before the trial until 16JUN96),
for agitation:
- oxazepam (10 mg qd PO started before the trial until 16JUN96),
- oxazepam (10 mg tid PO from 10NOV96 on ongoing at the end of the trial),
for cigarette burn of 1st degree on nose:
- povidone-iodine (qd TO from 20JUN96 to 19JUL96),
- sulfadiazine silver (bid TO from 04JUL96 to 17JUL96),
for constipation:
- bisacodyl (2 tabs/ 3/week PO started before the trial and ongoing at the end of the trial),
for headache:
- paracetamol (500 mg prn PO started before the trial until 30JUN96),
for insomnia:
- nitrazepam (5 mg qd PO started before the trial and ongoing at the end of the trial),
- nitrazepam (5 mg prn PO from 06JUL96 on ongoing at the end of the trial),
for schizophrenia:
- haloperidol (5 mg qd PO started before the trial until 16JUN96),
for self inflicted scratches:
- silicon (bid TO from 02OCT96 to 18OCT96),
- tetracycline (bid TO from 16SEP96 to 01OCT96).

Other adverse events:

- dizziness (moderate; drug-related; adverse event resolved) from 18JUN96 to 19JUN96,
- dizziness (moderate; drug-related; adverse event resolved) from 23JUN96 to 25JUN96,
- fatigue (moderate; drug-related; adverse event resolved) from 18JUN96 to 19JUN96,
- headache (mild; possibly drug-related; adverse event still present) from 18JUN96 on,
- insomnia (mild; drug-related; adverse event still present) from 18JUN96 on,
- vomiting (moderate; drug-related; adverse event resolved) from 18JUN96 to 19JUN96,
- injury (moderate; not drug-related; adverse event resolved) from 20JUN96 to 19JUL96,
- injury (moderate; not drug-related; adverse event resolved) from 16SEP96 to 18OCT96.

Volume 1/Page 238

JJRPprev 00380115
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Janssen Research Foundation

NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

Evaluation of glucose metabolism with risperidone

76

JRF-RIS-INT-23

- agitation (mild; possibly drug-related; adverse event still present) from 10NOV96 on.

The following important laboratory abnormalities were detected:

Chloride (Baseline: 102 meq/l /Pathol.limits:94-111 meq/l): 92 meq/l at Month 6 , 92 meq/l at Endpoint

Haematocrit (Baseline: 36.2 % /Pathol.limits:35-55 %): 31 % at Week 4 , 33 % at Month 2 , 31.5 % at Month 6 , 31.5 % at Endpoint

Haemoglobin (Baseline: 11.6 g/dl /Pathol.limits:11.5-19.9 g/dl): 10 g/dl at Week 4 , 10.9 g/dl at Month 2 , 10.2 g/dl at Month 6 , 10.2 g/dl at Endpoint

Volume 1/Page 239

JJRPprev-00380116
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R. 6152

**RISPERIDONE-RIS-USA-70
SERIOUS ADVERSE EVENT/PREMATURE DISCONTINUATION
SUMMARY**

COUNTRY:	USA
INVESTIGATOR:	J. Tomlinson, MD
PATIENT:	RED #2916
STUDY MEDICATION:	Risperidone 0.5-1.0 mg QD
SERIOUS ADVERSE EVENT:	Hospitalization: choking, possible aspiration, and pneumonia
REASON FOR DISCONTINUATION:	Chose to Discontinue: Family Request

RED an 83-year-old Black female with dementia entered RIS-USA-70 on December 22, 1995. The patient's medical history included: bronchitis, sore throat, constipation, diarrhea, urinary incontinence, urinary tract infection and diabetes. Physical examination at baseline revealed a left lens implant and upper and lower dentures. Electrocardiogram was abnormal with sinus rhythm, however not clinically significant, with right bundle branch block.

She was treated with open-label risperidone 0.5 mg starting on December 22, 1995 and increasing to 1.0 mg on December 29, 1995. She remained on risperidone 1.0 mg until January 18, 1996. Study medication was discontinued on January 18, 1996 at the family's request.

She was admitted to the hospital on January 5, 1996 after choking on food for possible aspiration and was subsequently diagnosed with pneumonia. This serious adverse event was considered not related to the study medication. The event resolved on January 9, 1996 with no residual effects.

Concurrent medications taken during the study included: insulin, human for diabetes, which was started prior to the study and ongoing at the end; and amoxicillin/clavulanate for pneumonia (January 9, 1996 to January 18, 1996). She also received intravenous antibiotics during hospitalization as noted on the hospital discharge summary.

No other adverse events were reported during the study.

Volume 1/Page 240

JJRPrev 00380117
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D807.255

**RISPERIDONE-RIS-USA-70
SERIOUS ADVERSE EVENT/PREMATURE DISCONTINUATION
SUMMARY**

COUNTRY:	USA
INVESTIGATOR:	S.R. Cohen, MD C.J. Hirsch, MD
PATIENT:	RED #4118
STUDY MEDICATION:	Risperidone 0.5 -2 mg QD
SERIOUS ADVERSE EVENTS:	Hospitalization: hyperglycemia
REASON FOR DISCONUATION:	Adverse event: confusion, abnormal gait, hyperglycemia

RED, a 94-year-old Caucasian female with dementia entered trial RIS-USA-70 on January 8, 1997. The patient's medical history included: cataract, macular degeneration, blepharitis, paroxysmal atrial fibrillation, peripheral edema, peptic ulcer disease, and mycotic toe nail infection. Physical examination at baseline recorded erythema on face, hands, feet, left eye cataract, irregular heart rhythm, systolic murmur over precordium (grade II/VI), pedal edema. Neurologic examination revealed there were no reflexes at the knees. Electrocardiogram was abnormal at baseline, with atrial fibrillation and incomplete left bundle branch block. These abnormalities were not considered to be clinically significant.

The patient was treated with risperidone 0.5 mg daily beginning on January 9, 1997, and the dose was kept at that level until October 18, 1997. The patient received a final dose of 0.25 mg on October 19, 1997, when the trial medication was stopped.

The patient discontinued the study prematurely after 284 days of treatment with risperidone on October 19, 1997, because of three adverse events: hyperglycemia, increased disorientation, and unsteady gait. Only the hyperglycemia was considered to be a serious adverse event as the patient was hospitalized for this condition. The three adverse events were rated as severe, but were not considered to be related to the trial medication.

During the trial, the patient was treated with the following concurrent medications that were started prior to the start of the trial and ongoing at the end: potassium supplement, aspirin, oxiconazol nitrate cream, and ocular vitamin. The patient was also treated with ranitidine (prior to study-May 21, 1997), ketoconazole (prior to study-February 26, 1997, teagen and famotidine (May 21, 1997-ongoing), furosemide and fluconazole (November 3, 1997-ongoing), insulin (October 21, 1997-ongoing), glyburide (October 30, 1997-ongoing), triamcindone cream and metronidazole (February 26, 1997-ongoing), acetaminophen (October 26, 1997 and March 23, 1997-March 24, 1997), oxygen (October 20, 1997-unknown), tetracycline (April 20, 1997-August 10, 1997), polyxin b sulfate (May 20, 1997-May 25, 1997), Rochefin (October 20, 1997-unknown), influenza vaccine (October 6, 1997), 5% dextrose/½ normal saline

Volume 1/Page 241

JJRPrev 00380118
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solution (October 21, 1997-October 23, 1997), milk of magnesia (July 2, 1997-July 29, 1997 and October 11, 1997-October 18, 1997), dulcolax (October 19, 1997-October 24, 1997), sulfamethoxazol/trimethoprim (January 29, 1997-February 6, 1997), alclometasone d. propionate cream (February 26, 1997).

In addition to the adverse events described above, the patient also experienced the following adverse events: constipation (July 12, 1997 and July 29, 1997), dysphagia (October 14, 1997-October 19, 1997 and November 4, 1997-ongoing), falls (July 15, 1997, August 29, 1997, September 7, 1997, October 9, 1997), fever (March 23, 1997-March 24, 1997) and October 26, 1997-October 30, 1997), skin infection left ear (April 25, 1997), edema (October 23, 1997-ongoing), pain right hip (July 15, 1997), urinary tract infection (January 28, 1997-February 6, 1997 and October 20, 1997-ongoing), vomiting (September 29, 1997), skin tear left forearm and left lower leg (February 26, 1997-March 13, 1997), weight loss (February 10, 1997-March 8, 1997), skin tear to right wrist (November 2, 1997-ongoing), skin tear left elbow (April 6, 1997-April 10, 1997), increased erythema and rosacea (April 25, 1997-ongoing), skin tear right shin (May 20, 1997), skin lesion right buttock (October 26, 1997-ongoing), hyperglycemia (October 17, 1997-ongoing), and skin tear left wrist (November 2, 1997-ongoing). None of these adverse events were considered to be related to the trial medication. Two more adverse events were reported more than 2 weeks after the trial treatment had been discontinued: congestive heart failure (November 3, 1997), and dysphagia (November 4, 1997); these AE were not considered to be risperidone-related, their outcome was not specified.

Volume 1/Page 242

JJRPprev 00380119
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D807.257

R. 6155

**RISPERIDONE-RIS-USA-70
SERIOUS ADVERSE EVENT/PREMATURE DISCONTINUATION
SUMMARY**

COUNTRY:	USA
INVESTIGATOR:	H. Farmer, DO
PATIENT:	RED #4206
STUDY MEDICATION:	Risperidone 0.5 mg-1.0 mg QD
SERIOUS ADVERSE EVENT:	Hospitalization: hyperglycemia
REASON FOR DISCONTINUATION:	Adverse Event: lethargy, poor appetite

RED an 86-year-old Caucasian female with dementia entered RIS-USA-70 on October 30, 1996. The patient's medical history included: arteriosclerotic heart disease, occasional diarrhea, bladder spasms, occasional urinary tract infection, osteoarthritis, decubitus on left hip, and allergy to penicillin. Her physical examination at baseline showed cachexia and very thin extremities with contractures. On neurologic examination, the patient was almost immobile and showed increased pyramidal tone, decreased gag reflex and movement of eyes, possible sensation to touch, urinary and fecal incontinence, positive grasp reflexes, increased extrapyramidal tone, facial mask, and disorientation. The electrocardiogram was unremarkable.

She was treated with risperidone 0.5 mg/day starting October 30, 1996. After 7 days of treatment, on November 6, 1996, the dosage was increased to 1.0 mg/day until January 30, 1997.

On January 31, 1997, the patient developed moderate lethargy and poor appetite, possibly related to risperidone therapy, and risperidone was temporarily discontinued, pending a re-evaluation of the patient's condition. Risperidone therapy was never resumed.

Eight days later, on February 7, 1997, the patient was hospitalized with severe hyperglycemia (646 mg/dL). In addition, she had severe dehydration and possible sepsis; right lower lobe pneumonia was present on radiographs. The patient was discharged from the hospital on February 13, 1997.

Before and throughout the study (ongoing at the end), the patient received the following concurrent medications: a multivitamin, nabumetone, and artificial tears.

In addition to the serious adverse event described above, the patient experienced moderate weight loss (October 16, 1996, to February 5, 1997).

Volume 1/Page 243

JJRPrev 00380120
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D807.258

Annex 4B: Narratives for adverse events of weight increase associated with discontinuation

Trial no. Patient no.	Treatment group	Adverse event (verbatim)
ADULTS (18-65 years)		
INT-3 (Double-blind short-term)		
0468	Risperidone	Weight gain > 15 lbs, bloating, epistaxis, and anemia
USA-112 (Double-blind short-term)		
A30517	Olanzapine	Weight gain
CHILDREN/ADOLESCENTS (<18 years)		
USA-97 (Open-label)		
A3069	Risperidone	Weight gain,
A3125	Risperidone	Weight gain

RISPERIDONE
PREMATURE DISCONTINUATION SUMMARY

PROTOCOL NUMBER: 64,766/0204-09
INVESTIGATOR: RAJIV TANDON, M.D.
PATIENT: RED #468
REASON FOR DISCONTINUATION: EPISTAXIS/ABDOMINAL
BLOATING/ANEMIA/WEIGHT GAIN

RED a 39-year-old black female, entered the study on 4/17/91. Her first psychotic symptoms began when she was 29 years old; she was diagnosed with schizophrenia-disorganized type. No family history of psychiatric or neurological disorders was reported. In the past six months, the patient received haloperidol 20 mg/day and benztropine 4 mg/day. At entrance to the study, the physical examination was negative and no pertinent medical history was noted. At selection, the patient's vital signs were: supine blood pressure 128/70 mmHg and heart rate 95 beats/min, and standing blood pressure 97/69 mmHg and heart rate 126 beats/min. All other safety tests were within normal limits except for decreased values for hemoglobin (11.5--normal range: 11.6-16.4 g/dL), hematocrit (33--normal range: 34-48%), RBC (3.8--normal range: 4.1-5.6x10⁶/μL) WBC (2.92--normal range: 4.36-10.74x10³/μL), and cholesterol (128--normal range: 140-261 mg/dL). At Visit 1, her weight was 72.5 kg.

The patient was randomized to double-blind medication on 4/22/91 after a three-day placebo washout period due to deteriorating condition. At Visit 3, the values for the hematology parameters continued to decrease: hemoglobin (10.5), hematocrit (31), and RBC (3.5). The values for the hematology parameters were out of the normal range during Visit 4. The hospital progress notes for 5/5/91 refer to "a right naris nosebleed," but severity or duration was not reported. On 5/8/91, a nosebleed was reported in the progress notes as "a self-induced trauma." There is no mention of severity or duration of the nosebleed. The patient also complained about abdominal bloating. At the final visit on 5/9/91, the vital signs were: supine blood pressure 128/62 and heart rate 96 beats/min, and standing blood pressure 86/37 and heart rate 150 beats/min. Her body weight was recorded as 71.5 kg. The weight gain was not reflected in the body weights recorded by the study coordinator during Visits 1 and 5. The weight gain was reported by the unit nurses when they weighed the patient. At discontinuation, the following out-of-range laboratory values were noted: hemoglobin (10.3), hematocrit (32), RBC (3.6), WBC (3.45), monocytes (11.3--normal range: 2.6-10.1%), and total iron (32--normal range: 35-140 μg/dL).

Concurrently, she received Maalox® 15 ml PRN for heartburn, Tylenol® 650 mg q4h for discomfort; Dulcolax® 1 tablet PRN, Colace® 100 mg b.i.d., and Peri-Colace® 1 tablet b.i.d. for constipation; a multivitamin as a dietary supplement; and Cogentin® 2 mg b.i.d. for EPS.

Upon completion of the trial and finalization of the database, it was determined that the patient was receiving risperidone 16 mg.

00-00461

Volume 1/Page 245

JJRPrev 00380122
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D807.260

JRF RIS-USA-112

796/861

JRF--TRIAL RIS-USA-112
PREMATURE DISCONTINUATION SUMMARY

Subject: RED #A10517	Investigator: REDDY N., MD
Age: 26 years	Trial medication: CLANZAPINE
Race: Black	Treatment duration: 63 days
Sex: female	DB duration: 0 days
Country: USA	Treatment start: February 12, 1998
Height: 67	Treatment stop: April 15, 1998

DISCONTINUATION OF TREATMENT:

Date: April 15, 1998, 63 days from the start of treatment

Cause: weight increase

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
weight increase (weight gain)	moderate	very likely	16APR98		treatment	64

** days after start treatment

BASELINE SUBJECT DATA

- Diagnosis: schizoaffective disorder
- Baseline Total PANES: 85
- Baseline Total EPRS: 6
- Schizophrenia Type: depressive type
- Age at onset Schizophrenia: 21
- Age at time of first psychiatric hospitalization: UNKNOWN
- Number of previous psychiatric hospitalization: 0
- NO There is a family history of neurological or psychiatric illness.
- Medical and surgical history: not significant
- Concomitant disorders: allergic/immunologic; ears, nose, throat; genito-urinary; other: elevated ldn 1/98
- Physical examination: no abnormalities
- Previous medications: fluphenazine hydrochloride (50 mg q 2 weeks taken for 337 days); trihexyphenidyl hydrochloride (1 mg bid taken for 176 days)

TREATMENT DATA:

Trt. Phase	Treatment	Start	Stop	Daily Dose (mg)	Duration
TREATMENT	CLANZAPINE	12FEB1998	15APR1998	10	63
TREATMENT	CLANZAPINE	16APR1998	16APR1998	0	1

CLINICAL NARRATIVE

The subject, a 26-year-old female, began study medication treatment on February 12, 1998. On April 15, 1998, after 63 days on study medication, she was permanently discontinued due to moderate weight gain (from 99.8 kg at baseline, to 116 kg at discontinuation). No follow-up information was available regarding the outcome of the event. The investigator considered weight gain to be very likely related to study medication.

ECG DATA

Date	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcF (ms)	QTcI (ms)
09FEB1998	Trt	SCREENING	69	148	80	398	427	417	418

Volume 1/Page 246

JJRPrev 00380123
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D807.261

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NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism
Evaluation of glucose metabolism with risperidone

84

JRF RIS-USA-112

797/861

ECG DATA

Date	Phase	Time	HR(bpm)	PR(ms)	QRS(ms)	QT(ms)	QTcB(ms)	QTcP(ms)	QTcI(ms)
16APR1998	Trt	DAY 64	99	142	84	362	465BL	428	423

(A=Above normal B=Below normal *=Abnormal P=Pathological BL=Borderline
FL=Prolonged)

VITAL SIGNS DATA

Date	Phase	Time	Weight (kg)	Pulse (b/min)	SBP (mmHg)	DBP (mmHg)	BMI
09FEB98	MO	SCREENING	99.8	80	108	72	35
12FEB98	Trt	BASELINE	99.8	80	108	72	35
20FEB98	Trt	WEEK 1		80	124	80	
27FEB98	Trt	WEEK 2		76	112	68	
06MAR98	Trt	WEEK 3		72	112	68	
13MAR98	Trt	WEEK 4		70	110	70	
26MAR98	Trt	WEEK 6		80	110	67	
16APR98	Trt	DAY 64	116	97	108	64	41

No other medications were taken by this subject.

No other adverse events were reported by this subject.

CLINICAL LABORATORY TESTS

No code-3, code-4 or code-5 important laboratory abnormalities were noted.
(Definitions: see footnote under first narrative)

The following laboratory tests had results outside of normal limits
during the trial:

Test (Laboratory limits, unit)

chloride (95-108 meq/L)

105 at baseline 109 at day 64

cholesterol (0-199 mg/dl)

222 at baseline 181 at day 64

cpk (0-190 U/L)

143 at baseline 205 at day 64

ldl (0-130 mg/dl)

148 at baseline 89 at day 64

triglycerides (0-199 mg/dl)

86 at baseline 211 at day 64

Volume 1/Page 247

JJRPrev 00380124
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D807.262

R. 6160

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism
Evaluation of glucose metabolism with risperidone

JRF--RIS-USA-97

93

85

JRF--TRIAL RIS-USA-97

PREMATURE DISCONTINUATION SUMMARY

Subject: RED CRF# A3069	Investigator: Aman M., MD
Age: 8 years	Trial Medication: risperidone
Race: Caucasian	Treatment Duration: 275 days (open-label treatment)
Sex: Male	Treatment Start: June 23, 1998 (open-label)
Country: USA	Treatment Stop: March 25, 1999

DISCONTINUATION OF TREATMENT: Permanent
Date: March 25, 1999 (date of last contact)
Cause: Adverse Event

Adverse Event	Severity	Related	Start	End	Days**
Weight Increase	Moderate	Possible	23Jun98	Ongoing	1

**Days after start of open-label treatment

BASELINE SUBJECT DATA

- Diagnosis: Axis I Disorder, Axis III (XTY karyotype, asthma), Borderline Mental Retardation
- Misonger Conduct Disorder Subscale score 43 at baseline*, ESRS at baseline*†; Parkinsonism (expressive automatic movements: 1-very mild decrease in facial expressiveness);
- Medical and Surgical History: Dermatological, Eyes, Neurological
- Concomitant Disorders: None
- Physical Examination: Allergic/Immunologic; Ears, Nose, Throat; Respiratory

*Value represents baseline at the start of double-blind treatment.

†ESRS assessments which were absent at baseline are not presented in this summary.

CLINICAL NARRATIVE

This 8-year-old Caucasian male reached his optimal dose of risperidone at 1.8 mg/mL daily on July 8, 1998, 15 days after the start of open-label treatment. The patient experienced moderate weight increase after the start of open-label treatment which was considered to be possibly related to study drug. When the dose was reduced the patient's weight increase was reduced; however, the effectiveness of the drug also diminished. His parents requested that study drug be discontinued because of concerns with family history of heart problems and diabetes. No concomitant medication was prescribe for his weight gain. The AE was reported as ongoing after study drug discontinuation.

BACKGROUND DATA

Date	Timepoint	Weight(lb)	Pulse (b/min)	SDP (mmHg)	DBP (mmHg)
30Jun98	Visit 2	---	85	114	76
7Jul98	Visit 3	---	85	100	64
14Jul98	Visit 4	---	92	108	68
21Jul98	Visit 5	99.5	96	112	80
18Aug98	Visit 6	---	97	114	64
15Sep98	Visit 7	106	81	112	68
12Oct98	Visit 8	---	88	104	60
9Nov98	Visit 9	---	84	106	74
7Dec98	Visit 10	111.3	80	110	76
5Jan99	Visit 11	---	88	104	66
2Feb99	Visit 12	---	92	110	74
4Mar99	Visit 13	116.3	72	114	78
25Mar99	EOS	118.5	81	110	76

EOS=end of study

CONCOMITANT MEDICATION

Medication	Dosage	Start	End
Albuterol	2 Puffs PRN	18Jul98	---
Slo-bid	300 mg PO	25Nov98	25Nov98
Amoxicillin	250 mg TID PO	29Dec98	7Jan99

OTHER ADVERSE EVENTS

Adverse Event	Severity	Related	Start	End
Somnolence	Mild	Definite	22Jul98	18Aug98
Asthma	Mild	Possible	25Nov98	14Dec98
Upper Respiratory Tract Infection	Mild	None	29Dec98	7Jan99
Injury	Mild	None	25Aug99	25Aug99
Eosinophilia	Mild	Possible	23Jun98	4Mar99
Hyperprolactinemia	Mild	Definite	23Jun98	Ongoing
Somnolence	Mild	Possible	13Oct98	13Nov98

CLINICAL LABORATORY TESTS

Clinically significant eosinophil and prolactin levels were reported for this patient.

Date	Test	Lab Value	Normal
Range			
21Jul98	Eosinophils	9*	0 - 5%
15Sep98	Eosinophils	9.4*	0 - 5%
7Dec98	Eosinophils	4.2	0 - 5%
4Mar99	Eosinophils	6*	0 - 5%
25Mar99	Eosinophils	7.6*	0 - 5%
21Jul98	Prolactin	33*	2-18 ng/mL
15Sep98	Prolactin	34*	2-18 ng/mL
7Dec98	Prolactin	22*	2-18 ng/mL
4Mar99	Prolactin	12	2-18 ng/mL
25Mar99	Prolactin	29*	2-18 ng/mL

*Value outside of normal range

CLINICAL ABNORMAL ECG FINDINGS

Date	Timepoint	HR (bpm)	QRS (ms)	QT (ms)	QTc (ms)	PR interval (ms)
7Dec98	Visit 10	66	80	396	415	108
25Mar99	EOS	72	80	380	416	124

EOS=end of study

QUALITATIVE ABNORMAL ECG FINDINGS

Date	Timepoint	Abnormality
7Dec98	Visit 10	Occasional premature atrial complexes

PREMATURE DISCONTINUATION SUMMARY

Subject: RED CRF#A3125	Investigator: Aman M., MD
Age: 5 years	Trial Medication: risperidone
Race: Caucasian	Treatment Duration: 149 days (open-label treatment)
Sex: Female	Treatment Start: October 3, 1998 (open-label)
Country: USA	Treatment Stop: March 1, 1999

DISCONTINUATION OF TREATMENT: Permanent
Date: March 1, 1999 (date of last contact)
Cause: Adverse Event

Adverse Event	Severity	Related	Start	End	Days**
Weight Increase	Moderate	Definite	3Nov98	Ongoing	31

**Days after start of open-label treatment

BASELINE SUBJECT DATA

- Diagnosis: Axis I Disorder, Axis III (night terrors), Borderline Mental Retardation
- Nisonger Conduct Disorder Subscale score 43 at baseline*, ESRS 0 at baseline*
- Medical and Surgical History: None
- Concomitant Disorders: ADHD
- Physical Examination: None

*Value represents baseline at the start of double-blind treatment.
†ESRS assessments which were absent at baseline are not presented in this summary.

CLINICAL NARRATIVE

This 5-year-old Caucasian female experienced moderate weight gain after 31 days of open-label treatment with study drug. This AE was considered to have a definite relationship to study drug. The patient's mother was concerned with the patient's weight gain because diabetes and heart problems are common in their family. The patient's mother withdrew consent because of this AE. The AE was reported as ongoing.

BACKGROUND DATA

Date	Time point	Weight(kg)	Pulse (b/min)	SBP (mmHg)	DBP (mmHg)
12Oct98	Visit 2	---	120	106	60
19Oct98	Visit 3	---	116	112	58
26Oct98	Visit 4	---	104	108	68
2Nov98	Visit 5	64	108	100	48
30Nov98	Visit 6	---	92	100	60
19Jan99	Visit 7	69.6	92	100	60
1Mar99	EOS	71.9	116	110	60

EOS=end of study

CONCOMITANT MEDICATION

Medication	Dosage	Start	End
Dimetapp	1 Tsp PO 1x	28Feb99	Ongoing

OTHER ADVERSE EVENTS

Adverse Event	Severity	Related	Start	End
Emotional Liability	Moderate	Possible	12Oct98	19Oct98
Influenza-Like Symptoms	Mild	None	28Feb99	Ongoing

CLINICAL LABORATORY TESTS

No clinically significant laboratory tests were observed.

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NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

Evaluation of glucose metabolism with risperidone

88

JRF-RIS-USA-97

104

CLINICAL ABNORMAL ECG FINDINGS

Date	Timepoint	HR (bpm)	QRS (ms)	QT (ms)	QTc (ms)	PR interval (ms)
1Mar99	EOS	96	72	320	400	120

EOS=end of study

QUALITATIVE ABNORMAL ECG FINDINGS

Date	Timepoint	Abnormality
1Mar99	EOS	Right ventricular hypertrophy possible biventricular hypertrophy

EOS=end of study

Volume 1/Page 251

JJRPrev 00380128
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R. 6164

JANSSEN RESEARCH FOUNDATION
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NDA 20-272, NDA 20-538
RISPERDAL® (risperidone) Tablets and Oral Solution

**Response to FDA Request for Information: Evaluation
of the Effect of Risperidone on Glucose Metabolism**

August 10, 2000
Vol. 15 of 15

JJRP 00383987
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D821.2

JANSSEN RESEARCH FOUNDATION
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INTERNATIONAL PHARMACOVIGILANCE REPORT	
R - number:	R064766 Non-proprietary Name: Risperidone
LMD No.:	153363 Report date: 23 June 2000
Title:	Reported disturbances of the glucose metabolism with risperidone: a post-marketing review.
Author(s):	Andy De Deene, M.D.; Tony Van Tittelboom, M.D.
Department:	International Pharmacovigilance Department, Janssen Research Foundation, B-2340 Beerse, Belgium

ABSTRACT

This report provides an overview of all world-wide reported postmarketing spontaneous adverse event (AE) reports on disturbances of the glucose metabolism in association with risperidone, received by the International Pharmacovigilance (IPV) Department of the Janssen Research Foundation since the first marketing of risperidone in May 1993 through 31 March 2000.

In total 202 spontaneous case reports, dealing with WHO-ART dictionary codes indicative for disturbances in the glucose homeostasis, have been retrieved from the international safety database. In 41 of the cases, newly recognised diabetes was diagnosed. In 60 patients diabetes was already pre-existent. In 26 from the remaining 101 cases the onset of the diabetes was not attributable; in the residual 75 cases a concise diagnosis of the underlying cause of the glucose homeostasis disturbance was impossible. Distinction between type I and type II Diabetes Mellitus (DM) was very difficult because of the scarcity of relevant information.

The available information on body weight was very limited. In the set of patients with glucose related AEs, the ratio for overweight and BMI was higher than in the none-glucose related group. This was to be expected, since overweight is a known risk factor for diabetes mellitus. The proportion of cases with "weight increase" during risperidone treatment, however seems not to be higher than in the none-glucose related group.

There was no relevant difference in the age distribution between the set of patients reported with glucose related AEs and those without.

A distinction in different subgroups in relation to the ethnicity was impossible because this information was not communicated by the reporters.

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Volume 15/Page 1

JJRP 00383989

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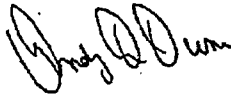
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Given the extensive cumulative exposure estimated at 3,541,514 patient years (through 31 March 2000) and with reference to literature data, the total of 41 cases of possible newly recognised diabetes cases can be considered to be extremely low. Even if the worst case scenario is adopted, meaning that all 202 cases are newly recognised diabetes, the report incidence of diabetes with risperidone exposure, remains extremely low.

It can be concluded that this report is in line with the previous IPV report on DM and that the incidence of DM does not seem to be increased by risperidone. The currently available cumulative spontaneous safety data do not point to a relationship between the use of risperidone and disturbances in the glucose homeostasis. As a result, the benefit/risk estimation specifically for this condition remains favourable and the current Company Core Data Sheet does not need to be changed.

Signature author,



Date: 23 June 2000

Signature author,



Date: 23 June 2000

TABLE OF CONTENTS

1. Methods and data	4
1.1. International database and retrieval	4
1.2. Number of reports per source	4
1.3. Cases and events reported per country	5
1.4. Frequency distribution of all relevant reported adverse events	6
1.5. Gender distribution	7
1.6. Age distribution	8
1.7. Reported total daily dose	8
1.8. Body weight	8
1.9. Ethnicity	9
1.10. Hereditary diabetes mellitus	9
1.11. Treatment duration	9
1.12. Concomitant treatment	10
1.13. Concomitant diseases and medical history	10
1.14. The diagnosis	10
1.15. Seriousness, causality assessment and outcome of the case reports	12
1.16. Disturbances of the glucose metabolism reported as most important reaction	13
1.17. Dechallenge and rechallenge	13
2. Patient Exposure	14
3. Literature	14
3.1. Literature case reports	14
3.2. Case reports on severe adverse events indicative for disturbances in the glucose metabolism	15
3.3. Some literature background data	15
4. Epidemiological calculations and assumptions	16
5. Discussion	16
6. Conclusion	18
7. References	19
8. Appendices	20
Appendix 1: Detailed information of the individual cases	21
Appendix 2: Detailed information on the patient exposure	50
Appendix 3: Attribution definitions of adverse events used by JRF	53
Appendix 4: Current Company Core Data Sheet dated December 1998	55
Appendix 5: Line listings of the individual cases	69

1. METHODS AND DATA

1.1. International database and retrieval

On 31 March 2000, the international safety database JIPSY contained 16,062 spontaneous adverse event (AE) case reports on risperidone. All cases containing following WHO-ART medical dictionary AE terms: *acidosis metabolic, blood sugar decreased, blood sugar increased, coma-diabetic, hypoglycaemia, glucosuria, glucose tolerance test abnormal, hyperglycaemic reaction, hypoglycaemia, hypoglycemic reaction, ketoacidosis, diabetes mellitus, diabetes mellitus aggravated, diabetes mellitus precipitated, osmolar coma, ketonuria, diabetes reactivated or diabetic keto-acidosis*, possibly indicative for disturbances in the glucose metabolism, were retrieved.

1.2. Number of reports per source

A total of 202 (1.2 %) glucose related cases, reported by either health care professionals, physicians, consumers, Regulatory Authority Bodies or from literature, were retrieved. Serious adverse events from clinical trials were not subject of this pharmacovigilance review.

Health Authority	8
Literature	5
Healthcare Professional, Consumer, Unknown source	189
Total:	202

1.3. Cases and events reported per country

COUNTRY	SPONTANEOUS CASES	
	CASE REPORTS (N)	ADVERSE EVENTS (N)
CANADA	7	7
FRANCE	7	7
GERMANY	3	3
ISRAEL	0	0
JAPAN	5	5
SOUTH AFRICA	0	0
SWEDEN	2	2
UNITED KINGDOM	7	7
USA	171	190
Total	202	221

Most cases came from USA. This figure confirms a general trend of a higher reporting rate of USA spontaneous case reports in general, in the pharmacovigilance database.

1.4. Frequency distribution of all relevant reported adverse events

REACTION TERMS	Total
ACIDOSIS METABOLIC	4
BLOOD SUGAR DECREASED	2
BLOOD SUGAR INCREASED	13
COMA DIABETIC	1
DIABETES MELLITUS	54
DIABETES MELLITUS AGGRAVATED	44
DIABETES MELLITUS, recoded to HYPERGLYCAEMIA ¹	3
DIABETES MELLITUS PRECIPITATED	1
DIABETES REACTIVATED	0
DIABETIC KETOACIDOSIS	1
GLUCOSE TOLERANCE ABNORMAL	1
GLUCOSURIA	5
HYPERGLYCAEMIA	46
HYPOGLYCAEMIA	30
HYPOGLYCAEMIC REACTION	1
KETOACIDOSIS	15
KETONURIA	0
OSMOLAR COMA	0
Total	221

All case descriptions were individually examined and entered on a spreadsheet for further analysis.

See Appendix 1 for more detailed information on all individual cases and Appendix 5 for complete line listings.

¹ While reading all the individual cases, the reaction term (Diabetes Mellitus) of three case report (JRFUSA1999003548) has been recoded to hyperglycaemia.

1.5. Gender distribution

There were 88 case reports on female patients and 106 on male patients. In 8 cases the gender was not stated. See table for full description.

MALE		FEMALE	
TOTAL DAILY DOSE	NUMBER OF PATIENTS	TOTAL DAILY DOSE	NUMBER OF PATIENTS
0.5	2	0.5	1
1	6	1	12
1.5	3	1.5	1
2	13	2	9
3	3	3	6
3.5	1	3.5	1
4	17	4	17
4.5	1	-	-
5	1	-	-
6	36	6	19
8	2	8	5
9	2	9	2
10	1	10	1
12	1	12	2
UNKNOWN	17	UNKNOWN	12
	TOTAL : 106		TOTAL : 88
Median : 4 mg		Median : 4 mg	

The slight difference between males and females could possibly be explained by the fact that more men than women have schizophrenia, and the higher back ground incidence of type II diabetes among men.

1.6. Age distribution

The reported ages for the female patients varied from 7 to 96 years. The median was 40. The reported ages for the male patients ranged from 8 to 84 years. The median age was 37.

AGE GROUPS	CASES WITH GLUCOSE AES (N)	%	CASES WITHOUT GLUCOSE AES (N)	%
missing	30	14.85	2,893	18.24
0-10	4	1.98	374	2.36
11-20	17	8.42	1,495	9.43
21-30	31	15.35	2,626	16.56
31-40	45	22.28	3,138	19.79
41-50	30	14.85	2,266	14.29
51-60	18	8.91	1,171	7.38
61-70	12	5.94	819	5.16
71-80	8	3.96	650	4.10
81-90	6	2.97	362	2.28
91-more	1	0.50	66	0.42
Total:	202	100.00	15,860	100.00

There was no relevant difference in the age distribution between the set of patients reported with glucose related AEs and those without.

1.7. Reported total daily dose

The highest total daily dose of risperidone taken by the female patients varied from 0.5 to 12 milligram, with a median of 4 mg. The highest dose taken by male patients varied from 0.5 to 12 mg; median dose was 4 mg (see also section 1.5). In the patient group with no glucose related AEs the median dose was 5 mg for males and 4 mg for female patients. This suggests a no dose-effect relationship.

1.8. Body weight

1.8.1. BODY WEIGHT ABOVE 100 KG

Only in 30 cases with glucose related events, body weight was reported. In 11 patients (36 %) body weight was above 100 kg. To compare this proportion of patients with a body weight above 100 kg, we examined the set of the none-glucose related AEs reported on risperidone for the same

parameter. Out of these 1,910 patients in which body weight was reported, in 143 (7.4 %) the body weight was above 100 kg.

1.8.2. BODY MASS INDEX (BMI)

BMI is calculated as weight in kg/(height in m)². In 14 (6.9 %) cases weight and height was reported so that the BMI could be calculated. In this small set of patients the mean BMI amounted to 33.06. In the set of the none-glucose related AE's, BMI could be calculated in 914 (5.7 %) cases, and the mean BMI amounted to 30.20.

1.8.3. WEIGHT INCREASE

In 11 cases with glucose related events the AE "weight increase" was reported. This equals 5.4 % (11 out of 202). In the set of the none-glucose related AEs the event "weight increase" was reported in 856 cases, which also equals 5.4 % (856/15860).

1.8.4. CONCLUSION

The available information on body weight was very limited. That in the set with glucose related AEs the ratio for overweight and BMI is higher, was to be expected, since overweight is a known risk factor for diabetes mellitus. The proportion of cases with "weight increase" during risperidone treatment, however seems not to be higher than in the none-glucose related group.

1.9. Ethnicity

A distinction in different subgroups in relation to the ethnicity was impossible because this information was seldom communicated by the reporters, (e.g. was available in 3 case reports from literature - see section 3.1)

1.10. Hereditary diabetes mellitus

Only in 16 patients (12.6 %) diagnosed for DM hereditary predisposition (first degree relative) was reported.

1.11. Treatment duration

Since one patient can have more than one event and as such can have more than one treatment duration, the shortest and the longest treatment duration (time from starting risperidone to event onset) per patient was calculated. In the set of the glucose metabolism related AEs the mean of the shortest

treatment duration was 46.6 days and the mean of the longest treatment duration was 56.8 days. In the set of the none-glucose related AEs the mean of the shortest risperidone treatment duration was 43.9 days and the mean of the longest treatment duration was 52 days.

1.12. Concomitant treatment

Within the concomitant taken drugs, reported for all cases, no specific trend could be detected. For a full description of all concomitant drugs we refer to the individual case descriptions (see Appendix 1).

1.13. Concomitant diseases and medical history

Within the reported concomitant diseases or reported medical history, no specific trend could be detected. For a full description of the concomitant diseases or medical history we refer to the individual case descriptions (see Appendix 1).

1.14. The diagnosis

1.14.1. DIAGNOSIS ON EVENT LEVEL

All 221 AEs related to disturbances in the glucose metabolism have been individually scrutinised. The cases for which DM specifically was mentioned in the case description, concomitant disease or medical history, were separated from those in which this was not specified (see table). 144 events were associated with DM. The remaining 77 events occurred most probably secondary to other underlying conditions (e.g. hyperglycaemia in pancreatitis).

Table: AEs association with DM

REACTION TERMS	NO DM	WITH DM	TOTAL EVENTS
ACIDOSIS METABOLIC	4	0	4
BLOOD SUGAR DECREASED	2	0	2
BLOOD SUGAR INCREASED	11	2	13
COMA DIABETIC	0	1	1
DIABETES MELLITUS	0	54	54
DIABETES MELLITUS AGGRAVATED	0	44	44
DIABETES MELLITUS, recoded to HYPERGLYCAEMIA ²	3	0	3
DIABETES MELLITUS PRECIPITATED	0	1	1
DIABETES REACTIVATED	0	0	0
DIABETIC KETOACIDOSIS	0	1	1
GLUCOSE TOLERANCE ABNORMAL	0	1	1
GLUCOSURIA	4	1	5
HYPERGLYCAEMIA	32	14	46
HYPOGLYCAEMIA	20	10	30
HYPOGLYCAEMIC REACTION	1	0	1
KETOACIDOSIS	0	15	15
KETONURIA	0	0	0
OSMOLAR COMA	0	0	0
Total	77	144	221

1.14.2. DIAGNOSIS ON CASE LEVEL

In 127 cases the reported AEs clearly occurred in association with diabetes.
In 75 cases a disturbance in the glucose metabolism occurred without specific mentioning of DM (see table).

Table: Number of patients with DM

DIABETES MELLITUS	YES	127
	NO	75
	TOTAL	202

² While reading all the individual cases, the reaction term (Diabetes Mellitus) of 3 case reports (JRFUSA1999003548, JAUSA33838, JAUSA33916) has been recoded to hyperglycaemia.

In the subgroup of 127 patients diagnosed for DM, we focussed on the patients suggestive for newly diagnosed diabetes. If in the narratives specifically was mentioned that the event occurred for the first time and if diabetes had been diagnosed, then the patient was considered to have newly diagnosed diabetes. In 60 cases the diagnosis of diabetes (mentioned either in the narratives, medical history or concomitant disease section of each case report) was pre-existent to the intake of risperidone. In 41 cases diabetes was first diagnosed at the time that the event was reported. In four cases classification was only indicative for pre-existent diabetes: JACAN16675, JAU40519, JAUSA11827, JUSA14248 and JAUSA14639; in three other cases JAFRA33412, JAKYO37458 and JAUSA12670 the diabetes was probably diagnosed for the first time. In 82 cases a classification or diagnosis was not possible because of lack of information.

Number of patients with DM and association with onset of diabetes

		DM FIRST TIME DIAGNOSED					
		NO	NO? (*)	YES	YES? (*)	UNKNOWN	TOTAL CASES
DIABETES MELLITUS DIAGNOSED	NO	2	1	9	0	63	75
	YES	60	4	41	3	19	127
	TOT	62	5	50	3	82	202

* = In some cases the narratives were unclear regarding onset of diabetes. In those cases the onset of the diabetes was difficult to attribute.

1.14.3. TYPE I VERSUS TYPE II DIABETES MELLITUS

A differentiation between type I and type II DM was, based on the scarce available information, virtually impossible. Therefore it seemed inappropriate to further comment on the subtypes of DM.

1.15. Seriousness, causality assessment and outcome of the case reports

From the reported 221 AEs, 114 were assessed as serious (as defined per ICH). It should be pointed out however that, when patients were hospitalised for diagnostic purposes, the AEs relevant for a disturbed glucose metabolism were also assessed as serious. Moreover in patients where other AEs led to a hospitalisation, the glucose-related AEs were rated as serious, even when these AEs were not serious from a medical point of view.

In one of the three cases reported with a fatal outcome, the patient died because of pulmonary embolism (JAUSA17398). In another case

(JAUSA33244) the cause of death was unknown. Finally, in one other case the patient was found dead. Post-mortem analysis revealed glucosuria and ketonuria. The pathologist "speculated" that the patient may have died from uncontrolled diabetes and subsequent ketoacidosis (JAUSA12135).

In the cases where the relation (see appendix 1) of the causality of the AE cannot be completely excluded for risperidone, the Janssen Research Foundation (JRF) assessment was 'possible'. This assessment was made in 121 out of the 202 cases. In 71 cases the assessment was 'doubtful' and in five cases 'probable'. In five cases no assessment was available. The reporters assessed 11 cases as 'not related', 13 as 'doubtful', 63 as 'possible', and 15 as 'probable'. In the remaining 100 cases the reporters did not make any assessment. For definitions of the causality attribution scale used at JRF, see Appendix 3.

Table: Causality per JRF and per reporter (on event and case level).

ASSESSMENT	CAUSALITY PER JRF		CAUSALITY PER REPORTER	
	# PATIENTS	# EVENTS	# PATIENTS	# EVENTS
MISSING	5	5	83	87
DOUBTFUL	71	79	13	16
INSUFFICIENT EVIDENCE	NA	NA	1	1
NOT ASSESS/NOT REPORT	NA*	NA*	14	14
NOT RELATED	NA*	NA*	11	12
POSSIBLE	121	131	63	70
PROBABLE	5	6	15	19
Total	202	221	202	221

* NOT APPLICABLE

1.16. Disturbances of the glucose metabolism reported as most important reaction

In 147 cases, an AE possibly indicative for a disturbance in the glucose metabolism was the reason for the spontaneous report. In 55 cases, these AEs were reported secondary to other important AEs.

1.17. Dechallenge and rechallenge

In five AEs the dechallenge was positive (#JAUSA15530, JAUSA21202, JAUSA25008, JAUSA28182, JAUSA31992); in seven events the dechallenge was negative (#HOAFF43451, JAUSA21847, JAUSA25627³, JAUSA26210, JAUSA36172, JRFUSA1999002436). Only in one event

³ In this case, two glucose-related AEs were reported and presented a negative dechallenge

("blood sugar increased") the rechallenge was positive (#JAUSA28182). There were no reports with a negative rechallenge in the database.

2. PATIENT EXPOSURE

Risperidone is marketed today in more than 70 countries. Through 31 March 2000, the total world-wide exposure to risperidone is estimated at more than 42,498,163 patient months. This corresponds with an estimated patient exposure of more than 3,541,514 patient years (see Appendix 2 for full calculation details).

3. LITERATURE

3.1. Literature case reports

Five case reports were derived from literature:

A 32-year-old male maintained (exact duration unknown) on haloperidol and doxepine was switched to risperidone 6 mg/d, because of treatment-refractory and extrapyramidal symptoms. He developed pancreatitis with leukocytosis and a slight glycemic elevation (#HOAFF31563)¹.

A 30-year-old black male who switched from various traditional antipsychotics to risperidone (dose unknown) developed hyperglycemia. Blood sugar levels remained elevated after stopping risperidone. His diabetes was controlled with glibenclamide. During previous treatment with clozapine, 3 years before, patient developed already hyperglycemic ketoacidosis. At that time, his diabetes resolved completely after withdrawal (#HOAFF43451)².

A 73-year-old African-American female patient treated with risperidone 1 mg/d for dementia developed a neuroleptic malignant syndrome. Laboratory analysis revealed a very high blood sugar of 523 mg% which stabilized to 291 after treatment. No other details on her glycemic status were provided in this publication (#JAUSA20807)³.

A 48-year-old white male developed hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone (SIADH) while taking risperidone 6 mg/d. During hospitalization an hyperglycemia of 174 mg% was detected. No other details on his glycemic status were available in this publication (#JAUSA25008)⁴.

A 41-year-old obese diabetic male was currently treated with risperidone 6 mg/d. His diabetes was controlled with 2.5 mg/d glyburide, an oral

sulfonylurea antidiabetic. For breakthrough and mood symptoms he received sertraline with gradual increased dose to 225 mg/d. During this period he developed several episodes of hypoglycemia, explained by the author as an interaction between sertraline and the sulfonylurea drug (#JRFBEL1999000201)⁵.

3.2. Case reports on severe adverse events indicative for disturbances in the glucose metabolism

In four cases "*metabolic acidosis*" was coded. Non of these cases were related to an alteration of the glucose metabolism. One case was in the context of an overdose with risperidone (#JAUSA1243); one related to a multi-organ disease ending with a cardiac arrest (#JAUSA14725); one case was due to NMS (#JAUSA16483); the last case was in the context of a severe intestinal necrosis (#JAUSA31098).

A 31-year-old female patient, with a family history of type II diabetes, treated since a couple of months with 6mg/d risperidone together with lithium and benztropine, was hospitalized with a "*diabetic coma*". Newly recognised diabetes was diagnosed and she was initiated on a treatment with glibenclamide. Lithium was discontinued on admission and was considered as suspected causative agent. Patient continued further her risperidone treatment (#JAUSA17530).

Finally in one case "*diabetic ketoacidosis*" was reported (#JRFUSA1999000568) and in 15 cases "*ketoacidosis*" was reported ((JAUSA13716, JAUSA13847, JAUSA14953, JAUSA15599). They were all in the context of diabetes. In five cases the patient had already pre-existing diabetes (#JRFUSA1999000568), (#JAUSA13716, JAUSA13847, JAUSA14953, JAUSA15599). In the remaining 11 cases newly recognised diabetes was on the origin of this event (JAUSA12135, JAUSA16748, JAUSA17398, JAUSA17400, JAUSA20238, JAUSA24447, JAUSA25108, JAUSA25627, JAUSA26210, JAUSA26686, JAUSA35464).

Cases with "*ketonuria*" and/or "*osmolar coma*", WHO-ART terms which could be also indicative for diabetes, could not be retrieved from the safety database.

3.3. Some literature background data

1. The incidence, prevalence, and deaths from diabetes at all ages of a representative population for Sweden, were since 1991 prospectively followed in the county of Skaraborg. The annual incidence of diabetes per 100,000 inhabitants in 1991-1995 was (mean +/- 95% CI) 14.7 +/- 3.2 for type I diabetes (diagnosed at 24.1 +/- 2.2 years of age) and 265.6 +/- 16.1 for type II diabetes (diagnosed at 66.6 +/- 0.6 years of age). The incidence of

Volume 15/Page 15

JJRP 00384003
Confidential/Produced in Litigation Pursuant to Protective Order
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type II diabetes was significantly ($P < 0.001$) higher among men. There was no significant change in the age at diagnosis of diabetes. Although the incidence rate and the age at diagnosis were constant, the prevalence of diabetes increased by 6% each year. The relative mortality risk for diabetic patients was almost four times higher than expected. The median age at death, however, increased significantly, from 77.2 to 80.2 years ($P < 0.05$), during the study.⁶

2. At the 150th annual meeting of the American Psychiatric Association (May 1997)⁷ a preliminary study was presented. All patients referred to a specialised atypical antipsychotic clinic were monitored. HbA1c was examined prior to and six months after risperidone therapy. Overall there were no significant changes in HbA1c associated with risperidone therapy. In the patients with pre-existing DM, however, there was a significant increase in HbA1c.

3. In various case reports^{8,9} patients with pre-existing DM were treated with risperidone without deterioration of the diabetes.

4. In one article¹⁰, it was stated that novel antipsychotics should be administered with great care to patients with risk factors for diabetes. A hypothesis that histaminic and possibly serotonergic antagonism induces weight gain, which in turn leads to changes in glucose homeostasis, was put forward. Additionally, serotonin_{1A} antagonism might decrease pancreatic B-cell responsiveness, resulting in inappropriately low insulin and hyperglycaemia.

It should be noticed that risperidone has no serotonin_{1A} antagonistic effect. (See also CCDS in Appendix 4).

4. EPIDEMIOLOGICAL CALCULATIONS AND ASSUMPTIONS

In the county of Skaraborg (Sweden), the annual incidence of diabetes per 100,000 inhabitants is about 14.7 for IDDM and 265.6 for NIDDM⁴. Over the last 7 years we collected 41 reports on 'newly recognised diabetes' on a total of about 3,541,514 patient years. This corresponds with a reporting incidence of 1.15 first-onset diabetes cases per 100,000. Of course the incidence of diabetes in a normal population can not be compared with the 'reporting incidence' of cases with newly recognised diabetes in our safety database, but it only puts our findings into perspective.

5. DISCUSSION

It is well known that spontaneous adverse reaction data are limited in several ways and their nature differs from AEs received during clinical trials. In addition, as neither the exact total number of occurred reactions, nor the

exact number of patients using the drug are known, numerical comparisons with background incidences of events made in this report have to be interpreted very broadly and with caution and can never give accurate incidence figures.

In 41 cases a diagnosis of newly recognised diabetes was made, and in 60 patients DM was already pre-existent. Unfortunately, direct comparison with epidemiological data is not feasible (e.g. because of different population groups, and because reporting rates would be compared with real incidences). However, the total number of reported cases with pre-existing diabetes or with so called newly diagnosed diabetes should be seen against the high cumulative exposure estimated at 3,541,514 patient years over the last 7 years.

In the previous report¹¹, dated March 1996, 32 cumulative spontaneous cases of newly diagnosed DM were identified. The total cumulative patient-exposure at that time was estimated at 3,923,885 patient months, corresponding with 326,990 patient years.

In this current report, 41 cases of patients with newly diagnosed diabetes were identified over a total of 42,498,163 patient months or 3,541,514 patient years. Even if the worst case scenario is adopted (meaning that all 202 cases would be newly diagnosed DM), the incidence of newly diagnosed DM associated with risperidone exposure, would be less than in the previous report. Thus, it can be concluded that this report is in line with the previous IPV report on diabetes and that the incidence of DM doesn't seem to be increased by the intake of risperidone, despite increasing attention for this condition in the medical world.

It is well known that within this psychiatric population, factors such as sedentary life style and uncontrolled eating habits may play an interactive role in the mechanism of obesity. It is also common medical knowledge that weight gain is a known risk factor for diabetes. In the Company Core Data Sheet (see appendix 4) weight gain is mentioned and the patient is cautioned in that regard in the warning section.

6. CONCLUSION

From 1993 till March 2000, 202 patients with adverse events related to disturbances in the glucose metabolism were retrieved from the international safety database, from which 41 were diagnosed as newly recognised diabetes. This is in line with the previous IPV report dated March 1996. The currently available cumulative spontaneous safety data do not suggest a relationship between the use of risperidone and disturbances in the glucose homeostasis. The benefit/risk estimation specifically for this condition remains favourable and the current CCDS does not need to be changed.

Volume 15/Page 18

JJRP 00384006

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D821.20

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Volume 15/Page 19

JJRP 00384007

Confidential/Produced in Litigation Pursuant to Protective Order

D821.21

8. APPENDICES

Volume 15/Page 20

JJRP 00384008

Confidential/Produced in Litigation Pursuant to Protective Order

D821.22

Appendix 1: Detailed information of the individual cases

Volume 15/Page 21

JJRP 00384009

Confidential/Produced in Litigation Pursuant to Protective Order

D821.23

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
BENZATROPINE MESILATE, DOXEPIN, NIFEDIPINE	HYPERCHOLESTEROLAEMIA, HYPERTENSION			N		32	M	HYPERGLYCAEMIA	Y	POSS		USA	HOAFF91663
INSULIN, DILTIAZEM, ESTROGENS CONJUGATED, GLYCERYL TRINITRATE, POTASSIUM CHLORIDE	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y		30	M	DIABETES MELLITUS	Y	POSS		USA	HOAFF43451
BENZATROPINE MESILATE, HALOPERIDOL, LORAZEPAM, OMEPRAZOLE	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, GLIGOPHRENIA			N		60	F	HYPOGLYCAEMIA	N	DOUB		CAN	JACAN15870
INSULIN	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, GLIGOPHRENIA			N	90.72	56	M	HYPOGLYCAEMIC REACTION	Y	POSS		CAN	JACAN16980
INTERM. ACT., LACTULOSE, SENNA, TICLOPIDINE, PHENYTOIN, LISINAPRIL, LEVOTHYROXINE, INSULIN RAPID ACT.	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, CONSTIPATION, CONSTIPATION, PROPHYLAXIS, ECLAMPSIA, HYPERTENSION, HYPOTHYROIDISM		NO	Y		72	F	HYPOGLYCAEMIA	Y	POSS		CAN	JACAN16241
	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO?	Y			M	DIABETES MELLITUS AGGRAVATED	N	POSS		CAN	JACAN16676
LOXAPINE SUCCINATE, AMISULPRIDE, VALPROATE SODIUM, PHENOBARBITAL, LAMOTRIGINE, CLOBAZAM	UNSPECIFIED PSYCHOSIS, UNSPECIFIED PSYCHOSIS, EPILEPSY, EPILEPSY, EPILEPSY, EPILEPSY, EPILEPSY	Grand uncle diabetic	NO	Y		51	M	DIABETES MELLITUS	Y	POSS	ASS. NOT REP.	FRA	JACFRA2000000083
NONE			YES	N		35	M	HYPERGLYCAEMIA	Y	POSS		FRA	JAFRA29489

CONC. DISEASE	CONC. DRUGS	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
INSOMNIA, HYPERGLYCEMIA	ZOPICLONE, AMISULPRIDE, ZOLPIDEM	GALACTORRHOEA WITH AMISULPRIDE; GLYCAEMIA OF 7 MMOL IN NOVEMBER 1995. DELIRIUM IN 1995; OVERWEIGHT	NO	Y	88	30	F	HYPERGLYCAEMIA	Y	DOUB	DOUB	FRA	JAFRA28835
	ALPRAZOLAM, CLOMIPRAMINE, CLORAZEPATE DIPOTASSIUM, CYAMEMAZINE, HALOPERIDOL, HEPTAMINOL, TRIHEXYPHENIDYL, ZOPICLONE	ALLERGY // FLUOXETINE; LOST 10 KG OF WEIGHT IN THE WEEKS PRIOR TO HOSPITALIZATION.		N	68	24	M	HYPERGLYCAEMIA	Y	POSS		FRA	JAFRA30831
	PAROXETINE		YES	Y			M	DIABETES MELLITUS	N	DOUB		FRA	JAFRA33408
			YES?	Y			M	DIABETES MELLITUS	N	DOUB		FRA	JAFRA33412
	CLORAZEPATE DIPOTASSIUM, MIANSERIN, NOCTAV(R)	ALCOHOL // NO; Parkinsonian (iatrogenic origin) Sudden-onset of traumatic origin.		N	76	54	M	HYPOGLYCAEMIA	Y	POSS		FRA	JAFRA37420
	THIORIDAZINE			N	68	62	F	BLOOD SUGAR INCREASED	N	POSS		GER	JAGER39772
	INSULIN			Y	64	65	M	DIABETES MELLITUS AGGRAVATED	N	POSS		GER	JAGER40008
	GLIBENCLAMIDE		NO	N		86	F	HYPOGLYCAEMIA	N	POSS		GER	JAGER40242
	PROMETHAZINE, THIORIDAZINE		NO	Y		72	F	BLOOD SUGAR INCREASED	N	DOUB	NOT REL	JAP	JAKYO33822

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
	COMPLICATION												
MAPROTRILINE,SULPIRIDE,P ROMETHAZINE,L- GLUTAMINE,FLUNITRAZEP AM,AMEZINIUM METILSULFATE	DEPRESSIVE DISORDER, NOT CLASSIFIED,DEPRESSIVE DISORDER, NOT ELSEWHERE CLASSIFIED,EXTRAPYRAM. SYMPTOMS,GASTRITIS,INS OMNIA,POLYP,GALLBLADD ER		YES?	Y		53	M	DIABETES MELLITUS	Y	DOUB	NOT REL.	JAP	JAKYO37458
SENNOSIDES,SODIUM PICOSULFATE,BROMPERID OL,CHLORPROMAZINE,PR OMETHAZINE,TRIAZOLAM	CONSTIPATION,CONSTIPA TION,HALLUCINOSIS- ALC,INSOMNIA,INSOMNIA,I NSOMNIA,NONE,OSTEOPO ROSIS,URAEMIA,GASTRITI S,IRON DEFICIENCY,CARDIAC- DISORDER			N		82	M	GLYCOSURIA	N	POSS	POSS	JAP	JAKYO37482
POLYENEPHOSPHATIDYLC HOLINE,PROTOPORPHYRI N,BROTIZOLAM,CLOCAPRA MINE,DOBUTAMINE,DOPAM INE,EPINEPHRINE,MAGNES IUM OXIDE,MOSAPRAMINE,NIT RAZEPAM,PROMETHAZINE, SENN	INSUFF. HEPATIC,INSUFF. HEPATIC,TRIGLYCERIDAE MA,ISCHEMIC HEART DISEASE	TOBACCO // CIGARETTES/DAY	10-20		76	47	F	HYPERGLYCAEMIA	Y	POSS		JAP	JAKYO39553
PERPHENAZINE,MAPROTI LINE,BIPERIDEN HYDROCHLORIDE,FLUNITR AZEPAM,NITRAZEPAM	INFANTILE AUTISM,DEPRESSIVE DISORDER, NOT CLASSIFIED,OTHER AND UNSPECIFIED EXTRAPYRAMIDAL DISEASES AND ABNORMAL MOVEMENT DISORDERS,INSOMNIA,INS OMNIA,DIABETES MELLITUS WITHOUT		NO	Y		36	M	DIABETES MELLITUS AGGRAVATED	N	POSS	POSS	JAP	JAKYO43515

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
	MENTION OF COMP												
CLONIDINE,INSULIN,METHYLPHENIDATE HYDROCHLORIDE	UNKNOWN,UNKNOWN,UNKNOWN	unknown		N		11	F	HYPERGLYCAEMIA	Y	POSS	ASS. /NOT REP.	CAN	JAOCAN1999000420
LAMOTRIGINE, GLIBENCLAMIDE, VALPROATE SEMISODIUM, FLUVOXAMINE MATE, FLUVOXAMINE MATE, FLUVOXAMINE MATE, FLUVOXAMINE MATE	UNKNOWN, DIABETES MELLITUS, BIPOLAR AFFECTIVE DISORDER, UNSPECIFIED, ANXIETY STATE, UNSPECIFIED, PANIC DISORDER, OBSESSIVE-COMPULSIVE DISORDERS, AFFECTIVE PERSONALITY DISORDER, DEPRESSIVE DISORDER, NOT ELSEW	Unknown	YES	Y	127	53	F	DIABETES MELLITUS	N	DOUB	NOT REL	CAN	JAOCAN1999000488
VENLAFAXINE, BUSPIRONE, PROPIOMAZINE, ZOLPIDEM	DEPRESSIVE DISORDER, NOT ELSEWHERE CLASSIFIED, ANOREXIA			N		20	F	HYPOGLYCAEMIA	Y	POSS	INSUFF. EVID.	SW E	JASWE40389
FOLIC ACID, POTASSIUM CHLORIDE, PROPIOMAZINE, MODURETIC	DIPOLAR DISORDER			N		82	F	HYPOGLYCAEMIA	Y	POSS		SW E	JASWE43623
INSULIN INTERM. ACT.	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION			Y		30	M	GLUCOSE TOLERANCE ABNORMAL	N	POSS		U.K.	JAUK21303
CLOTRIMAZOLE, ITRACONAZOLE, EUGYNON	CANDIDIASIS, CANDIDIASIS, PROPHYLAXIS, DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION	DIABETES-MELLIT. GESTATIONAL	NO	Y		26	F	DIABETES MELLITUS	N	POSS		U.K.	JAUK28592
	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, OLIGOPHRENIA	DIET // FOR DIABETES	NO	Y		20	M	HYPOGLYCAEMIA	N	POSS		U.K.	JAUK30285
UNSPECIFIED	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y			UNKNOWN	HYPOGLYCAEMIA	N	POSS	NOT REL	U.K.	JAUK34341

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
METHYLPHENIDATE	OTHER UNKNOWN AND UNSPECIFIED CAUSE OF MORBIDITY OR MORTALITY		Y YES	Y		7	F	DIABETES MELLITUS	Y	DOUB		U.K.	JAUK36849
INSULIN	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		N NO?	N			F	HYPERGLYCAEMIA	N	POSS	PROB	U.K.	JAUK40519
PROCYCLIDINE	PROPHYLAXIS		Y YES	Y	75	44	F	DIABETES MELLITUS	Y	POSS		U.K.	JAUK43298
CARBAMAZEPINE, PHENYTOIN, VALPROATE SODIUM, LEVOTHYROXINE	ECLAMPSIA, ECLAMPSIA, ECLAMPSIA, ECLAMPSIA, OUGOPHRENIA	SEIZURES : IN 1978 WHILE TAKING HALOPERIDOL		N		38	F	HYPERGLYCAEMIA	Y	PROB		USA	JAUSA10879
GLIBENCLAMIDE	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION			N		32	M	HYPOGLYCAEMIA	N		DOUB	USA	JAUSA11156
HALOPERIDOL	UNSPECIFIED SCHIZOPHRENIA, DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		Y NO	Y		35	M	HYPERGLYCAEMIA	N	DOUB	PROB	USA	JAUSA11459
INSULIN, ALPRAZOLAM, TIOXENE	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, INFANTILE AUTISM, TOURETTE, OLIGOPHRENIA		Y NO	Y		19	M	DIABETES MELLITUS AGGRAVATED	N	POSS		USA	JAUSA11728

REFNO	COUNTRY	CAUSREP	CAUSHO	SERIOUS	REACTION	SEX	AGE	WEIGHT	DIABETES	FIRST TIME REPORTED	HISTORY	CONC. DISEASE	CONC. DRUGS
JAUSA11827	USA		DOUB	Y	DIABETES MELLITUS AGGRAVATED	F	33	128.82	Y	NO?	ALCOHOL // NONE, DRUGS // ABUSE (UNSPECIFIED), PHYSICALLY ABUSED DURING CHILDHOOD. PEDAL EDEMA WHILE ON NIFEDIPINE 31-JAN-84, TOBACCO // HEAVY SMOKER, TWO TO THREE PACKS PER DAY.	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, BIPOLAR DISORDER, EXTRAPYRAMS, AGITATION, PROPHYLAXIS, HYPERTENSION, MOOD SWINGS, UNSPECIFIED CHRONIC BRONCHITIS, OBESITY, UNSPECIFIED DISOR	GLIBENCLAMIDE, LITHIUM, BENZATROPINE MESILATE, CLONAZEPAM, LO-ORAZEPAM, LO-OVRAL, NADOLOL, CARBAMAZEPINE, HALOPERIDOL, HALOPERIDOL DECANOATE, MYLANTA
JAUSA11832	USA	POSS	DOUB	Y	DIABETES MELLITUS AGGRAVATED	M	52		Y	NO		DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION	BENZATROPINE MESILATE, GEMFIBROZIL, TIOTIXENE
JAUSA11889	USA	PROB		N	DIABETES MELLITUS AGGRAVATED	M	24	139.28	Y	NO		DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, INSOMNIA, DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, OBESITY	INSULIN, DIPHEHYDRAMINE, LORAZEPAM
JAUSA12027	USA	PROB		N	HYPOGLYCAEMIA	F	18		N				BENZATROPINE MESILATE
JAUSA12029	USA	PROB		Y	HYPOGLYCAEMIA	F			Y	NO		DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION	PAROXETINE
JAUSA12185	USA		DOUB	Y	DIABETES MELLITUS	M	55	98.18	Y	YES	ABDOMINAL SURG. ADHESIONS, ALCOHOL // NEGATIVE	HYPERPOTASSEMIA, LEUKOCYTOSIS, ANAEMIA, MICROCYT, ABDOMINAL SURG., HYPERCHOLESTEROLAEMIA, APPENDECTOMY, CHOLECYSTECTOMY, HEPATOMEGALY, HYPERTROPHY CARDIAC	CARBAMAZEPINE, CHLORPROMAZINE, LITHIUM, METHYLPHENIDATE, PHENELZINE, TIOTIXENE
JAUSA12135	USA		DOUB	Y	KETOACIDOSIS	M	55	98.18	Y	YES			
JAUSA12262	USA	POSS	DOUB	N	DIABETES MELLITUS AGGRAVATED	U	NK		Y	NO		DIABETES MELLITUS WITHOUT MENTION OF	

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
	COMPLICATION												
	PROPHYLAXIS, DEPRESSIVE DISORDER, NOT ELSEWHERE CLASSIFIED, PSYCHIATRIC TROUBLES, SUICIDAL ATTEMPT	ALCOHOL // ABUSE, DEPRESSION : ATYPICAL WITH ALCOHOL ABUSE, PSYCHIATRIC TROUBLES : TWELVE YEAR HISTORY INCLUDING DEPRESSION AND AFFECTIVE DISORDER, SUICIDAL ATTEMPT : FIVE SUICIDE ATTEMPTS BY MULTIPLE METHODS INCLUDING DRUG INGESTION.		N		29	F	ACIDOSIS METABOLIC	Y	DOUB		USA	JAUSA12434
	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, HYPOTHYROIDISM	OTHERS // TENDS TO BE SENSITIVE TO MEDICATIONS	NO	Y		38	F	HYPOGLYCAEMIA	N	POSS		USA	JAUSA12584
	RHINITIS, RHINITIS	POSITIVE PPD SKIN TEST. "THICK TONSILS AND NASAL OBSTRUCTION" MANIFESTED AS "NOISY NIGHTTIME BREATHING".	YES?	Y	73.84	15	F	HYPERGLYCAEMIA	Y	POSS	DOUB	USA	JAUSA12670
	INSULIN, LEVOTHYROXINE												
	BECLOMETASONE DIPROPIONATE, SONIAZID												

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
INSULIN	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y		81	F	DIABETES MELLITUS AGGRAVATED	N	DOUB	POSS	USA	JAUSA12859
BENZATROPINE MESILATE	SCHIZO-AFFECTIVE TYPE II SCHIZOPHRENIA, CONSTIPATION, HERPES SIMPLEX, DEPRESSIVE DISORDER, NOT ELSEWHERE CLASSIFIED, SEBORRHEA, EXTRAPYRAM. SYMPTOMS, GI COMPLAINTS, DIABETES MELLITUS WITHOUT MENTION OF COMPLICAT	ALCOHOL // DEPENDENCE, DRUGS POLYSUBSTANCE DEPENDENCE, COMPLAINTS : GI UPSET	YES	Y	127.01	35	M	DIABETES MELLITUS AGGRAVATED	Y	POSS	POSS	USA	JAUSA13133
HALOPERIDOL DECANOATE, DOXUSATE SODIUM, DIAZEPAM, DOXEPI N, PROPRANOLOL, VALPROATE SEMISODIUM			NO	Y		30	M	DIABETES MELLITUS AGGRAVATED	N	POSS	NOT REL	USA	JAUSA13714
ANTACIDS, BENZATROPINE MESILATE, HALOPERIDOL, L ORAZEPAM, PARACETAMOL, RANITIDINE, VALPROATE SEMISODIUM	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, OBESITY, HYPERTRIGLYCERID		NO	Y		38	M	DIABETES MELLITUS AGGRAVATED	Y	POSS	NOT REL	USA	JAUSA13718
			NO	Y		38	M	KETOACIDOSIS	Y	POSS	NOT REL	USA	JAUSA13716
			YES	Y			UNK N O W N	DIABETES MELLITUS	Y	POSS	POSS	USA	JAUSA13719
INSULIN, LITHIUM	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, ACUTE PANCREATITIS	ALCOHOL // TWO SIX PACKS OF BEER TWICE PER WEEK, DIET // DIABETIC PANCREATITIS : PRIOR EPISODES	NO	Y		33	M	HYPERGLYCAEMIA	Y	DOUB	DOUB	USA	JAUSA13847
			NO	Y		33	M	KETOACIDOSIS	Y	DOUB	DOUB	USA	JAUSA13847

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
INSULIN INTERM.ACT., FLUOXETINE, TACRINE, LITHIUM, CAPTOP RIL, GUAFENEBIN, CAPTOP RIL	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, DEPRESSI VE DISORDER, NOT ELSEWHERE CLASSIFIED, ALZHEIMERS DISEASE, BIPOLAR DISORDER, PROPHYLAXIS, COPD, DIABETIC NEPHROPATHY, CHOLECYST TOMY, OBESITY	ALLERGY // SULFA AND PENICILLIN CHOLECYSTECTOMY 1972, DRUGS NONCOMPLIANCE WITH MEDICATIONS AND OXYGEN, HERNIA ING. REPAIR : 1987, REQUIRED ONE MONTH OF MECHANICAL VENTILATION AND TRACHEOSTOMY, TOBACCO // FOUR PACKS PER DAY	NO?	Y		64	F	DIABETES MELLITUS AGGRAVATED	Y	POSS		USA	JAUSA14248
BENZATROPINE MESILATE				N	80.4	48	M	HYPERGLYCAEMIA	Y	PROB		USA	JAUSA14282
VALPROATE SODIUM	OBESITY			N		30	F	HYPOGLYCAEMIA	N	POSS		USA	JAUSA14314
GLIBENCLAMIDE	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO?	Y		48	F	HYPERGLYCAEMIA	N	DOUB		USA	JAUSA14639
			YES	N		34	M	HYPERGLYCAEMIA	N	POSS		USA	JAUSA14670
INSULIN	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y		45	F	DIABETES MELLITUS AGGRAVATED	N	DOUB		USA	JAUSA14894
AMITRIPTYLINE, THIORIDAZ INE	SCHIZO-AFFECTIVE TYPE SCHIZOPHRENIA, SCHIZO- AFFECTIVE SCHIZOPHRENIA, LEIOMYO MA OF UTERUS, UNSPECIFIED, CONSTIPATI ON, IRRITABLE COLON			N		65	F	ACIDOSIS METABOLIC	Y	POSS		USA	JAUSA14726
GLIBENCLAMIDE, FAMOTID INE, LITHIUM CARBONATE, MAXIDEX, VAL PROATE SODIUM	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y		48	F	BLOOD SUGAR INCREASED	N	DOUB		USA	JAUSA14782

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
PAROXETINE, NIFEDIPINE, A MANTADINE, POTASSIUM CHLORIDE	DEPRESSIVE DISORDER, NOT CLASSIFIED, ELSEWHERE N, DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION	DIET // 1600 ADA DIET	NO	Y	60.78	64	F	HYPOGLYCAEMIA	Y	DOUB	POSS	USA	JAUSA14884
	POLYDIPSIA, POLYURIA	PREGNANCY RELATED DIABETES MELLITUS.	NO	Y		40	F	DIABETES MELLITUS AGGRAVATED	Y	DOUB		USA	JAUSA14853
			NO	Y		40	F	KETOACIDOSIS	Y	DOUB	DOUB	USA	JAUSA14853
VALPROIC ACID			YES	N		32	F	HYPERGLYCAEMIA	N	POSS	POSS	USA	JAUSA14890
ZALCITABINE, ACETAZOLAMIDE, CLONIDINE, ISONIAZID, PHENOBARBITAL, VALPROATE SODIUM	AIDS	PATIENT IS IN AN INVESTIGATIVE STUDY FOR TREATMENT OF AIDS WITH DDC		N		40	M	HYPOGLYCAEMIA	N	DOUB	PROB	USA	JAUSA15182
GLIBENCLAMIDE, AMFEBUTAMONE	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y		25	F	DIABETES MELLITUS AGGRAVATED	N	DOUB	POSS	USA	JAUSA15252
INSULIN INTERMEDIATE ACT.	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y		65	M	DIABETES MELLITUS AGGRAVATED	N	DOUB	POSS	USA	JAUSA15347
				N		31	M	BLOOD SUGAR INCREASED	N	POSS		USA	JAUSA15517
	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION	LIFELONG HYPOPITUITARY DISORDER	NO	Y		67	F	DIABETES MELLITUS AGGRAVATED	N	DOUB	POSS	USA	JAUSA15530
GLIBENCLAMIDE, NORTRIPTYLINE, VALPROATE SODIUM, PROPRANOLOL, PRINZIDE, LEVOTHYROXINE, BENZATROPINE MESILATE	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, BIPOLAR DISORDER, BIPOLAR DISORDER, HYPERTENSION, HYPERTENSION, HYPOTHYROIDISM, OBESITY		NO	Y	133.36	49	F	DIABETES MELLITUS AGGRAVATED	Y	DOUB	PROB	USA	JAUSA15589
			NO	Y	133.36	49	F	KETOACIDOSIS	Y	DOUB	PROB	USA	JAUSA15589

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
GLIBENCLAMIDE	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y		68	F	DIABETES MELLITUS AGGRAVATED	Y	POSS	POSS	USA	JAUSA10114
CLONIDINE, FLUOXETINE, LITHIUM, TRAZODONE, VALPROATE SODIUM				N		35	M	BLOOD SUGAR INCREASED	N	DOUB	POSS	USA	JAUSA16398
	OLIGOPHRENIA, AGITATION	NMS WITH HALOPERIDOL 1992.		N		68	M	ACIDOSIS METABOLIC	Y	PROB	POSS	USA	JAUSA16483
CHLORPROMAZINE, LITHIUM, PEMOLINE				N		18	F	HYPOGLYCAEMIA	N	POSS	POSS	USA	JAUSA16653
RANITIDINE	ABDOMINAL PAIN	STRONG FAMILY HISTORY OF DIABETES PATIENT EXPERIENCED DIARRHOEA, ABDOMINAL DISCOMFORT AND INSOMNIA 3 WEEKS AGO (REFNO-32853)		Y		40	M	DIABETES MELLITUS	N	DOUB	DOUB	USA	JAUSA16686
TIOXENE, AMITRIPTYLINE, AMITRIPTYLINE, DIPHENHYDRAMINE	PARANOID TYPE SCHIZOPHRENIA, DEPRESSIVE DISORDER, NOT CLASSIFIED, INSOMNIA, INSOMNIA, OBESITY	DRUGS // ABUSE: HEROIN, PCP, COCAINE, METHAMPHETAMINE, HEAD INJURY RESULTING IN COMA AGE 28		Y		35	M	DIABETES MELLITUS	Y	POSS	DOUB	USA	JAUSA16748
			YES	Y		35	M	KETOACIDOSIS	Y	POSS	DOUB	USA	JAUSA16748
CLOZAPINE	UNSPECIFIED SCHIZOPHRENIA		YES	Y		28	M	DIABETES MELLITUS	N	POSS		USA	JAUSA16851

JRF Pharmacovigilance Report

33

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
		CLOZAPINE FOR 5 WEEKS PRIOR TO SWITCHING TO RISPERIDONE.	YES	Y		26	M	DIABETES MELLITUS	Y	POSS	POSS	USA	JAUSA16897
				N			F	HYPERGLYCAEMIA	N		POSS	USA	JAUSA16969
VALPROATE SODIUM			YES	N		34	F	HYPERGLYCAEMIA	N	POSS	PROB	USA	JAUSA17311
				N			M	BLOOD SUGAR DECREASED	N	POSS	POSS	USA	JAUSA17334
CLOZAPINE, CHLORPROMAZINE	UNSPECIFIED SCHIZOPHRENIA, AGITATION		YES	Y		40	M	DIABETES MELLITUS	Y	POSS	POSS	USA	JAUSA17398
			YES	Y		40	M	KETOACIDOSIS	Y	POSS	POSS	USA	JAUSA17398
VALPROATE SODIUM	ECLAMPSIA	FAMILY HISTORY OF EMPHYSEMA AND CANCER.	YES	Y		28	M	DIABETES MELLITUS	Y	POSS	POSS	USA	JAUSA17400
			YES	Y		28	M	KETOACIDOSIS	Y	POSS	POSS	USA	JAUSA17400
LITHIUM, BENZATROPINE MESILATE, FERROUS SULFATE, METOPROLOL	DEPRESSIVE DISORDER, NOT ELSEWHERE CLASSIFIED, OBESITY	STRONG FAMILY HISTORY OF TYPE II DIABETES MELLITUS. PATIENT HAS HISTORY OF SUICIDE ATTEMPT.	YES	Y	77	31	F	COMA DIABETIC	Y	POSS	POSS	USA	JAUSA17530
LORAZEPAM, ATENOLOL, D OXAZOSIN, NIFEDIPINE, CHL ORPROMAZINE, GAVISCON /OLD FORM/, PIROXICAM, DIMETI CONE, ACTIVATED, VALPROIC ACID	ANXIETY STATES, HYPERTENSION, H YPERTENSION, HYPERTEN SION, BIPOLAR AFFECTIVE DISORDER, MIXED, DIAPHRAGMATIC HERNIA WITHOUT MENTION OF OBSTRUCTION OR GANGRENE, PHARYNGITIS	TOBACCO // HEAVY SMOKER BUT QUIT JUNE 95	YES	N		41	M	HYPERGLYCAEMIA	Y	POSS	POSS	USA	JAUSA17614

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
CHLORPROPAMIDE, GLIPIZIDE, QUINAPRIL, BENZATROPINE, MESILATE, CALCIUM, FLUOXETINE, MULTIVITAMINS, VERAPAMIL	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, HYPERTENSION, OLIGOPHRENIA		NO	Y		42	F	HYPERGLYCAEMIA	N	DOUB	POSS	USA	JAUSA17744
	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y			M	DIABETES MELLITUS AGGRAVATED	N	DOUB	DOUB	USA	JAUSA17767
	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y			M	DIABETES MELLITUS AGGRAVATED	N	DOUB	DOUB	USA	JAUSA17768
	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, DEPRESSIVE DISORDER, NOT ELSEWHERE CLASSIFIED		NO	Y			M	DIABETES MELLITUS AGGRAVATED	N	DOUB	NOT REL	USA	JAUSA17771
HALOPERIDOL	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y			M	DIABETES MELLITUS AGGRAVATED	Y	DOUB	NOT REL	USA	JAUSA17772
BISACODYL, MAGNESIUM HYDROXIDE, PARACETAMOL, PARACETAMOL, ACETYLSALICYLIC ACID, APRACLOINIDINE, DILTIAZEM, DUCUSATE SODIUM, FINASTERIDE, FLUOXETINE, ZOLPIDEM	CONSTIPATION, CONSTIPATION, PYREXIA OF UNKNOWN ORIGIN, PAIN, ALZHEIMERS DISEASE, CAD, ARTHRITIS	ALLERGY // PENICILLIN, SWEET POTATOES; PREVIOUSLY HAD LASER TRABECULOPLASTY		N	53.8	78	M	HYPERGLYCAEMIA	Y	POSS		USA	JAUSA17875
INSULIN, METFORMIN	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y		33	F	HYPOGLYCAEMIA	Y	POSS	NOT REL	USA	JAUSA18451
CLONIDINE, SERTRALINE, VALPROATE SODIUM	DEPRESSIVE DISORDER, NOT ELSEWHERE CLASSIFIED	ALCOHOL // ABUSE; DRUGS // ABUSE		N		13	F	GLYCOSURIA	N	PROB	POSS	USA	JAUSA18128

REFNO	COUNTRY	CAUSREP	CAUSHO	SERIOUS	REACTION	SEX	AGE	WEIGHT	DIABETES	FIRST TIME REPORTED	HISTORY	CONC. DISEASE	CONC. DRUGS
JAUSA19128	USA	POSS	PROB	N	HYPERGLYCAEMIA	F	13		N				
JAUSA19142	USA	POSS	DOUB	Y	DIABETES MELLITUS AGGRAVATED	M	18		Y	NO		DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, DEPRESSIVE DISORDER, NOT ELSEWHERE CLASSIFIED	INSULIN, SERTRALINE, LITHIUM
JAUSA19351	USA	POSS	POSS	N	HYPERGLYCAEMIA	UNKNOWN			N				
JAUSA19548	USA	POSS	POSS	Y	HYPERGLYCAEMIA	F	63	77.79	Y	NO		DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, OBESITY	GLIBENCLAMIDE, INSULIN, A MANTADINE, CLONAZEPAM, DIPHENHYDRAMINE
JAUSA20190	USA	POSS	POSS	Y	HYPOGLYCAEMIA	M	58		N				
JAUSA20238	USA	POSS	POSS	Y	DIABETES MELLITUS	M	27		Y	YES		ANXIETY STATES	
JAUSA20238	USA	POSS	POSS	Y	KETOACIDOSIS	M	27		Y	YES			
JAUSA20269	USA	POSS	DOUB	N	DIABETES MELLITUS AGGRAVATED	F	60		Y	NO		DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION	INSULIN
JAUSA20419	USA	POSS	POSS	Y	HYPOGLYCAEMIA	M	25		N			UNSPECIFIED PROTEIN-CALORIE MALNUTRITION, OTHER AND UNSPECIFIED MITRAL VALVE DISEASES, ASTHMA	BISMUTH SUBSALICYLATE, PROCHLOPERAZINE
JAUSA20807	USA	POSS	PROB	Y	DIABETES MELLITUS AGGRAVATED	F	73		Y			DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, CAD, COPD, COPD, CVA, ALZHEIMERS DISEASE, CAD, COPD, CVA, HYPERTENSION	INSULIN, GLYCERYL TRINITRATE, PREDNISONE, SALBUTAMOL, Docusate Sodium, LORAZEPAM
JAUSA21202	USA	POSS	POSS	Y	GLYCOSURIA	M	29		Y	YES			
JAUSA21202	USA	POSS	POSS	Y	HYPERGLYCAEMIA	M	29		Y	YES			

REFNO	COUNTRY	CAUSREP	CAUSHO	SERIOUS	REACTION	SEX	AGE	WEIGHT	DIABETES	FIRST TIME REPORTED	HISTORY	CONC. DISEASE	CONC. DRUGS
JAUSA21243	USA	POSS	POSS	N	HYPERGLYCAEMIA	F	42		N	YES			DESIPRAMINE,DIPHENHYDRAMINE
JAUSA21308	USA	POSS	POSS	N	DIABETES MELLITUS AGGRAVATED	M	64		Y			DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION,DEPRESSIVE DISORDER, NOT ELSEWHERE CLASSIFIED,ADENOMA,PROSTATE	INSULIN,VENLAFEXINE,DILTIAZEM
JAUSA21548	USA		DOUB	N	DIABETES MELLITUS	M	32		Y		ALCOHOL // ABUSE; DRUGS // ABUSE		
JAUSA21587	USA	POSS	DOUB	N	DIABETES MELLITUS AGGRAVATED	M	60		Y	NO		DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION	INSULIN
JAUSA21847	USA	POSS	DOUB	N	DIABETES MELLITUS	M	60		Y	YES	ALCOHOL // ABUSE	PRIMARY TUBERCULOUS INFECTION,HYPERTENSION,HYPERTENSION	ISONIAZID,DIAZIDE,NIFEDIPINE
JAUSA22283	USA		POSS	N	HYPOGLYCAEMIA	M	48		Y	NO		DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION	INSULIN
JAUSA22346	USA	DOUB	DOUB	Y	DIABETES MELLITUS AGGRAVATED	M	44		Y	NO		DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION	INSULIN,PAROXETINE
JAUSA22608	USA	POSS	DOUB	N	HYPERGLYCAEMIA	M			N				
JAUSA23378	USA	POSS	DOUB	N	BLOOD SUGAR INCREASED	UNKNOWN			N				
JAUSA23648	USA	POSS	DOUB	N	HYPERGLYCAEMIA	F	17	108.88	Y	NO	DIABETES MELLITUS "TEARS AGO" CONTROLLED	ANXIETY STATES,BIPOLAR DISORDER,DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION,OBESITY	BUSPIRONE,VALPROATE SODIUM,AMLODIPINE,CHLORPROMAZINE,CLONAZEPAM,DIPHENHYDRAMINE,NORTRIPTYLINE
JAUSA23738	USA	POSS	POSS	N	HYPOGLYCAEMIA	M			N				

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
BENZATROPINE MESILATE, HALOPERIDOL, UNO SPECIFIED	OTHER UNKNOWN AND UNSPECIFIED CAUSE OF MORBIDITY, OTHER UNKNOWN AND UNSPECIFIED CAUSE OF MORBIDITY OR MORTALITY, OBESITY, HYPOTHYROIDISM			Y		62	F	HYPOGLYCAEMIA	Y	POSS	POSS	USA	JAUSA23833
INSULIN	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y		35	F	HYPOGLYCAEMIA	N	POSS	PROB	USA	JAUSA23955
GLIPIZIDE, ANTIPSYCHOTICS	HYPERGLYCEMIA, DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, OBESITY	DIABETES MELLIT. FAMILY HISTORY OF DIABETES	NO	Y	200	28	M	DIABETES MELLITUS	N	DOUB		USA	JAUSA24010
GLIPIZIDE, CARBAMAZEPIN, EVENLAFEXINE	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, OTHER UNKNOWN AND UNSPECIFIED CAUSE OF MORBIDITY, OTHER UNKNOWN AND UNSPECIFIED CAUSE OF MORBIDITY OR MORTALITY			Y	200	28	M	HYPERGLYCAEMIA	N	DOUB		USA	JAUSA24010
BENZATROPINE MESILATE	OBESITY			Y		39	M	HYPERGLYCAEMIA	N	POSS		USA	JAUSA24223
NONE		FAMILY HISTORY OF DIABETES		Y		23	F	DIABETES MELLITUS	Y	DOUB	POSS	USA	JAUSA24343
				Y		32	M	DIABETES MELLITUS	Y	DOUB	POSS	USA	JAUSA24344

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
DIAZEPAM, CLONIDINE, FOLIC ACID, INSULIN, MULTIVITAMINS, CONLUNETT, VALPROATE SODIUM	AGITATION, OBESITY, CONSTIPATION, HYPERPROLACTINEMIA, PROFOUND MENTAL RETARDATION, DEAF MUTISM	ALLERGY // TRAZODONE; HYPERPROLACTIN. SECONDARY HALOPERIDOL	YES	Y	74.39	30	F	DIABETES MELLITUS PRECIPITATED	Y	DOUB	PROB	USA	JAUSA24447
ANTACIDS, DIPHENHYDRAMINE	OBESITY	ALCOHOL // BINGE DRINKING; ALLERGY // NONE	YES	N	74.39	30	F	KETOACIDOSIS	Y	DOUB	PROB	USA	JAUSA24447
				N		20	M	HYPERGLYCAEMIA	Y	POSS	POSS	USA	JAUSA24498
				N		8	M	GLYCOBURIA	Y	POSS	POSS	USA	JAUSA24880
				N		8	M	HYPERGLYCAEMIA	Y	POSS	POSS	USA	JAUSA24890
INSULIN, BENAZEPRIL, FURSEMIDE, ISOSORBIDE DINIT	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, HYPERTENSION, HYPERTENSION		NO	Y		43	M	DIABETES MELLITUS AGGRAVATED	Y	POSS		USA	JAUSA24939
INSULIN, PHENYTOIN	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, ECLAMPSIA, CEREBROVASC., APHASIA, HEMIPARESIS	CEREBROVASC. : 1992 & JUL-98		Y		51	M	DIABETES MELLITUS AGGRAVATED	Y	DOUB	NOT REL.	USA	JAUSA24949
NONE	UNSPECIFIED DISORDERS OF NERVOUS SYSTEM, PARANOID TYPE SCHIZOPHRENIA, FUNCTIONAL AND UNDIAGNOSED CARDIAC MURMURS	NEUROL.DISE.UNSP. HISTORY OF TREATMENT WITH NEUROLEPTICS SINCE 1989		N	78.02	48	M	HYPERGLYCAEMIA	Y	POSS	PROB	USA	JAUSA25008
METFORMIN, ERYTHROPOIETIN, ASCORBIC ACID, BACLOFEN, LITHIUM, MULTI-TABS, RANITIDINE	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, HAEMOGLOBIN DECREASED, HYPERTENSION		NO	Y		75	F	HYPOGLYCAEMIA	N	POSS	POSS	USA	JAUSA25075
				N			U	BLOOD SUGAR	N	POSS		USA	JAUSA25080

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
							UNKNOWN	INCREASED					
	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y		83	F	DIABETES MELLITUS AGGRAVATED	N	POSS	PROB	USA	JAUSA25083
FLUOXETINE, TRAZODONE		ALCOHOL // ABUSE, DRUGS // COCAINE ABUSE, FAMILY HISTORY OF DIABETES.		Y		39	F	DIABETES MELLITUS	Y	POSS	POSS	USA	JAUSA25088
FLUOXETINE	OBESITY		YES	Y		25	M	DIABETES MELLITUS	Y	DOUB	PROB	USA	JAUSA25108
			YES	Y		25	M	KETOACIDOSIS	Y	DOUB	PROB	USA	JAUSA25108
INSULIN INTERM. ACT., INSULIN RAPID ACT.	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y		35	F	DIABETES MELLITUS AGGRAVATED	N	POSS	PROB	USA	JAUSA25307
GLIBENCLAMIDE, METFORMIN, ISONIAZID, LORAZEPAM, PAROXETINE, VALPROATE SODIUM	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION			N			M	HYPERGLYCAEMIA	N	POSS	POSS	USA	JAUSA25424
LORAZEPAM, VALPROATE SODIUM			YES	N		18	F	HYPERGLYCAEMIA	N	POSS	POSS	USA	JAUSA25488
GLIBENCLAMIDE, CIMETIDINE	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y		71	M	DIABETES MELLITUS AGGRAVATED	N	POSS	NOT REL.	USA	JAUSA25498
DEXFENFLURAMINE, BENZATROPINE MESILATE, LITHIUM	OBESITY			Y		40	F	DIABETES MELLITUS	N	POSS		USA	JAUSA25585
VALPROATE SODIUM			YES	Y			M	DIABETES MELLITUS	Y	POSS	PROB	USA	JAUSA25627
			YES	Y			M	KETOACIDOSIS	Y	POSS	PROB	USA	JAUSA25627

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
VALPROATE SODIUM, LORAZEPAM	BIPOLAR DISORDER		Y YES		34	M	HYPERGLYCAEMIA	Y	DOUB		USA	JAUSA26210
			Y YES		34	M	KETOACIDOSIS	Y	DOUB	POSS	USA	JAUSA26210
	OLIGOPHRENIA	CHILD'S MOTHER IS RETARDED-POOR HISTORIAN.	Y YES		18	M	DIABETES MELLITUS	N	DOUB		USA	JAUSA26548
			Y YES		23	M	DIABETES MELLITUS	Y	DOUB		USA	JAUSA26686
			Y YES		23	M	KETOACIDOSIS	Y	DOUB		USA	JAUSA26686
BUSPIRONE, HALOPERIDOL, PAROXETINE, ZIDOVUDINE	OBESITY, NONSPECIFIC ELEVATION OF LEVELS OF TRANSAMINASE OR LACTIC ACID DEHYDROGENASE (LDH), HAEMOGLOBIN DECREASED, HYPERTRIGLYCERID	ALCOHOL // ABUSE; DRUGS // ABUSE	N		30	F	BLOOD SUGAR INCREASED	N	POSS	POSS	USA	JAUSA26741
			N		14	F	HYPOGLYCAEMIA	N	DOUB		USA	JAUSA26788
LITHIUM, LEVOTHYROXINE, CLONAZEPAM, TRIHEXYPHENIDYL	BIPOLAR DISORDER, HYPOTHYROIDISM	HISTORY OF TREMOR PRIOR TO RISPERIDONE USE.	N		48	F	BLOOD SUGAR INCREASED	N	POSS		USA	JAUSA26991
			Y			UNK KNOW N	DIABETES MELLITUS	N	DOUB		USA	JAUSA27366
SERTRALINE, CLONAZEPAM, PROPRANOLOL	DEPRESSIVE DISORDER, NOT CLASSIFIED, DEPRESSIVE DISORDER, NOT ELSEWHERE CLASSIFIED	SUBSTANCE ABUSE.	N	105	42	M	BLOOD SUGAR INCREASED	N	POSS	POSS	USA	JAUSA27428

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
DIPHENHYDRAMINE	HYPERCHOLESTEROLAEMIA	EXTRAPYRAMIDAL SYMPTOMS, PATIENT IN A MENTAL FACILITY.			103 N	37	M	BLOOD SUGAR INCREASED	N	POSS	POSS	USA	JAUSA27441
MAGNESIUM HYDROXIDE, CLANZAPINE, VALPROATE SODIUM	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, SCHIZO-AFFECTIVE TYPE SCHIZOPHRENIA, NEUROPATHY	DIABETES MELLITUS, CONTROLLED BY DIET/HAS HAD ONE EPISODE OF HYPERGLYCEMIA >1800MG/DL	NO	Y		50	F	DIABETES MELLITUS	Y	DOUB		USA	JAUSA27702
	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION			N			M	BLOOD SUGAR INCREASED	N	POSS		USA	JAUSA28182
		FAMILY HISTORY OF DIABETES MELLITUS	YES	Y			F	DIABETES MELLITUS	Y	DOUB		USA	JAUSA28420
	OBSESSIVE-COMPULSIVE DISORDERS, UNSPECIFIED DELAY IN DEVELOPMENT	STRONG FAMILY HISTORY OF DIABETES MELLITUS.	YES	Y		15	M	DIABETES MELLITUS	Y	DOUB		USA	JAUSA28741
VALPROATE SODIUM		FAMILY HISTORY OF DIABETES (PATIENT'S GRANDMOTHER)	YES	Y		28	M	DIABETES MELLITUS	Y	DOUB		USA	JAUSA28990
INSULIN, COLESTYRAMINE, GEMFIBROZIL, IRON, LORAZEPAM, MIRTAZAPINE	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION, HYPERCHOLESTEROLAEMIA, HYPERCHOLESTEROLAEMIA		NO	Y		61	F	DIABETES MELLITUS AGGRAVATED	N	DOUB		USA	JAUSA29108
			YES	N		27	F	HYPERGLYCAEMIA	N	DOUB		USA	JAUSA29273
				N		30	F	GLYCOBURIA	N	DOUB		USA	JAUSA29279
	INFANTILE AUTISM		YES	Y		25	F	DIABETES MELLITUS	Y	DOUB		USA	JAUSA29371

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
FLUPHENAZINE,LITHIUM				N		45	M	HYPOGLYCAEMIA	N	DOUB		USA	JAUSA28954
CLONAZEPAM,HALOPERIDOL	UNSPECIFIED CIRCULATORY SYSTEM DISORDER,PARESIS,AGITATION	CVA : RIGHT HEMIPARESIS, SURG.LEGS DEBRIDEMENT DONE FOLLOWING AN ULCER	YES	Y		82	M	DIABETES MELLITUS	Y	DOUB		USA	JAUSA31021
THYROID,LORAZEPAM,TRAZODONE	HYPOTHYROIDISM,UMBILICAL HERNIA WITHOUT MENTION OF OBSTRUCTION OR GANGRENE,PARANOID TYPE SCHIZOPHRENIA,HYPOTENSION	HERNIA-UMBILICAL : DONE AS A CHILD; TOBACCO // SMOKER (NOS)		N	49.9	42	F	ACIDOSIS METABOLIC	Y	POSS		USA	JAUSA31088
INSULIN	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION			Y		45	F	DIABETES MELLITUS AGGRAVATED	N	POSS		USA	JAUSA31168
METFORMIN	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION,UNSPECIFIED SCHIZOPHRENIA		NO	Y		32	F	DIABETES MELLITUS AGGRAVATED	N	POSS		USA	JAUSA31711
INSULIN	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION		NO	Y		80	M	DIABETES MELLITUS AGGRAVATED	N	POSS		USA	JAUSA31992
IBUPROFEN,THEOPHYLLINE			YES	Y		96	F	HYPERGLYCAEMIA	N	DOUB		USA	JAUSA32202
CLONAZEPAM	DEPRESSIVE DISORDER, NOT ELSEWHERE CLASSIFIED	ALLERGY // NO, DRUGS // NO, MOM-HIGH BLOOD SUGAR, DEPRESSION, GRANDMOTHER-DEPRESSION, PSYCHOLOGICAL PROBLEMS., TOBACCO // NO.		N	122.47	31	M	HYPERGLYCAEMIA	N	POSS		USA	JAUSA32568

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
	UNSPECIFIED DELAY IN DEVELOPMENT, INFANTILE CEREBRAL Palsy, UNSPECIFIED			N		38	M	HYPERGLYCAEMIA	N	POSS		USA	JAUSA32920
		SOMATIC DELUSIONS.	YES	Y		38	M	DIABETES MELLITUS	Y	DOUB		USA	JAUSA32941
BENZATROPINE MESILATE, DOCUSATE SODIUM, FLUPHENAZINE, IBUPROFEN, LORAZEPAM, VALPROATE SODIUM	ARTHRITIS		YES	Y		50	F	HYPERGLYCAEMIA	Y	POSS		USA	JAUSA33244
HALOPERIDOL	UNSPECIFIED PSYCHOSIS, PARANOID TYPE SCHIZOPHRENIA			N		30	F	HYPERGLYCAEMIA	N	POSS		USA	JAUSA33466
	OLIGOPHRENIA	ALCOHOL // NONE		N		51	F	HYPERGLYCAEMIA	Y	POSS		USA	JAUSA33498
			YES	N		35	M	DIABETES MELLITUS RECODED TO HYPERGLYCEMIA	Y	DOUB		USA	JAUSA33838
TRIAMCINOLONE, CHLORHEXIDINE, HYDROCHLOROTHAZIDE, LISINAPRIL, AMFEBUTAMONE, SALBUTAMOL, VITAMINS	ASTHMA, PROPHYLAXIS, HYPERTENSION, HYPERTENSIVE ON, HEPATITIS, UNSPECIFIED, HERNIORRHAPHY, PARANOID TYPE SCHIZOPHRENIA, BRONCHITIS, NOT SPECIFIED AS ACUTE OR CHRONIC, MICROCEPHALUS, RENAL IMPAIRMENT, RENAL INSUFF.	ALLERGY // CEF-ALOXINE, HYPOKALAEMIA SECONDARY TO DRUG THERAPY IN 1994 PREVIOUSLY TREATED WITH HALOPERIDOL, THIORIDAZINE, LORAZEPAM AND DOXEPIN. PERFORATED EARDRUM, TOBACCO // 3 CIGARETTES/DAY		N		39	M	DIABETES MELLITUS RECODED TO HYPERGLYCEMIA	Y	POSS		USA	JAUSA33916

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
METFORMIN,NONE	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION,INJURY,HEAD,UNSPECIFIED SCHIZOPHRENIA	ALCOHOL // DENIED, DIABETES-MELLIT. HISTORY, TOBACCO // DENIED	YES	Y		40	M	DIABETES MELLITUS	N	POSS		USA	JAU3A33949
	LIVER DYSFUNCTION	ALCOHOL // ABUSE		N		44	M	HYPERGLYCAEMIA	Y	POSS		USA	JAU3A34228
			YES	Y			M	DIABETES MELLITUS	N	POSS		USA	JAU3A34246
UNSPECIFIED	POSITIVE,UNSPECIFIED DELAY IN DEVELOPMENT	FAMILY HISTORY OF HIV DIABETES MELLITUS. SHE WAS ABUSED BY HER BROTHER WHO ALSO PROSTITUTED HER.	YES	Y		36	F	DIABETES MELLITUS	N	POSS		USA	JAU3A34362
LORAZEPAM,BETAXOLOL, CARBAMAZEPINE	AGITATION,RETENTION OF URINE,DEMENTIA			N		84	M	HYPOGLYCAEMIA	N	POSS		USA	JAU3A34406
				Y		9	M	DIABETES MELLITUS	Y	DOUB		USA	JAU3A34454
GLIBENCLAMIDE,ALPRAZOLAM,BETAXOLOL,IMPRAMI NE,VERAPAMIL	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION,ANXIETY STATES,GLAUCOMA		NO	Y		65	F	DIABETES MELLITUS AGGRAVATED	N	POSS		USA	JAU3A35038
INSULIN	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION	LONG HISTORY OF CHRONIC PSYCHIATRIC ILLNESS, HOSPITALIZED SINCE 1983. NON-COMPLIANCE WITH DIABETES MANAGEMENT.	NO	Y		25	M	DIABETES MELLITUS AGGRAVATED	N	POSS		USA	JAU3A36042
GLIPIZIDE	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION,OBESITY		NO	Y		35	M	DIABETES MELLITUS AGGRAVATED	Y	POSS		USA	JAU3A35234

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
LOXAPINE,SERTRALINE,VALPROATE SODIUM		HISTORY OF DIABETES MELLITUS ON FATHER'S SIDE (NOS).	YES	Y		20	M	DIABETES MELLITUS	Y	POSS		USA	JAU3A35464
			YES	Y		20	M	KETOACIDOSIS	Y	POSS		USA	JAU3A35464
		ALCOHOL // DEPENDENCE: PATIENT'S BROTHER IS A DIABETIC.	YES	Y		40	M	DIABETES MELLITUS	Y	POSS		USA	JAU3A35494
TROGLITAZONE	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION,ANXIETY STATES		NO	Y		67	F	DIABETES MELLITUS AGGRAVATED	N	POSS		USA	JAU3A35623
HYPOGLYCEMICS,MOEXIP RIL	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION,HYPERTENSION		NO	Y			M	DIABETES MELLITUS	N	POSS		USA	JAU3A35888
CLONAZEPAM,LITHIUM,VALPROATE SODIUM	BIPOLAR DISORDER		YES	Y		34	F	DIABETES MELLITUS	Y	POSS		USA	JAU3A36172
CARBAMAZEPINE,LITHIUM,SERTRALINE HYDROCHLORIDE	BIPOLAR AFFECTIVE DISORDER, MIXED,BIPOLAR AFFECTIVE DISORDER, MIXED,DEPRESSIVE DISORDER, ELSEWHERE CLASSIFIED,ANXIETY STATES	ALLERGY // PENICILLIN		N		42	M	BLOOD SUGAR INCREASED	N	POSS	NOT ASS. /NOT REP.	USA	JAU3A36349
			YES	Y		30	F	DIABETES MELLITUS	Y	POSS		USA	JAU3A36554
VALPROATE SODIUM,PAROXETINE,VALPROATE SODIUM,NEFAZODONE,ME THYLPHENDATE,RANITIDINE,OMEPRazole,DOCUSATE	BIPOLAR AFFECTIVE DISORDER, MIXED,OBSESSIVE-COMPULSIVE DISORDERS,OBSESSIVE-COMPULSIVE DISORDERS,DEPRESSIVE	Allergy/nitrous oxide, haloperidol		N		30	F	HYPERGLYCAEMIA	N	DOUB	NOT ASS. /NOT REP.	USA	JAU3A36635

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
SODIUM,CILEST,FUROSEMI DE,VITAMINB	DISORDER, NOT ELSEWHERE CLASSIFIED,CATAPLEXY AND NARCOLEPSY,ESOPHAGEA L REFLUX,UNSPECIFIED GAS												
			YES	Y			UNKNOWN	DIABETES MELLITUS	Y	POSS		USA	JAUSA36831
FLUOXETINE	DEPRESSIVE DISORDER, NOT ELSEWHERE CLASSIFIED,DELUSIONS		YES	Y		50	F	DIABETES MELLITUS	Y	POSS		USA	JAUSA37073
	ACUTE PANCREATITIS		YES	Y		44	F	DIABETES MELLITUS	Y	POSS	DOUB	USA	JAUSA37223
BENZATROPINE,GLIBENCL AMIDE,SERTRALINE,FURO SEMIDE	UNKNOWN,DIABETES MELLITUS,SCHIZO- AFFECTIVE TYPE SCHIZOPHRENIA,EDEMA,P URE HYPERCHOLESTEROLEMIA ,HEPATITIS, UNSPECIFIED	21-year history of schizoaffective disorder. Hepatitis secondary to valproic therapy. Episodes of blackout during heavy alcohol consumption several years previously. Birth hypoxia. Minor head injury.	NO	N		41	M	HYPOGLYCAEMIA	Y	DOUB	DOUB	CAN	JRFBEL1888000201

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
FLUOXETINE HYDROCHLORIDE,TRAZOD ONE	HUMAN IMMUNODEFICIENCY VIRUS INFECTION WITH SPECIFIED CONDITIONS	No family history of diabetes; used thiothixene and olanzapine in the past. No alcohol use 2-3 weeks prior to event. Smokes one pack daily for six years. No known drug allergies.		Y		42	M	DIABETIC KETOACIDOSIS	Y	POSS	ASS. /NOT REP.	USA	JRFUSA1999000668
TRIFLUOPERAZINE HYDROCHLORIDE,LITHIUM, HYDROCHLORIDE,LITHIUM, TAMOXIFEN CITRATE	SCHIZO-AFFECTIVE TYPE SCHIZOPHRENIA,BIPOLAR AFFECTIVE DISORDER, MIXED,ESSENTIAL AND OTHER SPECIFIED FORMS OF TREMOR,CONVULSIONS,N EED FOR UNSPECIFIED PROPHYLACTIC MEASURE,NEOPLASM OF UNSPECIFIED NATURE	Hysterectomy Allergic to haloperidol, phenothiazine, laundry detergent mastectomy - breast cancer Stopped smoking 4 years ago Endometrial biopsy-1991 Brain tumor removed-1990 Frequent psychiatric hospitalizations and "shots" in the liver, stomach and kid		Y		51	F	DIABETES MELITUS AGGRAVATED	N	POSS	ASS. /NOT REP.	USA	JRFUSA1999001217

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
LORAZEPAM, BERTRALINE HYDROCHLORIDE	UNKNOWN, PARANOID TYPE SCHIZOPHRENIA, PARANOID TYPE SCHIZOPHRENIA	Multiple psychiatric hospitalizations. On fluphenazine decanoate, and olanzapine in past. History of non-compliance with medication. No significant medical history or allergies		N	102	66	F	HYPERGLYCAEMIA	Y	POSS	NOT ASS. /NOT REP.	USA	JRFUSA1999001399
VALPROATE SEMISODIUM, MIRTAZAPIN, PARACETAMOL, DIPHENHYDRAMINE, MAGNESIUM HYDROXIDE, MYLANTA, PROPRANOLOL	BIPOLAR AFFECTIVE DISORDER, MIXED SEVERE DEGREE, SPECIFIED AS WITH PSYCHOTIC BEHAVIOR, OTHER INSOMNIA, OBESITY	Unknown		N		43	M	HYPERGLYCAEMIA	Y	POSS	NOT ASS. /NOT REP.	USA	JRFUSA1999001817
BENZATROPINE MESILATE, LITHIUM, LITHIUM CARBONATE	UNKNOWN, MANIC-DEPRESSIVE PSYCHOSIS, UNSPECIFIED, DEPRESSIVE DISORDER, NOT ELSEWHERE CLASSIFIED	Used trifluoperazine in past. Anemia, "low iron" Allergy// penicillin		N		36	F	HYPOGLYCAEMIA	N	POSS	NOT ASS. /NOT REP.	USA	JRFUSA1999002213
	DIABETES MELLITUS	Unknown		Y	NO		M	DIABETES MELLITUS, AGGRAVATED	N	POSS	NOT ASS. /NOT REP.	USA	JRFUSA1999002303
		No family history of diabetes mellitus.		Y	YES	8	M	DIABETES MELLITUS	Y	DOUB	NOT ASS. /NOT REP.	USA	JRFUSA1999002438
		No prior history of hypoglycemia		N		80	M	HYPOGLYCAEMIA	Y	POSS	NOT ASS. /NOT REP.	USA	JRFUSA1999003388
		Unknown		N			F	BLOOD SUGAR DECREASED	N	POSS	NOT ASS. /NOT REP.	USA	JRFUSA1999003476
ACETYSALICYLIC ACID		Smoking// 1 cigar daily		N		37	M	DIABETES MELLITUS RECODED TO HYPERGLYCEMIA	Y	POSS	NOT ASS. /NOT REP.	USA	JRFUSA1999003548
AMFEBUTAMONE HYDROCHLORIDE	DEPRESSIVE DISORDER, NOT ELSEWHERE CLASSIFIED, OTHER AND	Multiple trauma including head injury following a work related accident. Grandfather		Y		30	M	DIABETES MELLITUS	N	POSS	NOT ASS. /NOT REP.	USA	JRFUSA1999004548

CONC. DRUGS	CONC. DISEASE	HISTORY	FIRST TIME REPORTED	DIABETES	WEIGHT	AGE	SEX	REACTION	SERIOUS	CAUSHO	CAUSREP	COUNTRY	REFNO
	UNSPECIFIED INJURY TO FACE AND NECK UNKNOWN, UNKNOWN, UNSPECIFIED ACQUIRED HYPOTHYROIDISM, SCHIZO-AFFECTIVE TYPE SCHIZOPHRENIA, SCHIZO-AFFECTIVE TYPE SCHIZOPHRENIA, OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS, OTHER ACNE, ANEMIA, UNSPECIFIED	had diabetes. Atrophy on CAT scan. Allergy // cats Adverse effects medications (NOS).	YES	Y	90.72	13	F	DIABETES MELLITUS	Y	DOUB	ASS. /NOT REP.	USA	JRFUSA2000000200
	VALPROATE SEMISODIUM, LITHIUM, LEVOTHYROXINE SODIUM, LOXAPINE SUCCINATE, SEROQUEL, TILACTASE, ERYTHROMYCIN, B, ENZATROPINE MESILATE, DOCUSATE SODIUM, DESMOPRESSIN, P, POLYCARBOPHIL CALCIUM, AMMONIUM LACTATE, TRAZODONE												

Janssen Research Foundation

NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

JRF Pharmacovigilance Report

50

Appendix 2: Detailed information on the patient exposure

Volume 15/Page 50

JJRP 00384038

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D821.52

Risperdal® number of patients

CL / PM / TN / MT / EV

Worldwide
Risperdal Patient Numbers
MarchTotal exposure (pt. months)
Total exposure (pt. years)42,498,163
3,541,514

	Sales	Dose		Avg. Treat. Days	Equiv. Month
	4,953,736				
Schizophrenia	2,273,903	4.8	66.1%	300	9.84
Bipolar	2,273,215	3	16.5%	120	3.93
Senile Dementia	2,274,394	1.4	11.6%	180	5.90
Neuroses/All Other	2,272,428	1.4	5.8%	90	2.95

Total Patients 9,033,939

Wtd. Avg. length of treatment: 173 days

The assumptions are the following:

1. Number of total patient months which is based on average daily dose of Risperdal divided by the length of treatment multiplied by the sales for each country.

2. Apply the percentage of Risperdal use within each indication to total patient months to get a total patient month figure by indication. Specifically:

Schizophrenia	66.1%
Bipolar	16.5%
Senile Dementia	11.6%
Neuroses/All Other	5.8%

3. Apply the average length of treatment for each indication
for example: average length of therapy for schizophrenia is 300 days divided by 30.5 yields 9.84 months.

	Days	Months treatment
Schizophrenia	300	9.84
Bipolar	120	1.90
Senile Dementia	180	5.90
Neuroses/All Other	90	2.95

4. Divide the patient months by indication (#2) by the average length of therapy in months (#3) which results in number of patients by indication. The sum of each indication then gives you total number of patients.

If you would like to calculate for your particular country, you can create this spreadsheet on your own and then insert the figure for total patient months for your country.

10-04-2000

Volume 15/Page 51

JJRP 00384039

Confidential/Produced in Litigation Pursuant to Protective Order

D821.53

Risperdal® Patient Months

CL / PM / TN / MI / EV

	1993 patient months	1994 patient months	1995 patient months	1996 patient months	1997 patient months	1998 patient months	1999 patient months	2000 patient months	cumulative 1993-2000 exposure	% elderly	Risperdal exposure elderly
Austria		7 368	15 331	28 743	28 175	41 827	54 672	13 018	194 236	14.9	27 451
Belgium / Lux.			781	20 248	79 656	82 072	121 628	33 243	337 627	14.9	50 306
C&E Europe			6 743	36 238	73 124	111 010	217 672	70 018	614 806	14.9	78 706
France				63 342	168 283	236 210	426 061	114 247	1 023 042	14.9	153 327
Germany	198	61 367	111 632	147 715	180 115	245 363	349 859	97 591	1 193 801	18	191 008
Greece		13 959	34 276	50 775	59 376	74 031	158 582	45 813	436 821	3	13 105
Italy			3 088	22 667	70 248	115 506	244 104	69 788	525 410	14.9	78 288
Netherlands		7 944	25 536	39 083	53 021	83 885	96 984	22 702	288 986	17	50 824
Portugal				3 806	9 595	12 242	28 215	14 712	66 572	14.9	9 919
Scandinavia	1 126	42 077	82 491	135 980	136 968	166 111	189 304	43 703	787 745	14.9	114 394
Spain		37 899	140 017	257 090	288 482	419 648	482 241	122 498	1 787 853	14.9	261 920
Switzerland		1 171	9 411	18 319	22 141	26 225	35 182	9 224	121 623	14.9	18 122
UK	25 372	83 214	151 851	240 784	229 478	206 511	239 785	68 423	1 253 409	17	213 080
Europe	26 695	264 858	631 125	1 079 758	1 398 643	1 780 546	2 623 159	722 896	8 487 911		1 258 449
Canada	37 532	107 187	177 050	248 421	295 594	331 878	379 974	107 257	1 684 882	14.9	251 049
Mex./Col./Venez.		6 812	12 085	30 035	55 813	74 272	191 923	54 406	425 152	8	12 755
USA		1 337 090	2 740 582	4 021 173	4 710 046	5 652 664	6 023 805	1 830 301	26 215 840	19	4 680 872
N. America	37 532	1 451 089	2 929 686	4 299 629	5 061 254	5 858 812	6 505 707	1 991 964	28 325 684		5 344 775
Argentina	2 990		12 486	17 248	23 781	31 635	43 225	7 510	139 235	14.9	20 746
Australia		6 183	65 667	121 486	151 297	141 898	182 859	42 608	711 907	14.9	106 074
Brazil			22 215	27 873	37 182	45 758	59 600	11 672	204 810	14.9	30 487
China					10 125	25 356	61 852	23 678	121 113	14.9	18 046
Hong Kong		108	1 267	2 175	4 458	5 467	10 848	3 133	27 455	14.9	4 081
India					417	1 575	2 963	789	5 744	14.9	856
Indonesia			2 750	3 833	5 181	1 846	4 924	1 355	19 801	14.9	2 964
Japan				404 517	812 676	742 746	1 279 876	328 167	3 567 833	14.9	531 623
Korea				20 433	44 158	59 875	92 859	23 022	220 246	14.9	32 817
M.East / W.Asia	86		4 210	6 581	48 352	48 982	181 154	63 168	352 113	14.9	62 463
Philippines			2 225	5 233	5 158	5 133	10 149	2 467	30 266	14.9	4 625
S. Africa	152	2 364	3 333	4 967	11 278	15 403	28 894	6 685	74 077	14.9	11 038
Sing./Mal.			495	2 105	4 619	6 762	11 808	4 902	30 689	14.9	4 573
Taiwan					7 029	32 286	60 904	25 235	146 493	14.9	21 822
Thailand				2 829	7 329	8 214	10 853	3 390	32 715	14.9	4 875
Others	3 229	6 656	114 647	619 390	1 173 050	1 151 749	2 082 766	531 081	5 684 568		847 001
Total	67 456	1 724 743	3 635 469	5 908 775	7 632 947	8 891 110	11 281 632	3 266 032	42 498 163 months 3 641 514 years		7 950 224

We have made a separate list of Risperdal use in the elderly (≥ 65 y) based on actual figures in the US, and based on weighted average of actual figures in Germany, Greece, Holland, Mexico and the UK extrapolated to the other countries. This still is likely and underestimate because as a rule doses used in the elderly are lower.

Listed above please find an estimated number of Risperdal patients months exposure.

Patient months are calculated by taking net trade sales, dividing by the average price of Risperdal in each given country, and dividing by 30 days. The actual number may vary ± 20%, if factors such as dose variations, retail inventory levels and the lack of sales information from South America and Eastern Europe are considered, however, it does provide us with a rough estimate of the overall patient number.

Please note that patient months are calculated in Baser using (from 1999 onwards) a dose of 5 mg a day for 75% of the patients and a dose of 3 mg for 25% of the patients.

Following doses were used until end 1988: Australia (4.5 mg); Austria (6.5 mg in '94; 4.5 mg in '95; 4 mg in '96); Canada (4.5 mg in '94; 4 mg in '95 and '96); Germany (4.8 mg); Japan (4.5 mg in '96 and '97); the Netherlands (5.6 mg); Spain (5 mg in '95; 4 mg in '96); Scandinavia (4 mg); Switzerland (5 mg in '95; 4.5 mg in '96); Thailand (4 mg in '97); UK (5 mg); USA (4.1 mg in '94; 3.8 mg in '95 and '96). In case the average daily dose is different in your country, you may wish to recalculate the numbers locally to more accurately reflect patient exposure in your country.

10-04-2000

Volume 15/Page 52

JJRP 00384040

Confidential/Produced in Litigation Pursuant to Protective Order

D821.54

Appendix 3: Attribution definitions of adverse events used by JRF

Volume 15/Page 53

JJRP 00384041

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D821.55

Attribution definitions of adverse events used by JRF

Not related

An adverse event which is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely - e.g. concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event which might be due to the use of the drug. An alternative explanation - e.g. concomitant drug(s), concomitant disease(s), - is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.

Probable

An adverse event which might be due to the use of the drug. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely - e.g. concomitant drug(s), concomitant disease(s).

Very likely

An adverse event which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation - e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

Janssen Research Foundation

NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

JRF Pharmacovigilance Report

55

Appendix 4: Current Company Core Data Sheet dated December 1998

Volume 15/Page 55

JJRP 00384043

Confidential/Produced in Litigation Pursuant to Protective Order

D821.57

R. 6221

1. TRADE NAME OF THE MEDICINAL PRODUCT

RISPERDAL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The tablets contain either 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 6 mg or 8 mg risperidone.

The oral solution contains 1 mg/ml risperidone.

3. PHARMACEUTICAL FORM

Film-coated tablets for oral use:

- 0.25 mg risperidone as yellow oblong biconvex tablets;
- 0.5 mg risperidone as brownish-red half-scored oblong biconvex tablets;
- 1 mg risperidone as white half-scored oblong tablets;
- 2 mg risperidone as orange half-scored oblong tablets;
- 3 mg risperidone as yellow half-scored oblong tablets;
- 4 mg risperidone as green half-scored oblong tablets;
- 6 mg risperidone as yellow circular biconvex tablets;
- 8 mg risperidone as green circular biconvex tablets.

Oral solution 1 mg/ml.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Risperdal is indicated for the treatment of a broad range of patients with schizophrenia, including first episode psychoses, acute schizophrenic exacerbations, chronic schizophrenia, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperdal alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. Risperdal is also indicated as long-term therapy for the prevention of relapse (acute exacerbations) in chronic schizophrenic patients.

Volume 15/Page 56

JJRP 00384044

Confidential/Produced in Litigation Pursuant to Protective Order

D821.58

In addition, Risperdal is indicated for the treatment of behavioural disturbances in patients with dementia in whom symptoms such as aggressiveness (verbal outbursts, physical violence), activity disturbances (agitation, wandering) or psychotic symptoms are prominent.

4.2. Posology and method of administration

Risperdal may be given as tablets or oral solution.

4.2.a. Schizophrenia

Switching from other antipsychotics.

When medically appropriate, gradual discontinuation of the previous treatment while Risperdal therapy is initiated is recommended. Also if medically appropriate, when switching patients from depot antipsychotics, initiate Risperdal therapy in place of the next scheduled injection. The need for continuing existing anti-parkinson medications should be reevaluated periodically.

Adults

Risperdal may be given once daily or twice daily.

Patients should start with 2mg/day Risperdal. The dosage may be increased on the second day to 4 mg. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6 mg. In some patients a slower titration phase and a lower starting and maintenance dose may be appropriate.

Doses above 10 mg/day have not been shown to be superior in efficacy to lower doses and may cause extrapyramidal symptoms. Since the safety of doses above 16 mg/day has not been evaluated, doses above this level should not be used.

A benzodiazepine may be added to Risperdal when additional sedation is required.

Elderly

A starting dose of 0.5 mg b.i.d. is recommended. This dosage can be individually adjusted with 0.5 mg b.i.d. increments to 1 to 2 mg b.i.d.

Risperdal is well tolerated by the elderly.

Children

Experience is lacking in children aged less than 15 years.

Renal and liver disease

A starting dose of 0.5 mg b.i.d. is recommended. This dosage can be individually adjusted with 0.5 mg b.i.d. increments to 1 to 2 mg b.i.d.

Risperdal should be used with caution in this group of patients until further experience is gained.

4.2.b. Behavioural Disturbances in patients with Dementia

A starting dose of 0.25 mg b.i.d. is recommended. This dosage can be individually adjusted by increments of 0.25 mg b.i.d., not more frequently than every other day, if needed. The optimum dose is 0.5 mg b.i.d. for most patients. Some patients, however, may benefit from doses up to 1 mg b.i.d.

Once patients have reached their target dose, a once daily dosing regimen can be considered.

4.3. Contraindications

Risperdal is contraindicated in patients with a known hypersensitivity to the product.

4.4. Special warnings and special precautions for use

Due to the alpha-blocking activity of Risperdal, (orthostatic) hypotension can occur, especially during the initial dose-titration period. Risperdal should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolaemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended (see Posology and method of administration). A dose reduction should be considered if hypotension occurs.

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterized by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. Because Risperdal has a lower potential to induce extrapyramidal symptoms than classical neuroleptics, it should have a reduced risk of inducing tardive dyskinesia as compared to classical neuroleptics. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

The Neuroleptic Malignant Syndrome, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels has been reported to occur with classical neuroleptics. In this event, all antipsychotic drugs, including Risperdal, should be discontinued. For specific dosology recommendations for elderly patients, patients with renal and liver disease and patients with dementia, it is referred to section 4.2.

Caution is also due when prescribing Risperdal to patients with Parkinson's disease since, theoretically, it might cause a deterioration of the disease.

Classical neuroleptics are known to lower the seizure threshold. Caution is recommended when treating patients with epilepsy.

Patients may be advised to refrain from excessive eating in view of the possibility of weight gain.

4.5. Interaction with other medicaments and other forms of interaction

The risk of using Risperdal in combination with other drugs have not been systemically evaluated. Given the primary CNS effects of Risperdal it should be used with caution in combination with other centrally acting drugs.

Risperdal may antagonize the effect of levodopa and other dopamine-agonists.

Carbamazepine has been shown to decrease the plasma levels of the active antipsychotic fraction of Risperdal. Similar effects may be observed with other hepatic enzyme inducers. On discontinuation of carbamazepine or other hepatic enzyme inducers the dosage of Risperdal should be re-evaluated and, if necessary, decreased.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of the antipsychotic fraction. Fluoxetine may increase the plasma concentration of risperidone but less so of the antipsychotic fraction. When Risperdal is taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

Food does not affect the absorption of Risperdal.

4.6. Pregnancy and lactation

The safety of Risperdal for use during human pregnancy has not been established. Although, in experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin- and CNS-mediated effects were observed. No teratogenic effect of risperidone was noted in any study.

Therefore, Risperdal should only be used during pregnancy if the benefits outweigh the risks.

It is not known whether Risperdal is excreted in human milk. In animal studies, risperidone and 9-hydroxy-risperidone are excreted in the milk. Therefore, women receiving Risperdal should not breast feed.

4.7. Effects on ability to drive and use machines

Risperdal may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8. Undesirable effects

Based on extensive clinical experience including long term use, Risperdal is generally well tolerated. In many instances it has been difficult to differentiate adverse events from symptoms of the underlying disease. Adverse events observed in association with the use of Risperdal are listed below:

Common:

insomnia, agitation, anxiety, headache.

Less common:

somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea/vomiting, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, urinary incontinence, rhinitis, rash and other allergic reactions.

Risperdal has a lower propensity to induce extrapyramidal symptoms than classical neuroleptics. However, in some cases the following extrapyramidal symptoms may occur: tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia. These are usually mild and are reversible upon dose reduction and/or administration of antiparkinson medication, if necessary.

Occasionally, (orthostatic) hypotension, and (reflex) tachycardia or hypertension have been observed following administration of Risperdal (see Precautions). A mild fall in neutrophil and/or thrombocyte count has been reported.

Risperdal can induce a dose-dependent increase in plasma prolactin concentration. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea. Weight gain (see Precautions), oedema and increased hepatic enzyme levels have been observed during treatment with Risperdal.

As with classical neuroleptics, the following have occasionally been reported in psychotic patients: water intoxication due to either polydipsia or the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), tardive dyskinesia, neuroleptic malignant syndrome, body temperature dysregulation and seizures.

4.9. Overdose

Symptoms

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. Overdosages of up to 360 mg have been reported. The available evidence suggests a wide safety margin. In overdose, rare cases of QT-prolongation have been reported.

In case of acute overdosage, the possibility of multiple drug involvement should be considered.

Treatment

Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to Risperdal. Therefore appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotonergic 5-HT₂ and dopaminergic D₂ receptors. Risperidone binds also to alpha₁-adrenergic receptors, and, with lower affinity, to H₁-histaminergic and alpha₂-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D₂ antagonist, which is considered to improve the positive symptoms of

schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2. Pharmacokinetic properties

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absorption is not affected by food and thus risperidone can be given with or without meals.

Risperidone is metabolized by cytochrome P-450 IID6 to 9-hydroxy-risperidone which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction. Another metabolic pathway of risperidone is N-dealkylation.

After oral administration to psychotic patients, risperidone is eliminated with a half-life of about 3 hours. The elimination half-life of 9-hydroxy-risperidone and of the active antipsychotic fraction is 24 hours.

Steady-state of risperidone is reached within 1 day in most patients. Steady-state of 9-hydroxy-risperidone is reached within 4-5 days of dosing. Risperidone plasma concentrations are dose-proportional within the therapeutic dose-range.

Risperidone is rapidly distributed. The volume of distribution is 1-2 l/kg. In plasma, risperidone is bound to albumin and alpha₁-acid glycoprotein. The plasma protein binding of risperidone is 88%, that of 9-hydroxy-risperidone is 77%.

One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine, risperidone plus 9-hydroxy-risperidone represent 35-45% of the dose. The remainder are inactive metabolites.

A single-dose study showed higher active plasma concentrations and a slower elimination of risperidone in the elderly and in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency.

5.3. Preclinical safety data

All other safety data relevant to the prescriber have been included in the appropriate section.

Volume 15/Page 62

JJRP 00384050

Confidential/Produced in Litigation Pursuant to Protective Order

D821.64

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Film-coated tablets:

Tablet core

Lactose monohydrate

Maize starch

Microcrystalline cellulose

Hypromellose 2910 15 mPa.s^(e)

Magnesium stearate

Colloidal anhydrous silica

Sodium lauryl sulphate

Film-coating

Hypromellose 2910 5 mPa.s

Propylene glycol

Titanium dioxide ^(a)

Talc^(a)

Quinoline yellow ^(b)

Indigotindisulphonate aluminum lake ^(c)

Orange yellow S aluminum lake ^(d)

Yellow Ferric Oxide ^(f)

Red Ferric Oxide ^(g)

11

^(a) Only in 0.25 mg, 0.5 mg, 2 mg, 3 mg, 4 mg, 6 mg and 8 mg tablets.

^(b) Only in 3 mg, 4 mg, 6 mg and 8 mg tablets.

^(c) Only in 4 mg and 8 mg tablets.

^(d) Only in 2 mg and 6 mg tablets.

^(e) Only in 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg tablets.

^(f) Only in 0.25 mg tablets

^(g) Only in 0.5 mg tablets

Oral solution:
Tartaric acid
Benzoic acid
Sodium hydroxide
Purified water

6.2. Incompatibilities

Risperdal tablets: none.

Risperdal oral solution: incompatible with tea.

6.3. Shelf life

Risperdal 1, 2, 3, 4 mg tablets: 3 years for all climatic zones when packed in PVC-PE-PVDC/Al blister.

Risperdal 6 mg and 8 mg tablets: 2 years for all climatic zones when packed in PVC-PE-PVDC/Al blister.

Risperdal 0.25 mg and 0.5 mg tablets: 2 years for all climatic zones when packed in PVC-PE-PVDC/Al blister.

Risperdal oral solution:

- 30 ml bottle: 2 years for all climatic zones when protected from freezing;

- 100 ml bottle: 3 years for all climatic zones when protected from freezing.

6.4. Special precautions for storage

Risperdal tablets should be stored between 15°C and 30°C.

Risperdal oral solution should be stored between 15°C and 30°C and should be protected from freezing.

Keep out of reach of children.

6.5. Nature and contents of container

Tablets:

PVC-PE-PVDC/Al blister consisting of aluminum foil 20 µm with a 6 g/m² heat-seal coating and a trilayer foil PVC 200 µm, LDPE 25 µm, PVCD 90 g/m².

Risperdal 1, 2, 3 and 4 mg tablets are packed in a blister which contains 10 tablets. Blisters are packed in a cardboard box (2 or 6 blisters per box).

Volume 15/Page 64

JJRP 00384052

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D821.66

Risperdal 6 mg and 8 mg tablets are packed in a blister (calendar pack) which contains 7 tablets. Blisters are packed in a cardboard box (4 blisters per box).

Risperdal 0.25 and 0.5 mg tablets are packed in a blister which contains 10 tablets. Blisters are packed in a cardboard box (6 blisters per box).

Oral solution:

30 ml and 100 ml amber glass bottle with plastic child resistant closure and a pipette of 3 ml, calibrated in milligrams and milliliters. The pipette has a minimum volume of 0.25 ml and a maximum volume of 3 ml.

6.6. Instructions for use/handling

30 ml bottle:

To open the bottle and use the pipette:

Fig. 1: The bottle comes with a child-proof cap, and should be opened as follows: push the plastic screw cap down while turning it counter clockwise.

Fig. 2: Insert the pipette into the bottle. While holding the bottom ring, pull the top ring up to the mark that corresponds to the number of millilitres or milligrams you need to give.

Fig. 3: Holding the bottom ring, remove the entire pipette from the bottle.

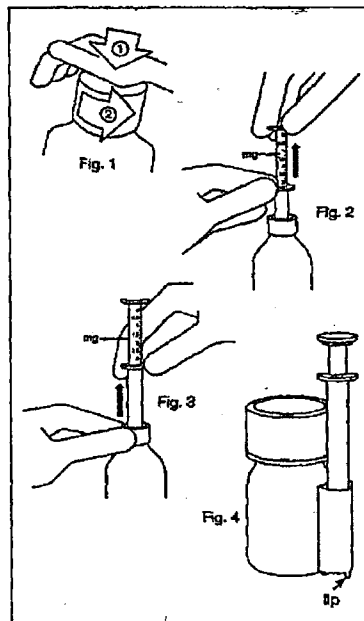
Empty the pipette into any non-alcoholic drink, except for tea, by sliding the upper ring down.

Close the bottle and rinse the pipette with some water.

To make a unit of pipette and bottle:

Fig. 4:

- take the holder and peel off the paper;
- stick the holder to the bottle so that the lip points down;
- insert the pipette into the holder; pipette and bottle now form a unit.



100 ml bottle:

Fig. 1: The bottle comes with a child-proof cap, and should be opened as follows:

push the plastic screw cap down while turning it counter clockwise.

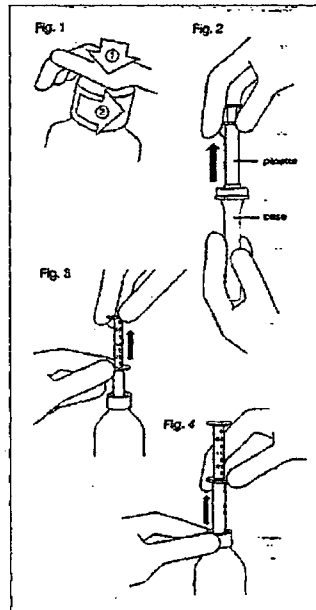
Fig. 2: Pull the pipette out of its case and insert it into the bottle .

Fig. 3: While holding the bottom ring, pull the top ring up to the mark that corresponds to the number of millilitres or milligrams you need to give.

Fig. 4: Holding the bottom ring, remove the entire pipette from the bottle.

Empty the pipette into any non-alcoholic drink, except for tea, by sliding the upper ring down.

Fit the empty pipette back into its case and close the bottle.



7. MARKETING AUTHORIZATION HOLDER

To be completed by the operating company.

8. MARKETING AUTHORIZATION NUMBER(S)

To be completed by the operating company.

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

To be completed by the operating company.

Volume 15/Page 67

JJRP 00384055

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D821.69

Janssen Research Foundation

NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

JRF Pharmacovigilance Report

68

10. DATE OF (PARTIAL) REVISION OF THE TEXT

December 1998

Volume 15/Page 68

JJRP 00384056

Confidential/Produced in Litigation Pursuant to Protective Order

D821.70

R. 6234

Janssen Research Foundation

NDA 20-272 and 20-388

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

JRF Pharmacovigilance Report

69

Appendix 5: Line listings of the individual cases

Volume 15/Page 69

JJRP 00384057
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D821.71

R. 6235

Ref.no. (vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction
ROAFF31583(1)	USA	literature	32yr	M	3 week(s) at onset	Recovered Serious	Pancreatitis (Unknown) Leukocytosis (Unknown) Hyperglycemia (Unknown)

tablet - - 6mg

Event Description: PUBLISHED IN: AM J PSYCHIATRY 154 (1), P.130-131, 1997.
A 32-YEAR-OLD MAN ADMITTED TO OUR HOSPITAL WITH A PRIMARY PSYCHIATRIC DIAGNOSIS THAT WAS CONSIDERED TO BE CHRONIC UNDIFFERENTIATED SCHIZOPHRENIA. HE HAD BEEN MAINTAINED ON A REGIMEN OF HALOPERIDOL, 6 MG B.I.D.; DOXEPIN, 150 MG B.I.D.; BENZOTROPINE MESYLATE, 2 MG B.I.D.; AND EXTENDED-RELEASE NIFEDIPINE, 60 MG/DAY. THE DECISION TO INTRODUCE RISPERIDONE WAS MADE ON THE BASIS OF PATIENT'S HISTORY OF TREATMENT-REFRACTORY AND EXTRAPYRAMIDAL SYMPTOMS. RISPERIDONE TREATMENT WAS INITIATED WITH A SIMULTANEOUS DECREASE OF THE HALOPERIDOL REGIMEN, AS PER OUR FACILITY'S PROTOCOL. HE EXPRESSED NO COMPLAINTS DURING THIS TITRATION PERIOD; FULL DOSING OF RISPERIDONE (6 MG/DAY) WAS ACHIEVED AFTER 2 WEEKS. ONE WEEK LATER, HE COMPLAINED OF DIFFUSE ABDOMINAL PAIN, NAUSEA, AND CONSTIPATION. AFTER CONSULTATION WITH THE INTERNAL MEDICINE DEPARTMENT, ACUTE PANCREATITIS WAS DIAGNOSED, ALONG WITH MILD LEUCOCYTOSIS AND SLIGHT GLYCEMIC ELEVATION. SGOT, SGPT, AND LDH INDICES REMAINED WITHIN NORMAL REFERENCE RANGE. HE WAS AFEBRILE, AND HIS COGNITIVE STATUS WAS UNCHANGED. THE NEXT DAY, HIS INITIAL AMYLASE LEVEL WAS 1047 IU/LITER. THE RISPERIDONE REGIMEN WAS REDUCED AND DISCONTINUED OVER THE SUBSEQUENT 2 WEEKS; AMYLASE LEVELS CORRESPONDINGLY DECLINED TO 147 IU/LITER.
HIS CLINICAL AND LABORATORY SYMPTOMS ABATED AFTER WITHDRAWAL OF RISPERIDONE WITHOUT FURTHER INTERVENTION OR CONSEQUENCES. OVER THE ENSUING 3 MONTHS, HE WAS STABILIZED ON A REGIMEN OF THIOTHIXENE; THERE WAS NO RECURRENCE OF THE HYPERAMYLASEMIA.

Causality Per Company: possible

Indications: Unspecified Schizophrenia

Concomitant Diseases: Hypercholesterolemia; Hypertension

Company Remarks: BOTH MOST FREQUENT REASONS FOR DEVELOPMENT OF PANCREATITIS: ALCOHOL AND CHOLELITHIASIS ARE NOT EXCLUDED.

ROAFF43451(1)	USA	literature	30yr	M		No Change/Not Yet Subsided Serious	Diabetes Mellitus (Unknown)

tablet - - -

Causality Per Company: possible

Indications: Unspecified Schizophrenia

Event Description: Case published in: 1999, Mohan D et al., The British Journal of Psychiatry 174, p.180-181.
In a 30-year-old black male on a trial of risperidone elevated blood sugar levels were noted.
The patient tried treatment with clozapine 3 years ago, but this treatment had to be discontinued because of hyperglycemia. His psychotic symptoms continued and his behaviour was highly disturbed and aggressive. Despite treatment with various traditional antipsychotic medications, he made no improvement for three years.
A trial of risperidone was started, but also this trial had to be discontinued because of elevated blood sugar levels. They remained elevated after withdrawal of risperidone. Control of his diabetes was achieved using an oral hypoglycaemic (glibenclamide).

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Volume 15/Page 70

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D821.72

JJRP 00384058

R. 6236

Ref.no. (vars.no.)	City	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction

Formul Strength-Unit dose (Therapy start date/end date)
Traditional antipsychotics were administered again. In the two years since traditional antipsychotic and oral hypoglycaemic medications have been prescribed together, he has continued to experience psychotic symptoms but has not acted violently anymore.

JACAN16870(1)	CAN health professional	80yr F	6 day(s) at onset	Unknown Not Serious	Hypoglycaemia (Unknown)	Causality For Company: doubtful
tablet 3 mg - 2ag						Indications: Bipolar Disorder

Event Description: Hospital pharmacist's report: 60 y.o. female Pt using risperidone for bipolar affective disorder received 6 days of therapy but began to experience hypoglycaemia and fluctuating blood glucose levels. (one day 4.0, next day: 6.8).

JACAN16880(1)	CAN health professional	58yr M	1 day(s) at onset	Recovered Serious	Hypothermia (14-APR-1996) Hypoglycaemic Reaction (14-APR-1996)	Causality Per Reporter: probable
tablet - - 3ag (13-APR-1996 / 14-APR-1996)						Causality Per Company: possible

Event Description: Pharmacist report: a 58 yr old mentally retarded male pt was hospitalised because of aggressive behaviour on 12 Apr 96 He had been receiving benztropine 2 mg qam, haloperidol 10mg bid plus 20 mg at bedtime and cimetidine 20mg od. On 13 Apr 96 his medications were changed and risperidone 3ag bid (without titration) was added to the regimen. Pt developed hypothermia (body temperature 33.3 C) and hypoglycaemia. Serum calcium low and magnesium high. All meds stopped and pt recovered.

Concomitant Diseases: Oligophrenia; Diabetes Mellitus
Without Mention Of Complication

JACAN18241(2)	CAN health professional	72yr F		Recovered Serious	Hypoglycaemia (28-FEB-1997) Convulsions (28-FEB-1997)	Causality For Company: possible
tablet 2 mg - 2ag (Unknown / 24-FEB-1997)						Indications: Unspecified Paranoid State; Delusions

Event Description: Diabetic patient was on risperidone. Risperidone was discontinued

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Volume 15/Page 71

Confidential/Produced in Litigation Pursuant to Protective Order
JJRP 00384059
D821.73

R. 6237

Ref.no. (vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction
Formul Strength-Unit dose (Therapy start date/end date) ===== suddenly and patient exhibited hypoglycemia. Follow-up is being attempted. =====							
JACAN16675(1)	CAN	health professional	geri M	stri	c	Recovered Not Serious	Diabetes Mellitus Aggravated (Unknown) Causality For Company: possible Concomitant Diseases: Diabetes Mellitus Without Mention Of Complication
tablet - - 1.6mg tablet - - .5mg							
Event Description: Spontaneous report from a pharmacist of an elderly male on risperidone 1.6 mg daily who had difficulty keeping his glucose levels under control. His dose was reduced to 0.5 mg daily with better glycemic control. =====							
JACFRA2000000063 (2)	FRA	health professional	48yr M	85 day(s)	at onset	Improved Serious	Diabetes Mellitus (12-JAN-2000) Causality For Reporter: probable Causality For Company: possible
tablet 4 mg - 4mg (19-NOV-1999 / Unknown) Event Description: From initial information received on 02-Feb-00:							
This 51 year-old male patient treated with Risperdal® (risperidone) 8 mg/day since 10-Nov-89 was hospitalized for an insulino-dependent diabetes in Jan-00. Concomitant drugs were Depakine chrono® (acide valproique) Loxapac® (loxapine) and Urbanyl® (clobazam) since several years, Lamictal® (lamotrigine) and Gardenal® (phenobarbital) since 1997. Further information has been requested. From additional information received on 22-Feb-00: This 48-year-old (not 51) male patient with Risperdal® (risperidone) 4 mg at dose of 8 mg/day since 19-Nov-89 was hospitalized for hyperglycemia (2,95 g/L) on 12-Jan-00, inaugurating of an insulino-dependent diabetes (pre-existing blood glucose was at 1g/L on 05-Jun-88). Concomitant drugs were Depakine® (valproate sodium) Urbanyl® (clobazam) since 1983, Lamictal® (lamotrigine) since 1996 and Loxapac® (loxapine) since 17-Sep-89. The patient had also received Gardenal® (phenobarbital) and Solian® (mianserin) from 1993 to 18-Nov-89. His past history was significant for a familial diabetes. Risperdal® was not stopped and the patient was treated with human insulin. His level of blood glucose normalised (no figures). According to the reporter, the patient had							Indications: Unspecified Psychosis

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Volume 15/Page 72

Confidential/Produced in Litigation Pursuant to Protective Order

JJRP 00384060

D821.74

R. 6238

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction
							4

Normal Strength-Unit dose (Therapy start date/end date)

Improved.
 The reporter considered the causal relationship of this event with risperidone to be probable.

////////////////////////////////////

JAFRA28489(2)	FRA health professional	35yr M	4 month(s) at onset	Unknown Serious	Hyperglycaemia (Unknown)
					Causality Per Company: possible
tablet 2 mg - -					Indications: Depressive Disorder, Not Elsewhere Classified

Event Description: PATIENT OF 35-40 YEARS OLD, WAS REFERRED TO HOSPITAL BY HIS TREATING PHYSICIAN FOR HYPERGLYCAEMIA OF 6 G. QUESTIONING REVEALED THAT PATIENT EXPERIENCED POLYURIA, POLYDIPSIA AND WEIGHT LOSS OF 6 KG FOR APPROXIMATELY 2 MONTHS. PATIENT HAS NO SPECIFIC HISTORY AND HIS GRANDFATHER HAD DIABETES. PATIENT HAS A DEPRESSIVE SYNDROME FOR SEVERAL YEARS BUT IS ON NO MEDICATION EXCEPT RISPERIDONE 4 MG/D WHICH WAS STARTED 4 MONTHS AGO. FURTHER INFORMATION HAS BEEN REQUESTED. CASE CLOSED 2JUL97 (NO FURTHER INFO AVAILABLE)

////////////////////////////////////

JAFRA28535(2)	FRA health professional	30yr F		No Change/Not Yet Subsided Serious	Hyperglycaemia (Unknown) Condition Aggravated (Unknown) Galactorrhoea (Unknown) Asthma (Unknown)
tablet 2 mg - 2mg (25-MAY-1996 / 06-SEP-1996)					

Event Description: MID JUNE 1996, THIS 32-YEAR-OLD FEMALE STARTED ON RISPERIDONE 4 MG/D. THE DOSE WAS DECREASED TO 2 MG/D IN JULY BECAUSE OF ASTHENIA AND GALACTORRHOEA. HYPERGLYCAEMIA OF 7 G/L WAS NOTED. PATIENT HAD ALREADY GLYCAEMIA OF 2 G/L BEFORE RISPERIDONE WAS STARTED. BEFORE RISPERIDONE, PATIENT WAS TREATED WITH AMISULPRIDE. FURTHER INFORMATION HAS BEEN REQUESTED. F O L L O W U P (12SEP96): PATIENT WAS TREATED WITH RISPERIDONE FROM 26MAY96 TO 6SEP96. CLINICAL SIGNS OF DIABETES APPEARED IN JULY 96 AND IN AUGUST, LAB DATA SHOWED GLYCAEMIA OF 6-7 G/L. BEFORE STARTING RISPERIDONE, HYPERGLYCAEMIA OF 1.8 G/L WAS NOTED IN THE MORNING (FASTING). RISPERIDONE WAS PERMANENTLY DISCONTINUED.

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JAFRA30831(5)	FRA health professional	24yr M	23 day(s) at onset	No Change/Not Yet Subsided Serious	Rhabdomyolysis (15-NOV-1998) Muscle Rigidity (24-OCT-1996) Pain (13-NOV-1996)

Volume 15/Page 73

Confidential/Produced in Litigation Pursuant to Protective Order
 JJRP 00384061
 D821.75

R. 6239

Ref.no. (vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	

Formul Strength-Unit dose (Therapy start date/end date)								
=====								
tablet 2 mg - 1mg (22-OCT-1998 / 23-OCT-1998)							Akinesia (24-OCT-1998)	
tablet 2 mg - 2mg (23-OCT-1998 / 15-NOV-1998)							Gait Rigid (24-OCT-1998)	
tablet 2 mg - 3mg (15-NOV-1998 / 17-NOV-1998)							Anxiety (13-NOV-1998)	
							Malaise (13-NOV-1998)	
							Dysphagia (13-NOV-1998)	
							Tremor (13-NOV-1998)	
							Shivering (13-NOV-1998)	
							Hyperglycaemia (15-NOV-1998)	
							Leucocytosis (15-NOV-1998)	

Event Description: RHABDOMYOLYSIS AND EXTRAPYRAMIDAL DISTURBANCES WERE NOTED IN A YOUNG MAN (AGE UNKNOWN) WITHOUT ANY SPECIFIC HISTORY. THE EVENTS OCCURRED AFTER A FEW DAYS OF RISPERIDONE THERAPY IN ASSOCIATION WITH CLORAZEPATE. RHABDOMYOLYSIS, WITHOUT FEVER, REQUIRED HOSPITALIZATION WITH FAVOURABLE EVOLUTION. DYSKINESIA (CHINING) PERSISTED AS WELL AS A DRY MOUTH. FURTHER INFORMATION HAS BEEN REQUESTED.

F O L L O W U P (WRITTEN REPORT) 18DEC98: PATIENT STARTED RISPERIDONE 2 MG/D ON 22OCT98. FROM 23OCT98 TILL 15NOV98, DOSE WAS INCREASED TO 4 MG/D. ON 24OCT98, PATIENT DEVELOPED AKINESIA WITH HYPERKINESIA AND RIGID GAIT. ON 13NOV98, THE PATIENT WAS ANXIOUS AND PRESENTED GENERAL MALAISE WITH DIFFUSE ABDOMINAL PAIN, CHEST OPPRESSION, DYSPHAGIA, CHILLS, TREMOR AND OROFACIAL DYSKINESIA. PATIENT'S CONDITION RAPIDLY DETERIORATED WITH SEVERE BACK PAIN. HE WAS HOSPITALIZED FROM 16 TO 19NOV98. LAB DATA OF 15NOV98 SHOWED LEUCOCYTOSIS OF POLYNEUTROPHILS, INCREASED LIVER ENZYMES AND MUSCULAR ENZYMES, AND GLYCAEMIA. CALCIUM WAS NORMAL. ON 17NOV98 RISPERIDONE WAS DISCONTINUED. MUSCULAR ENZYMES HAVE NORMALIZED ON 25NOV98, RESULTS OF LFT UNKNOWN. ON 5DEC98 PAIN HAS DISAPPEARED BUT PATIENT STILL SUFFERED FROM RIGID GAIT AND DYSKINESIA OF FACE. ACCORDING TO THE REPORTER, RELATION WITH RISPERIDONE IS VERY LIKELY.

Hepatic Function Abnormal (15-NOV-1998)

5

Causality Per Reporter: very likely/certain

Causality Per Company: possible

JAFRA33408(2)	FRA health professional	M	7 month(s) at onset	Unknown Not Serious	Diabetes Mellitus (Unknown)
					Causality Per Company: doubtful

Event Description: A male patient treated with risperidone 4 mg daily for approximately 7 months, developed insulin dependent diabetes. Patient has no medical history of diabetes.

JAFRA33412(3)	FRA health professional	M		Unknown Not Serious	Diabetes Mellitus (Unknown)
					Causality Per Company: doubtful

Event Description: A male patient on risperidone for a few months developed diabetes requiring treatment with oral antidiabetics. Case closed on 07-MAY-97 without any possibility to obtain additional information. (patient lost to follow up)

JAFRA37429(4)	FRA health professional	54yr M	10 month(s) at onset	No Change/Not Yet Subsided	Liver Function Tests Abnormal Nos (77-NOV-1997) Hypoglycaemia (23-JAN-1998)

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Serious	Confusion (77-NOV-1997)
Formul	Strength-Unit dose (Therapy start date/end date)					Outcome Seriousness	Reaction
							6
							Somnolence (77-NOV-1997)

tablet 2 mg - 2mg (15-JAN-1997 / 12-JAN-1998)

Event Description: A 45-year-old male patient with parkinsonian syndrome of iatrogenic origin (no other medical history) was treated with risperidone 8 mg/day since NOV-97, in association with clonazepam and piribedil.

IN JAN-98, he was hospitalized due to confusion and somnolence. SGOT and SGPT were elevated (3 times normal value). SGOT was normal. The patient is not alcoholic. Further examination (in particular hepatic echography and viral serology) is ongoing.

Risperidone was discontinued and replaced by loxapine.

Further information is expected.

F O L L O W U P (18-FEB-98):

The patient is 54 years old and was treated with risperidone 8 mg/day since JAN-97 for delusion of persecution.

In NOV-97, he developed somnolence and mental confusion associated with elevated liver functions and hypoglycaemia. The reporter relates somnolence and mental confusion to drug abuse: intake of Noctran(R) during the day. Risperidone was stopped on 12-JAN-98. The patient was hospitalized twice for his events: from 13 to 24-JAN-98 and from 07 to 11-FEB-98.

Hepatitis B and C tests were negative.

On 16-FEB-98, insomnia was disappeared and hepatic function was almost normal (NOS).

Hypoglycaemia is under investigation.

According to the reporter, the causal relation with increased hepatic enzymes and risperidone is probable.

No further information is expected.

Causality Per Reporter: probable

Causality Per Company: possible

Indications: Persecution Delusion

JAGER09772(1)	GER health professional	52yr F	No Change/Not Yet Subsided Not Serious	Blood Sugar Increased (Unknown) Prolactin Increased (Unknown)

tablet - - 3mg

Causality Per Company: possible

Indications: Schizo-Affective Type Schizophrenia

Event Description: Routine control revealed prolatinaemia in this 52-year-old, female patient treated with risperidone. Moreover patient complained of feeling of tension in her breast. Daily blood sugar profile was remarkable up to 227 mg%. As patient was compliant, medication was maintained.

JAGER40008(1)	GER health professional	55yr M	Unknown Not Serious	Diabetes Mellitus Aggravated (Unknown)

Causality Per Reporter: possible

1debazack 16JUN98

Volume 15/Page 75

Confidential/Produced in Litigation Pursuant to Protective Order
 JJRP 00384063
 D821.77

R. 6241

Ref.no. (vers.no.)	City	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction
Formul Strength-Unit dose (Therapy start date/end date)							
tablets - .25g (15-JUN-1997 / Unknown)							
Event Description: A 65-year-old, male patient on risperidone therapy experienced fluctuations in blood sugar level (hyper- and hypoglycaemia), which, according to the diabetologist, seems most likely caused by the medication.						Causality Per Company: possible	
						Indications: Paranoid Type Schizophrenia	
						Concomitant Diseases: Unspecified Schizophrenia	

JACER40242(1)	CER health professional	86yr F	2 day(s) at onset	Recovered Not Serious	Apathy (07-JUL-1998) Tiredness (07-JUL-1998) Hypoglycaemia (07-JUL-1998)
tablets - .5mg (05-JUL-1998 / 07-JUL-1998)					
Event Description: A 86-year-old, female patient who recently started on risperidone therapy experienced apathy, tiredness and reluctance to eat and drink on her own. Additionally, hypoglycaemia was observed after dinner. Symptomatology resolved after discontinuation of risperidone and glibenclamide.					Causality Per Reporter: possible
					Causality Per Company: possible
					Indications: Unspecified Nonpsychotic Mental Disorder Following Organic Brain Damage

JAKY033822(1)	JPH health professional	72yr F	4 day(s) at onset	Recovered Not Serious	Blood Sugar Increased (06-NOV-1996) Causality Per Reporter: not related
tablets - .5mg (02-NOV-1996 / 23-JAN-1997)					
Event Description: A 72-year-old female treated with risperidone for schizophrenia since 02-NOV-96 developed increased sugar blood level on 06-NOV-96. The patient has diabetes mellitus as concurrent disease. No further information is available.					Causality Per Company: doubtful
					Indications: Unspecified Schizophrenia
					Concomitant Diseases: Diabetes Mellitus Without Mention Of Complication

JAKY037458(2)	JPH health professional	53yr M	8 week(s) at onset	No Change/Not Yet Subsided	Diabetes Mellitus (10-JAN-1997) Hepatic Function Abnormal (10-JAN-1997)

Volume 15/Page 76

Confidential/Produced in Litigation Pursuant to Protective Order
JJRP 00384064
D821.78

R. 6242

Ref.no.(vers.no.)	Cty	Prin. source	Age	Sex	Latency	Outcome Seriousness	Reaction	
Formal Strength-Unit dose (Therapy start date/end date)								
//////////								
granules	-	-	5mg (15-NOV-1998 / 22-NOV-1998)				Causality Per Reporter: not related	
granules	-	-	1mg (23-NOV-1998 / 13-DEC-1998)					
granules	-	-	2mg (14-DEC-1998 / 25-FEB-1997)				Causality Per Company: doubtful	
Event Description: A 53-year-old, male patient on risperidone for treatment of schizophrenia, developed diabetes and hepatic function disorder on 10-JAN-97. At time of this report, patient had not yet recovered. No further information is available.							Indications: Unspecified Schizophrenia	
							Concomitant Diseases: Polyp,Gallbladder	
//////////								
JAKY037482(1)	JPN	health professional	62yr M		27 day(s) at onset	Recovered Not Serious	Glycosuria (14-FEB-1997)	
tablet - - 2mg (18-JAN-1997 / 18-APR-1997)							Causality Per Reporter: possible	
Event Description: A 62-year-old male patient, on risperidone sedation for schizophrenia developed glycosuria. Further information is not expected.							Causality Per Company: possible	
							Indications: Unspecified Schizophrenia	
							Concomitant Diseases: Iron Deficiency; Cardiac-Disorder; Gastritis; Osteoporosis; Urasnia	
//////////								
JAKY039553(6)	JPN	health professional	47yr F			Death Serious	Rhabdomyolysis (13-OCT-1997) Cardiac Arrest (10-OCT-1997) Pulmonary Collapse (10-OCT-1997) Fibrillation Ventricular (10-OCT-1997) Oedema Cerebral (11-OCT-1997) Intracranial Pressure Increased (11-OCT-1997) Leukocytosis (10-OCT-1997) Hepatic Enzymes Increased (10-OCT-1997) Condition Aggravated (10-OCT-1997) Hyperglycaemia (10-OCT-1997) Hypokalaemia (10-OCT-1997)	
tablet - - 4mg (11-JUL-1997 / 13-OCT-1997)								
Event Description: A 47-year-old female on risperidone medication died from cardiac arrest. Autopsy revealed rhabdomyolysis. Further information is expected.							Causality Per Reporter: unknown	
F O L L O W U P (13-JUN-98):								
AFTER HER DISCHARGE FROM THIS HOSPITAL ON 19-JUL-98, THE PATIENT VISITED THE HOSPITAL TWICE A MONTH. SHE SOMETIMES COMPLAINED OF AUDITORY HALLUCINATION AND INSOMNIA, AND SHE SUFFERED FROM A STRONG NEGATIVE SYMPTOM, AND WAS UNABLE TO DO HOUSEWORK ETC.								
27-JUN-97; ABNORMAL HEPATIC FUNCTION WAS NOTED.								
11-JUL-97; RISPERIDONE WAS STARTED. HEPATIC FUNCTION WAS STILL ABNORMAL; EKG SHOWED SINUS								

1dsbaack 16JUN00

Volume 15/Page 77

Confidential/Produced in Litigation Pursuant to Protective Order
JJRP 00384065
D821.79

R. 6243

Ref.no. (Vers.no.)	Cty	Prim.	Source	Age	Sex	Latency	Outcome Seriousness	Reaction	
Formal Strength-Unit dose (Therapy start date/end date)									
TACHYCARDIA									
THE PATIENT COULD MANAGE TO DO HOUSEWORK SOMEHOW WITH HER HUSBAND'S HELP, BUT SHE TENDED TO STAY IN BED IN THE DAYTIME. SHE HAD NOT CONSULTED THE PHYSICIAN SINCE LAST SEP-97. THEREFORE, THE PHYSICIAN DID NOT KNOW HER CONDITION IN DETAIL BEFORE THE ADVERSE EVENT OCCURRED.								Causality For Company: possible	
10-OCT-97: CARDIAC ARREST DEVELOPED.								Indications: Unspecified Schizophrenia	
NEURILEPTIC MALIGNANT SYNDROME WAS SUSPECTED, BUT THE DEFINITE DIAGNOSIS WAS NOT MADE.								Concomitant Diseases: Triglyceridemia; Ischemic Heart Disease	
13-OCT-97: THE PT DIED OF CARDIAC AND RENAL FUNCTION IMPAIRMENT DUE TO RHYTHMOLYSIS. DETAILED INFORMATION WILL FOLLOW.								Company Remarks: Patient was on multiple concomitant drugs.	
FOLLOW UP (10-OCT-97):									
10-OCT-97: When the pt's husband returned home, he could hear her crying in the washroom and found she had fallen down there.									
At 22:54 h the ambulance was called.									
At 23:00 h the ambulance was arrived at her house, who confirmed cardiopulmonary arrest and immediately performed cardiopulmonary resuscitation.									
At 23:24 the ambulance arrived at the emergency department of another hospital. The consciousness level was 300 with dilated pupils. Neither light reflex nor spontaneous respiration was observed. Carotid artery was not palpable. Cardiac arrest was noted on ECG monitoring. With continuous cardiac compression, endotracheal intubation was implemented. The venous pathway was maintained and a total of 9 mg of epinephrine was administered. As ventricular fibrillation developed, DC defibrillator was used once at 200 J without effects.									
From 23:50 o'clock cardiac compression was performed for several minutes, and then the heart beat resumed with a systolic blood pressure of 50 mmHg. With continuous administration of dopamine, her blood pressure gradually elevated up to 80/50 mmHg. Chest X-ray findings revealed 80% of cardiothoracic index and a slight decrease in X-ray permeability in the right upper lung field.									
11-OCT-97: At 1:00 h the pt was admitted to ICU after exposed to the head computerized tomography, which confirmed cerebral swelling with no bleeding. ECG revealed sinus rhythm and ST-depression. In order to maintain blood pressure, a continuous IV drip infusion was performed with dopamine, dobutamine, norepinephrine or epinephrine. At 3:00 h spontaneous respiration was noted and the pupil diameter gradually contracted.									
At 9:00 h the pupil diameter became 4.5 mm without light reflex.									
At 13:00 h a catheter to continuously monitor jugular blood oxygen saturation and another catheter to measure intracranial pressure were inserted. Jugular blood oxygen saturation was 78% at insertion and then remained higher. Intracranial pressure was 22 mmHg at insertion. At 18:00 h spontaneous respiration disappeared. Despite administration of osmotic diuretic, intracranial pressure elevated.									
At 21:00 the pupils dilated again.									
12-OCT-97: At 0:00 h, intracranial pressure elevated to 70 mmHg and intracranial perfusion pressure became 0.									
Following her family's request, an active treatment was stopped except artificial ventilation and catecholamine. Judgement of brain death was not conducted.									
13-OCT-97: At 12:12 h the pt died.									
Based on the results of autopsy, it was concluded that the death was caused by cardiac									

1daboeck 18JUN00

Volume 15/Page 78

JJRP 00384066

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D821.80

R. 6244

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction
10							

Formul Strength-Unit dose (Therapy start date/end date)

and renal failure due to rhabdomyolysis.
 NO FURTHER INFORMATION IS AVAILABLE.

JAKV043615(1)	JPN health professional	36yr M	8 week(s) at onset	Unknown Not Serious	Hyperlipaemia (07-JAN-1999) Diabetes Mellitus Aggravated (07-JAN-1999)

tablet - - 2mg (05-NOV-1998 / Unknown)

Event Description: A 36-year-old male patient, on risperidone, developed hypercholesterolaemia, hypertriglyceridaemia and positive urine sugar. Further information is not expected.

Causality Per Reporter: possible

Causality Per Company: possible

Indications: Unspecified Schizophrenia

Concomitant Diseases: Diabetes Mellitus Without Mention Of
 Complication; Other And Unspecified Hyperlipidaemia

JACCAN1999000420(9)	CAN health professional	11yr F		No Change/Not Yet Subsided Serious	Hyperglycaemia (Unknown) Causality Per Reporter: not assessed/not reported

solution 1 mg/mL - .5mg

Causality Per Company: possible

Event Description: Spontaneous report from a pharmacist of an 11-year-old female patient on risperidone solution, 0.5 mg p.o. bid (indication not specified) who has a blood glucose reading of 40 mmol/L. Concomitant medications include insulin, methylphenidate and clonidine. The reporter did not provide a causality assessment. The reporter was contacted for follow-up but did not wish to disclose further details until she had a chance to review the case more thoroughly. She indicated that clonidine was suspected as a potential cause of the hyperglycaemia.

Indications: Unknown

FOLLOW-UP On 22-Dec-99: Patient was buying from other pharmacies different brands of insulin. Now that part is settled, patient is on Lilly brand insulin. According to pharmacist the suspect drug was clonidine. Risperidone solution has been changed to tablets. Pharmacist doesn't want to give more information.

JACCAN1999000488(4)	CAN physician	53yr F		No Change/Not Yet Subsided Not Serious	Diabetes Mellitus (77-JUL-1999) Movements Involuntary (28-OCT-1999) Tremor (28-OCT-1999)

Volume 15/Page 79

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JJRP 00384067

D821.81

R. 6245

Parkinsonism (28-OCT-1999)

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome	Reaction	
						Seriousness		
Formal Strength Unit dose (Therapy start date/end date)								
tablett 1 mg - 1.5mg (20-MAY-1999 / Unknown)								
tablett 1 mg - 1mg (Unknown / 22-JUN-1999)								
tablett 1 mg - 1.5mg (23-JUN-1999 / 11-JUL-1999)								
tablett 1 mg - 2.5mg (12-JUL-1999 / 27-SEP-1999)								
tablett 1 mg - 1mg (77-SEP-1999 / 30-SEP-1999)								
tablett 1 mg - 2mg (01-OCT-1999 / 18-OCT-1999)								
tablett 1 mg - 1.5mg (20-OCT-1999 / 09-NOV-1999)								
tablett 1 mg - 1mg (10-NOV-1999 / 14-NOV-1999)								
tablett 1 mg - .5mg (15-NOV-1999 / 18-NOV-1999)								
Causality Per Reporter: not related								
Causality Per Company: doubtful								
Indications: Prolonged Posttraumatic Stress Disorder								
Concomitant Diseases: Other And Unspecified Disc Disorder Of Cervical Region; Obesity; Other Isolated Or Simple Phobias								

Event Description: Spontaneous report from a physician of a 53 year old female who received risperidone since 20-May-99, (dose range titrated 0.5 - 3 mg - 0.5 mg). She is experiencing involuntary movements in her left hand, which she can stop when she is aware of them. Also in Jul-99 she was diagnosed with diabetes insipidus after experiencing polyuria and polydipsia on 3 mg daily dose. Dose has been subsequently reduced gradually to 0.5 mg daily.

Additional information received 22-Feb-00: Physician reports that this patient, initials [redacted] was taking risperidone at a maximum dose 1.5 mg bid for post traumatic stress disorder. The patient's medical history includes: Bipolar affective disorder (Type II), panic disorder with agoraphobia, simple phobia, degenerative disc disease, dysthymia with major depressive episodes (1st) double depression, seasonal affective disorder, obsessive compulsive disorder and a generalized anxiety disorder. This patient developed diabetes mellitus in Jul-99 and not diabetes insipidus, and the physician thinks this is not related to risperidone. On 28-Oct-99, this patient developed left wrist and hand rolling with involuntary movements of the left fingers which last until 28-Dec-99 (2 months). Risperidone was discontinued 18-Nov-99 and the voluntary movements have decreased, but the patient still has intermittent fine tremor. A specialist thinks this may be early Parkinsons based on EEG findings. Concomitant medications are divalproex sodium 1500 mg per day, fluvoxamine 150 mg per day and glyburide 5 mg per day.

JASRE40386 (2)	SWE regulatory authority	20yr F	8 week(s) at onset	Recovered Serious	Suicide Attempt (11-JUL-1998) Overdose Effect (11-JUL-1998) Hypoglycemia (11-JUL-1998) Unconsciousness (11-JUL-1998) Tachycardia (11-JUL-1998) Hyperreflexia (11-JUL-1998) Hallucination (11-JUL-1998) Respiratory Depression (11-JUL-1998) Aspiration (11-JUL-1998)
tablett 2 mg - . (15-MAY-1998 / Unknown)					
Event Description: The patient, a 20-year-old female, was intoxicated by the following drugs: risperidone tablets, propofol tablets, buspirone tablets, venlafaxine tablets and capsules, and zolpidem tablets. She developed hypoglycemia and was admitted to intensive care. The patient recovered without sequelae.					

1daback 16JUN00

Volume 15/Page 80

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JJP 00384068
D821.82

R. 6246

Ref.no.(vers.no.) Ctry Prim. source Age Sex Latency Outcome Reaction 12
Seriousness

Formul Strength-Unit dose (Therapy start date/end date)

PO L L O W U P (18-SEP-98):

11-JUL-88: Because of suspected intoxication, the patient was admitted to the hospital's medical ICU. She was found outdoors unconscious. BP was 105/18 mmHg, pulse rate 140/min, peripheral tendon reflexes increased, normal pupils constricted to light. She gave no adequate contact and seemed to hallucinate. Empty tablet packages (risperidone, buspirone, venlafaxine, zopiclone, propiomazine, zolpidem) and a farewell letter was found in her flat. She had a medical history of depression and anorexia since the age of 12 years. No pharmacological treatment of these conditions until MAY-88 when risperidone and venlafaxine were commenced. During the night after admission, her condition deteriorated with decreased consciousness and respiratory depression with an oxygen saturation of 78 %. Hypoglycaemia (B-glucose = 1.9, ref: 3.0 - 6.0 mmol/l) was revealed. She was treated with 30 % glucose 30 ml IV followed by 10 % glucose infusion. She was also intubated and treated with respirator. Hypoglycaemia reappeared twice, though glucose infusion continued. She was treated with glucagon and steroids. Erythromycin was also initiated due to a possible aspiration pneumonia. On 13-JUL-88, glucagon, steroids were discontinued and she was extubated when she was awake and adequate. There was no drug concentration analysis performed. She was discharged on 15-JUL-88 with follow up visit to her psychiatrist. The reporter considered the assessment unclassifiable due to complex conditions in relation to suicide attempt.

Causality Per Company: possible

Indications: Depressive Disorder, Not Elsewhere Classified

Concomitant Diseases: Anorexia

Company Remarks: This is a case of acute overdose with multiple drug involvement. Cases of hypoglycaemia in patients using propiomazine have been reported.

JASWE43623(3) SWE regulatory 82yr F

Recovered
Serious

Hypothermia (06-JAN-1998)
Drop Attacks (05-JAN-1999)
Cardiac Failure (06-JAN-1998)
Hypokalaemia (06-JAN-1999)
Hypoglycaemia (06-JAN-1998)

solution 1 mg/mL - 3mg (16-DEC-1998 / 04-JAN-1999)

Event Description: A 82-year-old female patient, on risperidone, developed hyperpyrexia. Risperidone was discontinued and the event resolved.

PO L L O W U P (31-MAR-88):

The event's name changed to hypothermia.

The patient, who was being treated at a psychiatric clinic for manic psychosis, developed an attack (not specified, but suspected to be epilepsy) 19 days after she started with risperidone. She developed again an attack the following day, and initially again suspected as epilepsy. B-glucose 2.9 and body temperature 32.8 °C, she was transferred to the department of medicine. Risperidone was changed to clozapine. Classified as a confusion caused by hypokalaemia with cardiac failure. The reporter suspected the hypothermia to be caused by risperidone.

PO L L O W U P (07-APR-88):

Glucose level was 2.9 mmol/l.

Causality Per Reporter: possible

Causality Per Company: possible

Indications: Manic Psychosis

Concomitant Diseases: Bipolar Disorder

Company Remarks: It is unclear when the hypothermia occurred in relation to the drop attacks. Since this is an authority report, no further information is expected.

JAUKE1303(2)

GER health

30yr M 4 day(s) at onset

Recovered

Glucose Tolerance Abnormal (22-OCT-1994)

1debaack 16/JUN90

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D821.83

Volume 15/Page 81

Janssen Research Foundation
NDA 20-272 and 20-588
Response to FDA Request for Information: Evaluation of the Effect of Risperidone on Glucose Metabolism
JRF Pharmacovigilance Report
81

R. 6247

Ref.no.(vars.no.)	Qty	Prin. source	Age	Sex	Latency	Outcome Seriousness	Reaction
Formul Strength-Unit dose (Therapy start date/end date)							
professional						Not Serious	
Causality Per Company: possible							

tablet 4 mg - 4mg (18-OCT-1994 / Unknown)

Event Description: The reporter stated that the IDDM patient experiences unstable blood glucose since the dose of risperidone has been increased from 3mg bd to 4mg bd. No further follow-up is expected.

JAVE28692(1)	GBR regulatory authority	20yr F	6 month(s) at onset	No Change/Not Yet Subsidized Not Serious	Diabetes Mellitus (04-APR-1995) Causality Per Company: possible
tablet - - 3mg (15-SEP-1995 / Unknown)					Indications: Unspecified Schizophrenia

Event Description: This is a health authority report and no further information is expected or likely.
Patient was gestational diabetic in 1984. Became insulin dependant diabetic 04-APR-88. ?
Drug related.

JAVK30285(2)	GBR health professional	20yr M	Recovered Not Serious	Hypoglycaemia (??-MAY-1995) Therapeutic Effect Unexpected (??-MAY-1995) Confusion (??-MAY-1995) Aggressive Reaction (??-MAY-1995) Personality Disorder (??-MAY-1995)
tablet - - -				Causality Per Company: possible
Event Description: Patient who was diabetic experienced normal blood sugar level after starting to use risperidone. On two or three occasions he had episodes which would fit for symptomatic hypoglycaemia.				Indications: Psychiatric Troubles
F O L L O W U P 23-DEC-95: The hypoglycaemia was never well documented. There was one occasion when he was severely symptomatic hypoglycaemic. Over the weekend he showed bizarre behaviour with excessive physical aggression and confusion. A BM stick showed a blood sugar level of 2 mmol/L throughout Saturday despite half hourly milky drinks with sugar added. He improved after 8-10 hours with a blood sugar between 7-9 mmol/L (BM stick readings taken by psychiatrist). Laboratory tests of his blood sugar were normal at 11.9 (Performed at diabetic clinic). The patient attended a disco on the Friday night and it was believed that he may have drunk some alcohol which the consultant physician from diabetic unit considered may have been the cause of the symptoms. The patient did not experience further episodes of hypoglycaemia after this event and there was no history of hypoglycaemia.				Concomitant Diseases: Oligophrenia; Diabetes Mellitus Without Mention Of Complication

JAVK34841(3)	GBR health professional	Unknown Not Serious	Hypoglycaemia (Unknown) Aggressive Reaction (Unknown)

Volume 15/Page 82

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JURP 00384070
D821.84

R. 6248

Ref.no. (vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome	Reaction	
Formul	Strength-Unit dose	(Therapy start date/end date)						
Event Description: Patient who was taking risperidone as well as numerous other unspecified medications experienced hypoglycaemia and became aggressive so that he had to move wards. F O L L O W U P (21-OCT-97): The patient's reported hypoglycaemia was related to management of diabetes and some possible inaccuracy in measuring blood sugar by finger-prick method. The reporting physician could not recall reporting that patient was aggressive in relation to using risperidone. THE INFORMATION AVAILABLE ON THIS CASE IS VERY SKETCHY; NO FURTHER DETAILS ARE EXPECTED (AND CASE HAS BEEN CLOSED).								
						Causality Per Reporter: not related		
						Causality Per Company: possible		
						Indications: Other Unknown And Unspecified Cause Of Morbidity Or Mortality		
						Concomitant Diseases: Diabetes Mellitus Without Mention Of Complication		
=====								
JAN30649(1)		GBS regulatory authority	1yr	F		Unknown Serious	Diabetes Mellitus (Unknown)	
						Causality Per Company: doubtful		
						Indications: Other Unknown And Unspecified Cause Of Morbidity Or Mortality		
Event Description: Patient developed insulin-dependent diabetes mellitus. Antibody result was positive. This is a health authority report and further information is not expected.								
=====								
JAN40519(4)		GBS health professional	F	14 day(s)	at onset	No Change/Not Yet Subided Not Serious	Hyperglycaemia (28-AUG-1998)	
						Causality Per Reporter: probable		
						Causality Per Company: possible		
						Indications: Unspecified Psychosis		
						Company Remarks: Hyperglycaemia was not documented by plasma levels of glucose.		
Event Description: Patient developed hyperglycaemia. This ADE report contains all available information; further details have been requested. The case is not reportable according to CIOMS criteria, as there is no patient information. F O L L O W U P (01-DEC-98): Patient's blood glucose increased from 18 to 23 mmol/l. The reporter said that the level had always been stable, and that the patient used to take olanzapine with no problems, but the blood sugar increase was seen 1 or 2 weeks after risperidone treatment. The patient was referred back to the psychiatrist by the diabetic nurse. The reporting pharmacist considered that the event was probably related to use of risperidone.								

1debacck 18JUN00

Ref.no.(vers.no.)	Qty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction
Formul Strength Unit dose (Therapy start date/end date)							
JAUR43298(1)							
CBR regulatory authority	44yr F	13 month(s) at onset	No Change/Not Yet Subsided	Serious	Diabetes Mellitus (14-SEP-1998)	Causality Per Company: possible	
tablet - - Bag (15-JUL-1997 / Unknown)						Indications: Unspecified Psychosis	

Event Description: Patient developed diabetes mellitus during the use of risperidone for psychosis.
 JUL-97: The patient started risperidone 9mg daily po.
 14-SEP-98: The patient developed diabetes mellitus.
 Lab tests revealed that the patients blood glucose = 19.1 (no normal range or units of measure specified).
 At the time of the report the diabetes mellitus was persisting.
 This is a health authority report and no follow up is expected.

JAUSA10078(5)	USA health professional	38yr F	Unknown	Serious	Convulsions (18-MAR-1994) Leucopenia (Unknown) Urticaria (24-MAR-1994) Allergic Reaction (24-MAR-1994) Fever (24-MAR-1994) Hyperglycaemia (25-MAR-1994) Thyroid Disorder (25-MAR-1994) Thrombocytopenia (25-MAR-1994) Erythrocytes Abnormal (25-MAR-1994)
tablet 1 mg - 1mg					
Event Description: PHYSICIAN REPORTS THIS PROFOUNDLY MENTALLY RETARDED PATIENT HAD "SOME TYPE OF SEIZURE - NOT GRAND MAL". THE PATIENT LIVES IN A GROUP HOME. EXACT DETAILS SURROUNDING EVENT NOT AVAILABLE AT THIS TIME. ACCORDING TO REPORTER, PATIENT DID EXPERIENCE ALTERATION OF CONSCIOUSNESS. LABORATORY TESTS AND EEG HAVE BEEN PERFORMED. ADDITIONAL INFORMATION HAS BEEN REQUESTED.					
F O L L O W U P (08-MAY-94): SEIZURE WAS TREATED WITH VALPROATE SODIUM, PHENYTOIN, AND CARBAMAZEPINE WITHOUT RECURRENCE OF THE SEIZURE. HOWEVER, EIGHT DAYS FOLLOWING THE SEIZURE, PATIENT PRESENTED WITH A TEMPERATURE OF 103 F, GENERALIZED URTICARIA, AND LEUKOPENIA (WBC APPROXIMATELY 3000). THE URTICARIA AND FEVER RESOLVED WITH CORTICOSTEROIDS, "ANTHRAX THERAPY", AND DISCONTINUATION OF RISPERIDONE. AN ALLERGIC REACTION TO RISPERIDONE, PHENYTOIN, CARBAMAZEPINE, OR VALPROATE SODIUM IS SUSPECTED. PHYSICIAN SUSPECTS THE LEUKOPENIA IS DUE TO THE RISPERIDONE. IT IS UNKNOWN AT THIS TIME IF THE LEUKOPENIA HAS RESOLVED. FOLLOW-UP IN PROGRESS.					Causality Per Reporter: possible Causality Per Company: probable
F O L L O W U P (26-SEP-94): PATIENT DID NOT RECEIVE "ANTHRAX" THERAPY. THIS WAS A TYPING ERROR AND SHOULD HAVE READ ATARAX (- HYDROXYZINE) THERAPY. SODIUM ON ADMISSION (DATE NOT SPECIFIED) WAS 137 BUT DECREASED TO 131 ON 25-MAR-94. THE WBC WAS 2.2 WITH ELEVATED BANDS (20%). THE EOSINOPHIL COUNT WAS NORMAL. ADDITIONAL LAB ABNORMALITIES ON 25-MAR-94, INCLUDED					Indications: Paranoid Type Schizophrenia Concomitant Diseases: Oligophrenia Company Remarks: MILD AND TRANSIENT LEUKOPENIA ARE WELL KNOWN WITH BOTH PHENYTOIN AND CARBAMAZEPINE.

Ldebaeck 18JUN00

Volume 15/Page 84

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 JRP 00384072
 D821.86

R. 6250

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction

Formul. Strength-Unit dose (Therapy start date/end date)
=====

HYPERGLYCAEMIA (173 NOT KNOWN IF A FASTING SAMPLE): T4 4.1; TSH 7.44; PLATELETS 125. CBC
SHOWED 1+ ANISOCYTOSIS, POIKILOCYTOSIS, POLYCHROMASIA, AND BASOPHILIC STIPPLING. RBC
INDICES WERE WITHIN NORMAL RANGE. BASELINE LABS ARE NOT AVAILABLE. IT IS NOT KNOWN IF
PATIENT HAS PREEXISTING HYPOTHYROIDISM, DIABETES, ANAEMIA, OR THROMBOCYTOPENIA.
PHYSICIAN REPORTS PATIENT'S RASH IS CLEARING AND WBC IS COMING UP TO NORMAL BY THE TIME
OF DISCHARGE. HE WILL FORWARD DISCHARGE SUMMARY WHEN IT BECOMES AVAILABLE.

=====

JAUSA11168(1)	USA health professional	32yr M		Recovered Not Serious	Hypoglycaemia (02-MAR-1994)

tablet 3 mg - 3mg

Causality Per Reporter: doubtful

Event Description: PATIENT DEVELOPED ASYMPTOMATIC HYPOGLYCAEMIA WHILE RECEIVING
RISPERIDONE. EVENT WAS TRANSIENT AND ATTRIBUTED TO DIETARY INEFFICIENCY.

=====

JAUSA11459(3)	USA health professional	35yr M	7 day(s) at onset	Recovered Not Serious	Hyperglycaemia (25-MAR-1994) Condition Aggravated (28-MAR-1994)

tablet 3 mg - 3mg (16-MAR-1994 / Unknown)

Causality Per Reporter: probable

Event Description: PATIENT WITH A HISTORY OF NON-INSULIN DEPENDENT DIABETES EXPERIENCED
HYPERGLYCAEMIA WHILE RECEIVING HALOPERIDOL. HALOPERIDOL DOSE WAS DECREASED, THE BLOOD
SUGAR STABILIZED (LESS THAN 200 MG/DL) AND HALOPERIDOL WAS THEN DISCONTINUED.
RISPERIDONE WAS STARTED AND AFTER ONE WEEK THE PATIENT EXPERIENCED ANOTHER EPISODE OF
HYPERGLYCAEMIA (FASTING BLOOD SUGAR 320 MG/DL). PATIENT HAS BEEN TREATED WITH
GLIBENCLAMIDE. RISPERIDONE CONTINUES. FOLLOW-UP BLOOD SUGARS ARE NOT YET AVAILABLE.
ADDITIONAL INFORMATION HAS BEEN REQUESTED.
F O L L O W - U P (JUL.94): PATIENT HAS BEEN STARTED ON INSULIN AND NOT ON GLIBENCLAMIDE
AS PREVIOUSLY REPORTED. RISPERIDONE HAS BEEN DISCONTINUED. FOLLOW-UP BLOOD SUGARS NOT
AVAILABLE.

Causality Per Company: doubtful
Indications: Unspecified Schizophrenia
Concomitant Diseases: Diabetes Mellitus Without Mention Of
Complication

=====

JAUSA11728(3)	USA health professional	18yr M	8 day(s) at onset	No Change/Not Yet Subsided Not Serious	Diabetes Mellitus Aggravated (17-APR-1994)

tablet 1 mg - 1.5mg (08-APR-1994 / Unknown)

Causality Per Reporter: possible
Causality Per Company: possible

Event Description: CONSUMER REPORTS HER DIABETIC SON HAS BEEN TAKING RISPERIDONE (0.5 MG
Indications: Unspecified Schizophrenia

1debsec: 16JUN00

Volume 15/Page 85

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JJRP 00384073
D821.87

R. 6251

Ref.no.(vers.no.) Cty Prim. source Age Sex Latency Outcome Reaction 17
Seriousness

Formal Strength-Unit dose (Therapy start date/end date)

IN THE MORNING) FOR APPROXIMATELY ONE WEEK WITHOUT ANY PROBLEMS. TWO DAYS AFTER INCREASING THE DOSAGE TO ONE MG IN THE MORNING AND 0.5 MG IN THE EVENING, HE EXPERIENCED AN ELEVATED FASTING BLOOD SUGAR OF 381. HE TOOK SEVEN UNITS OF REGULAR INSULIN. BY NOON, AFTER TAKING RISPERIDONE, THE BLOOD SUGAR INCREASED TO 467, WITHOUT ANY MEALS. THREE HOURS LATER, AFTER THREE MORE UNITS OF INSULIN, BLOOD SUGAR DECREASED TO 133. THIS MORNING (18-APR-94), THE FASTING BLOOD SUGAR WAS 217. PATIENT CONTINUES RISPERIDONE.

F O L L O W - U P (JUL94): AN INSULIN-DEPENDENT DIABETIC PATIENT EXPERIENCED ELEVATED BLOOD SUGARS NECESSITATING INCREASES IN INSULIN THERAPY AFTER STARTING RISPERIDONE. FASTING GLUCOSE LEVELS PRIOR TO RISPERIDONE RANGED FROM 79 TO 284 MG/DL. AFTER RISPERIDONE, VALUES RANGED FROM 54 TO 467 MG/DL. RISPERIDONE DOSE HAS BEEN GRADUALLY INCREASED TO 5 MG BID. HYPERGLYCEMIA CONTINUES. NPH INSULIN HAS BEEN INCREASED FROM 58 UNITS ON 28-MAR-94 TO 41 UNITS AS OF 17-MAY-94. ADDITIONAL INFORMATION REQUESTED.

JAUSA11827(11) USA health 33yr F 17 day(s) at onset Death
professional Serious

tablet - - Reg (14-APR-1994 / 06-MAY-1994)

Event Description: THIS 33-YEAR-OLD MORBIDLY OBESE PATIENT WITH BIPOLAR DISORDER AND PERSONALITY DISORDER WAS STARTED ON RISPERIDONE ON 20-APR-94, ON ONE MG BID. SHE WAS TITRATED TO 2 MG BID THE FOLLOWING DAY; THEN 3 MG BID ON DAY THREE OF THERAPY. THERE WERE NO REPORTED PROBLEMS WITH DOSE ESCALATION. HER ORAL HALOPERIDOL WAS CONTINUED HOWEVER THE DOSE WAS DECREASED FROM 35 MG DAILY TO 25 MG DAILY ON 28-APR-94, AND TO 20 MG DAILY ON 04-MAY-94. THERE WAS A NOTABLE WEIGHT INCREASE FROM 250 POUNDS ON 28-APR-94, TO 284 POUNDS ON 04-MAY-94, WITH DAILY INCREASES NOTED. ABDOMINAL X-RAYS AND SONOGRAMS DONE ON 04-MAY-94, WERE REPORTEDLY NORMAL. SGGT AND ALKALINE PHOSPHATASE WERE CHRONICALLY ELEVATED BUT NOTED IN RECENT WEEKS TO BE INCREASED ABOVE THE PATIENT'S BASELINE. ON 06-MAY-94, THE PATIENT'S BLOOD PRESSURE (BP) WAS ELEVATED AT 142/96. SHE WAS NOTED TO HAVE DYSPNOEA AFTER CLIMBING ONE FLIGHT OF STAIRS (WHICH HAD BEEN OBSERVED FOR SOME TIME). AT 3:00 P.M. SHE COMPLAINED OF FEELING TIRED AND WENT TO BED AT THE HALFWAY HOUSE WHERE SHE RESIDED. AT 3:30 P.M. SHE WAS FOUND DEAD IN HER BED. AN AUTOPSY REVEALED THE CAUSE OF DEATH TO BE: 1) DIABETES MELLITUS; 2) CARDIOMEGALY; 3) OBESITY; 4) AND BIPOLAR DISORDER. NO EVIDENCE OF MYOCARDIAL INFARCTION OR PULMONARY EMBOLUS. THERE WERE NO RECENT ECG'S PERFORMED ON THIS PATIENT. FOLLOW-UP INFORMATION HAS BEEN REQUESTED.

F O L L O W - U P 24-MAY-94:

PATHOLOGIST STATES GROSS EXAMINATION REVEALED: HYPERTROPHIC CARDIOMYOPATHY (HEART WEIGHT 760 GRAMS, NORMAL IS UP TO 350 GRAMS); ENLARGED GRANULAR KIDNEYS POSSIBLY INDICATING HYPERTENSION; AND A BRUISED LEFT OCCIPUT WITHOUT SKULL FRACTURE OR BRAIN TRAUMA. NO "THIRD SPACING" OF EXTRACELLULAR FLUID SEEN. NO EVIDENCE OF BRAIN. PRESUMED CAUSE OF DEATH: ELECTRICAL CONDUCTION DISTURBANCE SECONDARY TO HYPERTROPHIC CARDIOMYOPATHY. PATHOLOGIST DOES NOT FEEL DEATH WAS RELATED TO RISPERIDONE USE. TOXICOLOGY SCREEN IS PENDING.

F O L L O W - U P (JUL94): POSTMORTEM PLASMA CONCENTRATION OF COMBINED RISPERIDONE AND 9-OH-RISPERIDONE IS 24.4 NG/ML.

Sudden Death (06-MAY-1994)
Weight Increase (28-APR-1994)
Liver Function Tests Abnormal Nos (Unknown)
Fatigue (06-MAY-1994)
Speech Disorder (25-APR-1994)
Diabetes Mellitus Aggravated (Unknown)
Urinary Incontinence (06-MAY-1994)

Causality Per Reporter: doubtful
Causality Per Company: doubtful

Indications: Bipolar Disorder; Schizo-Affective Type
Schizophrenia

Concomitant Diseases: Psychopathic State; Obesity; Insuff.
Respir.; Unspecified Disorder Of Liver; Hypertrophy Cardiac

Company Remarks: This obese patient had a cardiac disease (hypertrophic cardiomyopathy was found on autopsy).

1debacck 16JUN00

Volume 15/Page 86

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JJRP 00384074

D821.88

R. 6252

Ref.no.(vers.no.) Cry Prim. source Age Sex Latency Outcome Reaction 13
Seriousness

Formul Strength-Unit dose (Therapy start date/end date)

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P O L L O W - U P 30-JAN-97:

FOLLOW-UP RECEIVED. THE LAST HOSPITALIZATION PRIOR TO RISPERIDONE WAS 28-MAR-94. RISPERIDONE WAS STARTED ON 14-APR-94 (AND NOT 20-APR-94 AS PREVIOUSLY REPORTED), AND WAS TITRATED TO A DOSE OF 3 MG BID ON THE THIRD DAY OF THERAPY. ON 25-APR-94 THE PATIENT EXPERIENCED SLURRED SPEECH. ON 28-APR-94 THE PATIENT REQUIRED AN INCREASE IN THE DOSE OF GLIBENCLAMIDE FROM 10 MG/DAY TO 20 MG/DAY DUE TO AN INCREASED BLOOD SUGAR (NOT SPECIFIED). THE INITIAL REPORT INDICATED THAT THE PATIENT WAS FOUND DEAD IN BED 30 MINUTES AFTER RETIRING TO HER ROOM. ADDITIONAL INFORMATION INDICATES THAT THE PATIENT WAS FOUND DEAD IN HER ROOM ON 06-MAY-94, ONE HOUR AFTER GOING TO HER ROOM TO CHANGE HER PANTS DUE TO INCONTINENCE. IT WAS PREVIOUSLY REPORTED THAT CANNOTOPATHY WAS DETERMINED TO BE THE CAUSE OF DEATH BY AUTOPSY. THE POSTMORTEM WEIGHT OF THE HEART WAS 760 GRAMS. THE TREATING PHYSICIAN SPECIFIES THE PATIENT'S DEATH WAS NOT RELATED TO RISPERIDONE THERAPY.

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JANSA11632(3)	USA health professional	52yr F	8 day(s) at onset	Unknown Serious	Psychosis (14-APR-1994) Cpk Increased (27-APR-1994) LDH Increased (27-APR-1994) Spot Increased (27-APR-1994) Diabetes Mellitus Aggravated (27-APR-1994) Fever (27-APR-1994) Renal Function Abnormal (27-APR-1994)

tablet 3 mg - 3mg (08-APR-1994 / 25-APR-1994)

Event Description: OUTPATIENT WITH A HISTORY OF PSYCHOSIS (NOT OTHERWISE SPECIFIED) WAS NOTED TO BECOME INCREASINGLY PSYCHOTIC AFTER BEING PLACED ON RISPERIDONE (THERAPY START DATE AND DOSE NOT AVAILABLE). ON 14-APR-94, PATIENT WAS ADMITTED FOR ACUTE PSYCHOSIS. ADMISSION MEDICATIONS INCLUDED RISPERIDONE, TIOTIENE, BENZTROPINE, AND CHLORPROMIZOL. PATIENT BECAME FEBRILE WITH A TEMPERATURE OF 103.5 F ON 28-APR-94. NEUROLEPTIC MALIGNANT SYNDROME (NMS) WAS SUSPECTED (LATER RULED OUT), AND RISPERIDONE WAS DISCONTINUED. PATIENT WAS TRANSFERRED FROM THE PSYCHIATRIC WARD TO THE MEDICAL INTENSIVE CARE UNIT (MICU) FOR EVALUATION. PATIENT DID NOT EXHIBIT RIGIDITY OR AUTONOMIC INSTABILITY. CPK WAS ELEVATED (2800 U/L), AS WELL AS LDH (1600 U/L), SCOT (700 U/L), AND BUN AND CREATININE (NOT SPECIFIED). PATIENT, WHO HAD PREVIOUSLY BEEN A DIET-CONTROLLED DIABETIC, DEVELOPED HYPERGLYCAEMIA (BLOOD GLUCOSE >400) REQUIRING GLYNASE THERAPY FOLLOWING MANAGEMENT WITH INSULIN SLIDING SCALE REGIMEN. AS OF 28-APR-94, PATIENT REMAINS IN MICU WITH PRIMARY CONCERN FOR THE POSSIBILITY OF DEVELOPMENT OF PYOMYOSITIS. SCOT, LDH, BUN, AND CREATININE ARE "NORMALIZING". CPK REMAINS ELEVATED.

P O L L O W - U P (29-AUG-94):
PATIENT'S MOTHER PROVIDED RISPERIDONE DOSE. PHYSICIAN WAS MOVED OUT OF STATE. NO FURTHER INFORMATION EXPECTED.

Causality Per Reporter: possible

Causality Per Company: doubtful

Indications: Unspecified Psychosis

Concomitant Diseases: Diabetes Mellitus Without Mention Of Complication

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JANSA11889(3)	USA health professional	24yr M	3 day(s) at onset	Recovered Not Serious	Hypertension (22-APR-1994) Diabetes Mellitus Aggravated (22-APR-1994)

tablet 3 mg - 3mg (18-APR-1994 / Unknown)

tablet 4 mg - 4mg

Causality Per Reporter: probable

Ldbanck 18JUN00

Volume 15/Page 87

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JJRP 00384075
D821.89

R. 6253

Ref.no.(vers.no.) City Prim. source Age Sex Latency Outcome Reaction 19
Seriousness

Formul Strength-Unit dose (Therapy start date/end date)

tablet 3 mg - 3mg

Indications: Unspecified Schizophrenia; Bipolar Disorder

Event Description: AN OBESE, INSULIN DEPENDENT DIABETIC PATIENT EXPERIENCED HYPERTENSION ONE DAY AFTER BEGINNING RISPERIDONE. BASELINE BLOOD PRESSURE PRIOR TO RISPERIDONE WAS 126/80 MMHG. BLOOD PRESSURE (BP) READINGS ONE DAY AFTER RISPERIDONE (20-APR-94) WERE 150/100 AND 156/102. ON 22-APR-94, BP RANGED FROM 140/100 TO 160/100. ON 23-APR-94, BP RANGED FROM 132/94 TO 162/92. ON 24-APR-94, BP RANGED FROM 152/90 TO 156/110. ON 25-APR-94, BP RANGED FROM 168/68 TO 178/98. BLOOD WORK WAS WITHIN NORMAL LIMITS EXCEPT FOR SLIGHT ELEVATED BLOOD GLUCOSE OF 116. PATIENT IS KNOWN TO BE NONCOMPLIANT WITH HIS DIABETIC DIET AND INSULIN THERAPY. THERE IS A FAMILY HISTORY OF HYPERTENSION. PHYSICIAN PLANS TO DECREASE THE RISPERIDONE DOSE AND OBSERVE THE SUBSEQUENT BLOOD PRESSURES. FOLLOW-UP IN PROGRESS.
FOLLOW-UP - U.P. 30-JUN-94:
RISPERIDONE DECREASED TO 6 MG DAILY AND BP STABILIZED. RISPERIDONE DOSE INCREASED SLOWLY TO 8 MG DAILY AND CONTINUES WITH STABLE BP.

Concomitant Diseases: Obesity; Diabetes Mellitus Without Mention Of Complication

JAUSA12027(1) USA health 16yr F
professional

Recovered
Not Serious

Hypoglycemia (Unknown)

Causality Per Reporter: probable

tablet 4 mg - 4mg

Indications: Not Specified

Event Description: FIRST OF TWO PATIENTS. PSYCHIATRIC INPATIENT WHO WAS STARTED ON RISPERIDONE ABOUT TWO WEEKS AFTER RECEIVING HER LAST INJECTION OF HALOPERIDOL DECANOATE. SHE WAS "NOT ACTING RIGHT" AND A BLOOD GLUCOSE LEVEL OF 42 WAS NOTED. PATIENT WAS TREATED (UNSPECIFIED) AND HAS RECOVERED. RISPERIDONE THERAPY HAS BEEN STOPPED.

JAUSA12028(1) USA health 2
professional

Recovered
Serious

Hypoglycemia (Unknown)

Causality Per Reporter: probable

tablet 2 mg - 2mg

Indications: Not Specified

Event Description: SECOND OF TWO PATIENT. PSYCHIATRIC INPATIENT WHO WAS RECENTLY STARTED ON RISPERIDONE EXPERIENCED HYPOLYCEMIA. PATIENT WAS ALSO RECEIVING PAROXETINE CONCOMITANTLY. PATIENT IS A DIET CONTROLLED NON-INSULIN DEPENDENT DIABETIC. AFTER COMPLAINTING OF NOT FEELING WELL A BLOOD GLUCOSE OF 11 WAS NOTED. REPEAT BLOOD GLUCOSE

Concomitant Diseases: Diabetes Mellitus Without Mention Of Complication

1debweek 18JUN00

Volume 15/ Page 88

JJRP 00384076

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D821.90

R. 6254

Ref.no. (vers.no.)	City	Prim. source	Age	Sex	Latency	Outcomes Seriousness	Reaction	20

Formal Strength/Unit dose (Therapy start date/end date)
 WAS 27. THE PATIENT WAS TRANSFERRED TO A MEDICAL UNIT WHERE SHE REQUIRED EMERGENCY
 TREATMENT (E.G. IV GLUCOSE). SHE REMAINED THERE FOR SEVERAL DAYS AND WAS THEN
 TRANSFERRED BACK TO THE PSYCHIATRIC UNIT. RECOVERED. RISPERIDONE THERAPY HAS BEEN
 STOPPED.

=====

JANSA12135(6)	USA health professional	55yr M	21 day(s) at onset	Death Serious	Ketocidosis (15-MAY-1994) Insomnia (15-APR-1994) Nightmares (25-APR-1994) Cramps Legs (25-APR-1994) Anxiety (25-APR-1994) Fatigue (07-MAY-1994) Weakness Generalized (10-MAY-1994) Nausea (14-MAY-1994) Malaise (14-MAY-1994) Diabetes Mellitus (Unknown) Dehydration (Unknown) Aspiration (Unknown)
tablet 1 mg - 1mg (31-MAR-1994 / 18-APR-1994) tablet 2 mg - 2mg (18-APR-1994 / 23-APR-1994) tablet 2 mg - 2mg (25-APR-1994 / 15-MAY-1994)					

Event Description: THIS 55-YEAR-OLD HOMOSEXUAL MALE WITH A HISTORY OF MIXED BIPOLAR
 DISORDER HAD BEEN TREATED FOR SOME TIME WITH LITHIUM 1200 MG, CARBAMAZEPINE 600 MG,
 PHENELZINE 90 MG, AND TIOTILONE 2-6 MG DAILY. IN LATE MARCH HIS MOOD WAS NOTED TO BE
 STABLE, BUT HE HAD SUICIDAL THOUGHT INTRUSIONS WHICH PROMPTED HIS PHYSICIAN TO BEGIN
 RISPERIDONE THERAPY AT ONE MG BID ON 31-MAR-94. RISPERIDONE WAS TITRATED UPWARD VERY
 SLOWLY TO 2 MG BID ON 18-APR-94, AND PATIENT RAN DOWNWARD TAPER OF HIS PREVIOUSLY
 PRESCRIBED MEDICATIONS. ON 18-APR-94 (TWO AND ONE HALF WEEKS AFTER STARTING
 RISPERIDONE), PATIENT COMPLAINED OF SLEEPING POORLY BUT OTHERWISE FELT WELL. ON 25-APR-
 94, HE COMPLAINED OF HAVING NIGHTMARES, INTENSE FEARS, AND MUSCLE CRAMPS IN HIS ARMS AND
 LEGS. RISPERIDONE WAS INCREASED TO 2 MG TID. ON 07-MAY-94, HE COMPLAINED OF WORSENING
 FATIGUE BUT HAD NO MORE THOUGHT INTRUSION. PHENELZINE WAS INCREASED FROM 90 MG TO 45 MG
 DAILY. ON 10-MAY-94, HE REPORTED STABLE MOOD AND ABSENCE OF DEPRESSION, ANXIETY, AND
 THOUGHT INTRUSION. HE DID COMPLAIN OF POLYDIPSIA, POLYURIA, EXHAUSTION, AND WEARINESS.
 PHENELZINE WAS DECREASED TO 15 MG FOR THREE DAYS THEN DISCONTINUED, AND HE WAS INSTRUCTED
 TO DRINK AN ELECTROLYTE FORTIFIED JUICE (GATORADE). ON 14-MAY-94, HE COMPLAINED OF
 WEARINESS, NAUSEA, AND "FEELING ILL", BUT REFUSED ADMISSION TO THE HOSPITAL. AT 8:00
 A.M., THE FOLLOWING MORNING HE WAS FOUND DEAD IN BED BY HIS MALE COMPANION. A FULL COUNT
 FAILED TO DEMONSTRATE A DRUG OVERDOSE. THERE WAS NO RECENT LABORATORY TESTING, SUCH AS
 ELECTROLYTES OR DRUG LEVELS PERFORMED. THERE WERE NO COMPLAINTS OF FEVER OR RIGIDITY.
 REPORTER RAISES THE POSSIBILITY OF AN ATYPICAL "SEROTONIN SYNDROME" IN THIS PATIENT.
 ACCORDING TO PRELIMINARY AUTOPSY RESULTS, GROSS EXAMINATION REVEALED: ENLARGED HEART,
 BRAIN APPEARED DUSKY, AND STOMACH WAS DISTENDED CONTAINING UNDIGESTED GASTRIC CONTENTS.
 THE LUNGS WERE CONGESTED WITH EITHER PULMONARY EDEMA OR ACURAL CONGESTION. THEY WEIGHED
 980 AND 860 GRAMS WHICH EXCEEDS NORMAL LIMITS. THERE WAS NOT GROSS EVIDENCE OF
 PNEUMONIA. INTRACULAR GLUCOSE WAS ELEVATED INDICATING POSSIBLE DIABETES, AND
 INTRACULAR SODIUM AND CHLORIDE WERE ALSO ELEVATED INDICATING POSSIBLE DEHYDRATION. GLUCOSURIA
 AND KETONURIA WERE ALSO DETECTED. ACETONEMIA WAS ALSO FOUND. PATIENT HAD NO HISTORY OF
 DIABETES MELLITUS BUT HAD NOT SEEN A PRIMARY CARE PHYSICIAN IN OVER ONE YEAR. A BLOOD
 GLUCOSE DONE IN 1991 WAS 123 MG/DL. SUBSEQUENT BLOOD GLUCOSE DETERMINATIONS IN 1992 WERE
 NORMAL. PATHOLOGIST SPECULATES THE PATIENT MAY HAVE DIED FROM UNCONTROLLED DIABETES AND
 SUBSEQUENT KETOACIDOSIS. TOXICOLOGY SCREEN IS NEGATIVE.

FOLLOW-UP 07-JUL-94:

1dbsack 16JUN00

Janssen Research Foundation
 NDA 20-272 and 20-588
 Response to FDA Request for Information: Evaluation of the Effect of Risperdal on Glucose Metabolism
 JRF Pharmacovigilance Report
 89

Volume 15/Page 89

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 JJRP 00384077
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R. 6255

Ref.no.(vera.no.)	Ctry	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction
21							

Formul Strength-Unit dose (Therapy start date/end date)

COMBINED POSTMORTEM RISPERIDONE AND 9-OH-RISPERIDONE PLASMA CONCENTRATION = 92.9 NG/DL.

F O L L O W - U P 18-AUG-94:

AUTOPSY REPORT. DECEDENT HAD ALSO BEEN TAKING METHYLPHENIDATE AND CHLORPROMAZINE. PHENELZINE DOSAGE WAS ADJUSTED FREQUENTLY. URINE WAS POSITIVE FOR BOTH GLUCOSE AND KETONES. THE FOLLOWING WERE DISCOVERED ON GROSS EXAMINATION: 1) HEAVY CONGESTED LUNGS; 2) CARDIOMEGALY; 3) HEPATOMEGALY; 4) DUSKY CONGESTED BRAIN; AND 5) ASPIRATION OF GASTRIC CONTENTS. TOXICOLOGY REPORT SHOWED NO ILICIT DRUGS DETECTED IN THE URINE, NO BLOOD ALCOHOL, AND THE PRESENCE OF ACETONE IN THE BLOOD. CAUSE OF DEATH WAS DIABETIC KETOACIDOSIS DUE TO DIABETES MELLITUS.

JAUSA12282(2)	USA health professional	Unknown	Diabetes Mellitus Aggravated (Unknown)
tablet - - -		Not Serious	Causality Per Reporter: possible

Event Description: DIABETIC PATIENT ON RISPERIDONE THERAPY DEVELOPED HYPERGLYCEMIA. THE INFORMATION AVAILABLE ON THIS CASE IS VERY SKETCHY; NO FURTHER DETAILS ARE EXPECTED (AND CASE HAS BEEN CLOSED).

Causality Per Company: doubtful

Concomitant Diseases: Diabetes Mellitus Without Mention Of Complication

JAUSA12434(8)	USA health professional	28yr F 13 day(s) at onset	Recovered Serious	Suicide Attempt (26-APR-1994) Overdose Effect (26-APR-1994) Tachycardia (26-APR-1994) QT Prolonged (26-APR-1994) Hypokalemia (26-APR-1994) Acidosis Metabolic (26-APR-1994) Drowsiness (26-APR-1994)
tablet 3 mg - 6mg (13-APR-1994 / 26-APR-1994)				
tablet 3 mg - 60mg (26-APR-1994 / 26-APR-1994)				
tablet 3 mg - 3mg				

Event Description: PATIENT RECEIVING APPROXIMATELY TWO WEEKS OF RISPERIDONE WITH A HISTORY OF FIVE PREVIOUS SUICIDE ATTEMPTS (INCLUDING DRUG INGESTION), ATTEMPTED SUICIDE BY INGESTING 60 MG OF RISPERIDONE. PATIENT WAS DISCHARGED ON 26-APR-94, FROM INPATIENT PSYCHIATRIC CARE AND WAS REPORTEDLY DOING WELL. ON 26-APR-04, PATIENT INGESTED 60 MG OF RISPERIDONE (THIRTY 3 MG TABLETS) AND 30 MINUTES POST INGESTION WAS LAVAGED AND GIVEN ACTIVATED CHARCOAL IN THE EMERGENCY ROOM (ER). PATIENT REMAINED RESPONSIVE AND ALERT FOLLOWING INGESTION. ON ADMISSION VITAL SIGNS WERE STABLE WITH BP OF 120/74 MMHG (SUPINE) AND HEART RATE OF 110 BEATS PER MINUTE. EKG REVEALED SINUS TACHYCARDIA WITH QT INTERVAL OF 366 M SECONDS; QTc INTERVAL 480 M SECONDS WITH SOME T WAVE CHANGES (NOT SPECIFIED). SERUM POTASSIUM WAS 3.2 MEQ/L (NL = 3.6-4.8) AND PATIENT RECEIVED ORAL POTASSIUM SUPPLEMENTATION. SODIUM WAS NORMAL AT 137 MEQ/L (NL = 135-145). PATIENT WAS NOTED TO HAVE METABOLIC ACIDOSIS WITH SERUM BICARBONATE OF 19 MEQ/L (NL = 22-28) WITH AN INCREASED ANION GAP OF 16 MEQ/L (NL = 7-15). THE METABOLIC ACIDOSIS WAS CORRECTED WITH

Causality Per Company: doubtful

Indications: Schizo-Affective Type Schizophrenia; Depressive Disorder, Not Elsewhere Classified

Company Remarks: THE HYPOKALEMIA COULD HAVE CONTRIBUTED TO THE QT-INTERVAL PROLONGATION.

1debasc 18JUN00

Volume 15/Page 90

Confidential/Produced in Litigation Pursuant to Protective Order
 JRP 00384078
 D821.92

R. 6256

Ref.no.(vers.no.) Qty Prim. source Age Sex Latency Outcome Reaction 22
Seriousness

Formul Strength-unit dose (Therapy start date/end date)

////////////////////////////////////
POTASSIUM SUPPLEMENTATION. PATIENT DID NOT AT ANY TIME EXHIBIT RIGIDITY OR EXTRAPYRAMIDAL
SYMPTOMS. TOXICOLOGY SCREEN (URINE AND BLOOD) WERE NEGATIVE. ON 27-APR-94, PATIENT'S
ONLY COMPLAINT INVOLVED DROWSINESS, BUT SHE REMAINED ALERT AND RESPONSIVE WITH STABLE
VITAL SIGNS. RISPERIDONE PLASMA LEVELS REVEALED A COMBINED CONCENTRATION OF RISPERIDONE
AND 9-HYDROXYRISPERIDONE TO BE 888 NG/ML, SUGGESTIVE OF AN OVERDOSE.
P O L L O W - U P (30-JUN-94):
PATIENT WAS DISCHARGED IN SATISFACTORY CONDITION ON 04-MAY-94. PATIENT RESUMED ALL
MEDICATIONS AND CONTINUES ON RISPERIDONE 8 MG DAILY.

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JAUSA12584(3) USA health 38yr F 1 day(s) at onset Recovered Hypoglycemia (13-MAY-1994)
professional Not Serious Condition Aggravated (13-MAY-1994)
Abdomen Enlarged (13-MAY-1994)

tablet 1 mg - .25mg (12-MAY-1994 / 06-JUN-1994)
tablet 1 mg - .125mg (07-JUN-1994 / Unknown)
tablet 1 mg - 1mg

Causality Per Company: possible

Indications: Unspecified Psychosis

Event Description: CONSUMER REPORTS SHE EXPERIENCED BILATERAL ANKLE OEDEMA ONE DAY AFTER
BEGINNING RISPERIDONE. SHE STATES SHE HAS A PRE-EXISTING "OEDEMA PROBLEM". THE PATIENT
STATES IT DOES NOT IMPROVE WITH ELEVATION AND IN FACT BELIEVES IT IS CONTRIBUTING TO AN
ENLARGED ABDOMEN. SHE IS AN INSULIN DEPENDENT DIABETIC AND IS ALSO EXPERIENCING
HYPOGLYCAEMIA (FASTING BLOOD SUGAR 45 MG/DL). THE OEDEMA IS RESPONDING TO A RISPERIDONE
DOSAGE DECREASE FROM 8 MG TO .25 MG DAILY; THE BLOOD SUGARS ARE IMPROVING SINCE
LOWERING THE INSULIN DOSE.
P O L L O W - U P 09-AUG-94:
PHYSICIAN REPORTS THIS PATIENT HAS HAD SWELLING IN HER LEGS FOR MANY YEARS. THERE WAS NO
CHANGE WITH RISPERIDONE IN DEGREE OF SWELLING BEFORE, DURING, OR AFTER RISPERIDONE
THERAPY.

////////////////////////////////////
JAUSA12670(1) USA health 16yr F 25 day(s) at onset Recovered Seizures Cerebral (15-MAY-1994)
professional Serious Apnoea (15-MAY-1994)
Hyperglycemia (15-MAY-1994)

tablet - - 6mg (21-APR-1994 / 18-MAY-1994)

Causality Per Reporter: possible

Causality Per Company: possible

Event Description: ADOLESCENT INPATIENT ON RISPERIDONE EXPERIENCED TWO EPISODES OF WHAT
ARE THOUGHT TO BE SEIZURES. THE FIRST EPISODE OCCURRED ON 15-MAY-94, AT WHICH TIME
PATIENT HAD NOTED "SHAKING" OF THE EXTREMITIES FOLLOWED BY A BRIEF PERIOD OF
UNCONSCIOUSNESS AND UNRESPONSIVENESS. EMERGENCY MEDICAL SERVICES (EMS) WAS CALLED AND BY
THE TIME THEY ARRIVED (APPROXIMATELY FIVE MINUTES), PATIENT HAD RECOVERED. PATIENT WAS
TRANSFERRED TO A UNIVERSITY MEDICAL CENTER FOR EVALUATION. DURING TRANSFER A FINGERSTICK
GLUCOSE CHECK WAS 97 MG/DL. UPON ARRIVAL IN THE EMERGENCY ROOM (ER) SERUM GLUCOSE WAS

Indications: Unspecified Schizophrenia

1debeack 16JUN00

Volume 15/Page 91

Confidential/Produced in Litigation Pursuant to Protective Order
JJRP 00384079
D821.93

R. 6257

Ref.no.(case.no.) Ctry Prim. source Age Sex Latency Outcome Reaction 23
Seriousness

Formul Strength-Unit dose (Therapy start date/end date)

287 mg/dL (OTHER ELECTROLYTES WERE REPORTEDLY NORMAL). PATIENT WAS ADMITTED, EVALUATED, AND DIAGNOSED WITH "POSSIBLE ONSET OF DIABETES MELLITUS TYPE II". SHE WAS DISCHARGED BACK TO THE STATE ADOLESCENT PSYCHIATRIC HOSPITAL WITH INSTRUCTIONS TO FOLLOW A DIABETIC CONTROLLED DIET. RISPERIDONE WAS CONTINUED. PATIENT DID WELL UNTIL 18-MAY-94. WHEN SHE EXPERIENCED ANOTHER EPISODE INVOLVING BRIEF LOSS OF CONSCIOUSNESS WITH FLACCIDITY. THIS EPISODE WAS WITNESSED BY REPORTING PHYSICIAN WHO SPECIFIES PATIENT HAD JAW CLENCING AND PERIODS OF APNEA MIXED WITH TACHYPNEA. PATIENT REQUIRED SUCTIONING OF LARGE AMOUNTS OF PHLEGM. VITAL SIGNS WERE NORMAL. AFTER AIRWAY WAS CLEARED, PATIENT REGAINED CONSCIOUSNESS AND RECOVERED COMPLETELY. ELECTROLYTES WERE OBTAINED SHORTLY AFTER THE EPISODE AND WERE NORMAL. BLOOD GASES WERE NOT OBTAINED AND REPORTER SPECIFIES PATIENT DID NOT EXPERIENCE ANY CLINICAL DECOMPENSATION IN RESPIRATORY STATUS. RISPERIDONE WAS DISCONTINUED ON 18-MAY-94, AS PSYCHIATRIST AND PEDIATRICIAN SUSPECTED PATIENT MAY HAVE EXPERIENCED SEIZURES DURING THESE EPISODES (NOT OTHERWISE CLASSIFIED DUE TO THEIR ATYPICAL NATURE). AN ECG WAS OBTAINED A FEW WEEKS AFTER THESE EVENTS AND DID NOT REVEAL ANY ABNORMAL ACTIVITY. ENDOCRINE STATUS REMAINS STABLE WITH NORMAL SERUM GLUCOSE LEVELS ON A DIABETIC DIET. PATIENT WILL UNDERGO AN EXT CONSULT FOR EVALUATION OF UNDERLYING NASAL OBSTRUCTION WHICH WAS PRESENT PRIOR TO RISPERIDONE AND MANIFESTED AS NOISY NIGHTTIME BREATHING. REPORTING PHYSICIAN INDICATES DAYTIME APNEA HAS NOT BEEN A PROBLEM BUT WANTS TO RULE OUT SLEEP APNEA. NO FURTHER INFORMATION EXPECTED.

JANSA12850(1) USA health 81yr F 0 day(s) at onset No Change/Not Yet Diabetes Mellitus Aggravated (17-JUN-1994)
professional Subsidized
Not Serious Causality Per Reporter: possible
tablet 1 mg - 1mg (07-JUN-1994 / 18-JUN-1994)
tablet 1 mg - .5mg (17-JUN-1994 / 20-JUN-1994) Causality Per Company: doubtful

Event Description: INSULIN DEPENDENT DIABETIC PATIENT EXPERIENCED AN INCREASE IN BLOOD GLUCOSE AFTER 1 1/2 WEEKS OF RISPERIDONE THERAPY. RISPERIDONE WAS DISCONTINUED TO EVALUATE THE SITUATION. RISPERIDONE MAY BE RECHALLENGED WITH A DOSE ADJUSTMENT IN INSULIN. FOLLOW-UP IN PROGRESS.

Indications: Dementia

JANSA13133(1) USA health 35yr M 4 week(s) at onset Recovered Diabetes Mellitus (20-JUN-1994)
professional Serious
Causality Per Reporter: possible
tablet - 6mg (18-MAY-1994 / Unknown)

Event Description: PATIENT DEVELOPED DIABETES MELLITUS WHILE ON RISPERIDONE. PATIENT HAS NO PRIOR HISTORY OF POLYDIPSIA, POLYURIA OR FAMILY HISTORY OF DIABETES. ON 18-MAY-94 RISPERIDONE WAS STOPPED. ON 20-JUN-94 PATIENT WAS UNABLE TO STAND AND FAMILY TOOK HIM TO Indications: Unspecified Schizophrenia

1debacck 18JUN00

Volume 15/ Page 92

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JURP 00384080
D821.94

R. 6258

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction
24							

Formal Strength-Unit dose (Therapy start date/end date)
 =====
 THE RX WHERE BLOOD GLUCOSE WAS 1008 MG./DL. HE WAS TREATED WITH INSULIN AND ADMITTED
 (AFTER STABILIZATION) TO THE PSYCHIATRIC UNIT. HE HAS BEEN RECEIVING DAILY INSULIN
 (INSULIN 20 UNITS) WITH STABLE GLUCOSE CHECKS (EVERY SIX HOURS) REMAINING NEAR 120MG/DL.
 RISPERIDONE CONTINUES AND PATIENT IS REPORTEDLY RESPONDING WELL TO THERAPY. FOLLOW-UP
 WITH ENDOCRINOLOGIST IS IN PROGRESS.

JANSA13714(5)	USA health professional	30yr M	29 day(s) at onset	Recovered Not Serious	Diabetes Mellitus Aggravated (12-OCT-1994) Face Oedema (12-OCT-1994) Enuresis (08-OCT-1994)

tablet 2 mg - 2mg (14-SEP-1994 / 12-OCT-1994)

Event Description: PATIENT ON RISPERIDONE THERAPY PRESENTED WITH DIABETIC MELLITUS AND
 PANCREATITIS. RISPERIDONE WAS DISCONTINUED AND PATIENT RECOVERED 3 WEEKS LATER. FOLLOW-
 UP IN PROGRESS.

F O L L O W - U P 22-NOV-94:

PATIENT IS PSYCHIATRIC INPATIENT WHO PRESENTED WITH DIZZINESS, ABDOMINAL PAIN, NAUSEA,
 WEIGHT LOSS, AND "PUFFY FACE" APPROXIMATELY ONE MONTH AFTER BEGINNING RISPERIDONE
 THERAPY. A POST-PRANDIAL GLUCOSE ON 12-OCT-94 WAS ELEVATED (475). FASTING SERUM GLUCOSE
 VALUES RANGED FROM 173 - 286 OVER THE FOLLOWING SIX DAYS. RISPERIDONE WAS DISCONTINUED
 AND GLIPIZIDE AND INSULIN THERAPIES WERE INITIATED. AS OF 04-NOV-94, THE PATIENT
 CONTINUES TO REQUIRE INSULIN THERAPY FOR THE DIABETES. HE DID NOT EXPERIENCE
 PANCREATITIS AS ORIGINALLY REPORTED. REPORTER FEELS THE RISPERIDONE AND HALOPERIDOL
 CONTRIBUTED TO THE EVENTS.

F O L L O W - U P 09-MAY-95:

PEARL D. REPORTS PATIENT HAD A HISTORY OF UNTREATED DIABETES MELLITUS (FASTING SERUM
 GLUCOSE 109-245) SEVEN MONTHS PRIOR TO RISPERIDONE THERAPY. HE HAD ALSO GAINED
 APPROXIMATELY 80 POUNDS OVER THE PRECEDING THREE YEARS. PATIENT EXPERIENCED ENURESIS ON
 08-OCT-94 AND THE DOXEPIN WAS DISCONTINUED. A URINALYSIS WAS NOT PERFORMED. HE THEN
 PRESENTED WITH THE DIZZINESS, ABDOMINAL PAIN, NAUSEA, WEIGHT LOSS AND EDEMA ON 12-OCT-94.
 URINE WAS 4+ FOR GLUCOSE; SERUM GLUCOSE WAS 475. IN CONTRAST TO ORIGINAL REPORT,
 REPORTER DOES NOT FEEL THE EVENTS ARE RELATED TO RISPERIDONE OR HALOPERIDOL THERAPY.

Causality Per Reporter: not related

Causality Per Company: possible

Indications: Schizo-Affective Type Schizophrenia

Concomitant Diseases: Obesity; Diabetes Mellitus Without
 Mention Of Complication

JANSA13716(5)	USA health professional	38yr M	23 day(s) at onset	Recovered Serious	Ketoacidosis (07-JUL-1994) Av Block (16-JUL-1994) Speech Disorder (07-JUL-1994) Diabetes Mellitus Aggravated (07-JUL-1994) Nose Dryness (07-JUL-1994)

tablet 1 mg - 1mg (16-JUN-1994 / 07-JUL-1994)

Event Description: PATIENT ON RISPERIDONE THERAPY DEVELOPED AV HEART BLOCK. FOLLOW-UP IN
 PROGRESS.

F O L L O W - U P (22-NOV-94):

APPROXIMATELY THREE WEEKS AFTER RISPERIDONE WAS BEGUN (07-JUL-94), A PSYCHOTIC INPATIENT
 PRESENTED WITH THIRST, WEIGHT LOSS, FRUITY BREATH, VOMITING, MODERATE HUNGER,

Causality Per Reporter: not related

Idabaack 18JUN90

Volume 15/Page 93

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 JJRP 00384081
 D821.95

R. 6259

Ref.no.(vers.no.) Cty Prim. source Age Sex Latency Outcome Reaction 25
Seriousness

Formul Strength-Unit dose (Therapy start date/end date)
INCONTINENCE, STAGGERING GAIT, GASTROINTESTINAL UPSET, DRY MUCUS MEMBRANES, AND SLURRED SPEECH. A FASTING GLUCOSE ON 08-JUL-04 WAS ELEVATED AT 882. DIABETES WAS DIAGNOSED AND INSULIN THERAPY WAS INITIATED. RISPERIDONE WAS DISCONTINUED AND THE HYPERGLYCAEMIA RESOLVED. NINE DAYS LATER (16-JUL-04), THE PATIENT DEVELOPED AV BLOCK. HE DENIED CHEST PAIN AND DYSPNOEA; THERE WERE NO MENTAL STATUS CHANGES. A PACEMAKER WAS INSERTED ON 02-JUL-04 AND THE PATIENT RECOVERED WITHOUT COMPLICATIONS. AS OF 04-NOV-04, THE PATIENT NO LONGER REQUIRES INSULIN THERAPY. THE REMAINING EVENTS WERE TREATED SUCCESSFULLY WITH CARAPATE, METOCLOPRAMIDE AND GEMFIBROZIL. COPIES OF THE EKG AND FURTHER DETAILS REGARDING THE CASE HAVE BEEN REQUESTED.
F O L L O W - U P (25-APR-06):

PATIENT'S PAST HISTORY IS SIGNIFICANT FOR ELEVATED FASTING SERUM GLUCOSE LEVEL (200) FOUR MONTHS PRIOR TO STARTING RISPERIDONE. HE HAS ALSO BEEN OBESE FOR THE YEAR PRECEDING RISPERIDONE THERAPY (OVERWEIGHT BY 100-130 POUNDS). BASELINE WEIGHT APPROXIMATELY THREE WEEKS PRIOR TO RISPERIDONE (24-MAY-04) WAS 317. PATIENT'S IDEAL BODY WEIGHT CALCULATED BY A DIETITIAN IS 172-189. CALORIC RESTRICTION WAS IMPLEMENTED AND HIS WEIGHT DECREASED TO 252 ON 01-JUL AND TO 262 ON 25-JUL. PATIENT IS ALSO KNOWN TO HAVE HYPERTRIGLYCERIDAEMIA (576). HOSPITAL PHARM.D. REPORTS PATIENT'S FINAL DIAGNOSIS WAS DIABETIC KETOACIDOSIS. A REPEAT FASTING GLUCOSE ON 16-JUL-04 (IN CONTRAST TO 08-JUL AS MENTIONED IN INITIAL REPORT) WAS 602. INSULIN THERAPY WAS INITIATED AND THEN DISCONTINUED AFTER HE DEVELOPED HYPOGLYCAEMIA. GLUCOSE CONTROL WAS MAINTAINED ON A DIABETIC DIET ONLY. PATIENT WAS READMITTED ON 16-MAR FOR EXACERBATION OF THE DIABETES (FASTING GLUCOSE 226), SECONDARY TO POOR DIETARY COMPLIANCE BY THE PATIENT. GLIPIZIDE WAS STARTED AND GLUCOSE LEVELS ARE REPORTEDLY NOW "CONTROLLED." SPECIFIC VALUES ARE NOT AVAILABLE. REPORTER STATES HOUSE STAFF AT THIS STATE HOSPITAL ARE CONCERNED ABOUT PATIENT'S SEQUESTERING CANDY AND HIGH CALORIC FOOD ITEMS IN THEIR BED AREAS WHICH ARE UNCONTROLLED BY STAFF. THEY ALSO FELT THAT RISPERIDONE WAS NOT A CAUSAL AGENT IN THIS CASE BUT HAPPENED TO BE NOTED DUE TO THE "STRONG AND POSITIVE INTEREST IN THIS NEW MEDICATION."

JAUSA13719(2) USA health Unknown Diabetes Mellitus (Unknown)
professional Serious Causality Per Company: possible
tablet

Event Description: PATIENT ON RISPERIDONE THERAPY DEVELOPED DIABETES MELLITUS. FOLLOW-UP IN PROGRESS. Causality Per Company: possible
THE INFORMATION AVAILABLE ON THIS CASE IS VERY SKETCHY; NO FURTHER DETAILS ARE EXPECTED (AND CASE HAS BEEN CLOSED).

JAUSA13847(4) USA health 33yr M 14 day(s) at onset Recovered Pancreatitis (05-AUG-1984)
professional Serious Ketoacidosis (05-AUG-1984)
Hypert triglyceridaemia (05-AUG-1984)

ldebaeck 16JUN00

Volume 15/Page 94

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R. 6260

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Resortion	26
Formul Strength-Unit dose (Therapy start date/end date).								
tablet 3 mg - 3ag (22-JUL-1994 / Unknown)								
Event Description: INSULIN-DEPENDENT DIABETIC PATIENT ON RISPERIDONE 6 MG DAILY FOR TWO WEEKS PRESENTED TO THE EMERGENCY ROOM (ER) WITH ABDOMINAL CRAFTS AND FEVER (100 F). PATIENT WAS ADMITTED TO THE HOSPITAL WITH A DIAGNOSIS OF PANCREATITIS AND DIABETIC KETOACIDOSIS. ABNORMAL LABS INCLUDED TRIGLYCERIDES 7000 MG/DL, BLOOD SUGAR 550 MG/DL, AND CHOLESTEROL 600 MG/DL. PHYSICIAN DOUBTS RISPERIDONE INVOLVEMENT SINCE PATIENT HAS A HISTORY OF PANCREATITIS PRIOR TO RISPERIDONE THERAPY. PANCREATITIS RESOLVED AND PATIENT WAS DISCHARGED WHILE CONTINUING RISPERIDONE THERAPY. FOLLOW-UP IN PROGRESS. F O L L O W - U P 16-SEP-94: PATIENT INDICATED HE HAD NOT BEEN COMPLIANT WITH HIS DIABETIC DIET AND HAD ALSO BEEN DRINKING TWO SIX PACKS OF BEER TWICE PER WEEK. LAB VALUES WERE PROVIDED AND WERE CONSISTENT WITH PANCREATITIS AND DIABETIC KETOACIDOSIS. TREATMENT DURING HOSPITALIZATION INCLUDED VIGOROUS I.V. FLUID REPLACEMENT AND AN INSULIN DRIP. PATIENT WAS MADE NPO (NOTHING BY MOUTH) AND HIS DIET WAS SLOWLY ADVANCED AS TOLERATED. HE WAS DISCHARGED ON A REGULAR DIABETIC DIET, INSULIN, CEFIBROZOL, KRON(R), LITHIUM, AND RISPERIDONE. ALL EVENTS RESOLVED.								
Hyperglycemia (05-APR-1994) Hypercholesterolemia (05-AUG-1994) Causality Per Reporter: doubtful Causality Per Company: doubtful Indications: Bipolar Disorder Company Remarks: This is unlikely related to the risperidone therapy.								
JAUSA14248(2) USA health 84yr F Death Serious tablet 2 mg - 2ag Event Description: A 64-YEAR-OLD FEMALE WITH A LONG HISTORY OF RESPIRATORY DISEASE, AS WELL AS DEMENTIA (ALZHEIMER'S TYPE) AND INSULIN-DEPENDENT DIABETES MELLITUS, WAS ADMITTED TO THE ICU ON 04-APR-94, IN RESPIRATORY DISTRESS. SHE HAD BEEN COMPLAINING OF SHORTNESS OF BREATH AND A PRODUCTIVE COUGH SINCE THE DAY BEFORE. PATIENT WAS TAKING MULTIPLE MEDICATIONS INCLUDING RISPERIDONE (DATE OF THERAPY AND DOSAGE UNSPECIFIED). CHEST X-RAY ON ADMISSION REVEALED A RIGHT MIDDLE AND LOWER LOBE PNEUMONIA. PATIENT WAS GIVEN OXYGEN WITH OXIMETRY TO KEEP HER OXYGEN SATURATION AT APPROXIMATELY 85% IN ORDER TO PRESERVE A HYPOKIC RESPIRATORY DRIVE. SINCE THE PATIENT HAD A PREVIOUS HISTORY OF PROLONGED MECHANICAL VENTILATION (IN 1987, FOLLOWING AN INCISIONAL HERNIA REPAIR), IT WAS FELT IT WOULD BE BEST TO TRY TO AVOID INTUBATION AND MECHANICAL VENTILATION IF AT ALL POSSIBLE. SALEDATAMOL AND CEFOTIXIME WERE STARTED. ON 06-APR-94, PATIENT HAD A LOW GRADE FEVER, WAS LESS RESPONSIVE, DYSPNEIC, AND TACHYPNEIC ON 60% OXYGEN. AMINOPIRYLLINE DRIP AND METHYLPREDNISOLONE WERE ADDED. SHE IMPROVED THE FOLLOWING DAY. CEFOTIXIME WAS REPLACED WITH CEFUROXIME AFTER A SPUTUM CULTURE CAME BACK POSITIVE FOR HEMOPHILUS INFLUENZAE. PATIENT BECAME AFEBRILE THE FOLLOWING DAY. HOWEVER, ON THE MORNING OF 08-APR-94, PATIENT'S BLOOD GASES DETERIORATED AND THE PATIENT WAS ELECTIVELY INTUBATED. A SUBCLAVIAN CENTRAL LINE WAS ALSO PLACED. I.V. FLUIDS WERE INCREASED BECAUSE OF CLINICAL DEHYDRATION. PATIENT BECAME MORE STABLE, WAS STARTED ON NASOGASTRIC (NG) FEEDINGS, STEROIDS WERE INCREASED, AND AN ATTEMPT WAS MADE TO DECREASE THE VENTILATORY SUPPORT. THE FOLLOWING DAY PATIENT WAS EASILY AROUSABLE AND SHE DENIED SPECIFIC COMPLAINTS. HOWEVER, ON 11-APR-94, PATIENT'S TEMPERATURE WAS 101 F. TWO DAYS LATER TEMPERATURE ROSE Hyperpyrexia Malignant (16-APR-1994) Shock Cardiogenic (16-APR-1994) Hypotension (15-APR-1994) Thrombocytopenia (16-APR-1994) Respiratory Failure (04-APR-1994) Pneumonia Lobar (03-APR-1994) Septicemia (Unknown) GI Haemorrhage (15-APR-1994) Diabetes Mellitus Aggravated (04-APR-1994) Causality Per Reporter: possible Causality Per Company: possible Indications: Bipolar Disorder Concomitant Diseases: Obesity Company Remarks: THERE IS NO EVIDENCE THAT THIS IS MALIGNANT HYPERPYREXIA. THIS LATTER IS A FULMINANT DISORDER WHICH OCCURRED IN ASSOCIATION WITH INHALATION ANAESTHETICS. THIS IS ALSO NO NEUROLEPTIC MALIGNANT SYNDROME. IT SHOULD BE NOTED THAT THE PATIENT WAS ADMITTED WITH A DOCUMENTED PNEUMONIA ON APRIL 4TH; LEUCOCYTES WERE 28,000/ML. PT WAS								

1dsbaeck 10JUN90

Volume 15/Page 95

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R. 6261

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction
Formal Strength-Unit dose (Therapy start date/end date)							
TO 103 F. SHE WAS RECULTURED, FOUND TO HAVE A STAPHYLOCOCCAL SPECIES AS WELL AS CANDIDA ALBICANS, AND WAS SWITCHED TO CEFTRIAXONE, AZTREONAM, AND FLUCONAZOLE. FEVER CONTINUED AND CEFTRIAXONE WAS REPLACED WITH PRIMAXIN(R). ON 15-APR-94, FEVER PERSISTED (104 F) AND PATIENT WAS LESS RESPONSIVE. CPK WAS SLIGHTLY INCREASED BUT PATIENT WAS NOT RIGID. AN INSULIN DRIP WAS STARTED FOR HYPERGLYCEMIA. AT 8:30 P.M., PATIENT DEVELOPED HYPOTENSION (SYSTOLIC BP RANGED FROM 60 TO 80 MMHG). A BOLUS OF I.V. FLUIDS AND DOPAMINE WERE GIVEN. AT 7:20 P.M., THE SYSTOLIC BP REMAINED IN THE 80'S DESPITE WIDE OPEN DOPAMINE. HEMOGLOBIN DROPPED TO 8.5. PACKED RED BLOOD CELLS WERE ADMINISTERED. AT 8:15 P.M., A LARGE AMOUNT OF 'COFFEE GROUND' MATERIAL WAS SEEN IN THE NG TUBE. ICED SALINE LAVAGE WAS GIVEN. THE FOLLOWING MORNING PATIENT'S TEMPERATURE INCREASED DRAMATICALLY TO 103 F. A BLOOD CULTURE HAD GROWN STAFF EPIDERMIDIS AND ALTHOUGH IT WAS SUSPECTED TO BE SKIN CONTAMINANT, VANCOMYCIN WAS STARTED. ICE LAVAGE WAS CONTINUED AND ICED ENEMAS WERE GIVEN IN AN ATTEMPT TO REDUCE THE FEVER. A DIFFERENTIAL DIAGNOSIS AT THIS TIME INCLUDED SEPSIS. ARRANGEMENTS WERE MADE TO TRANSFER THE PATIENT TO A TERTIARY CARE FACILITY. A NEUROLOGIST WAS CONSULTED TO DETERMINE IF THERE WAS A CNS ETIOLOGY FOR THE HIGH TEMPERATURE. PATIENT THEN DEVELOPED CARDIOGENIC SHOCK. SYSTOLIC BP DROPPED TO 60 AND PATIENT WAS GIVEN NOREPINEPHRINE, SEDUCRIFTINE, AND DANTROLENE. A LUMBAR PUNCTURE WAS ORDERED BUT THE PATIENT DIED BEFORE IT COULD BE PERFORMED. DATE OF DEATH IS UNSPECIFIED BUT WAS STATED AS 24-48 HOURS AFTER TRANSFER TO THE TERTIARY CARE FACILITY. AN AUTOPSY WAS DENIED BY THE FAMILY. A CONSULTING PULMONOLOGIST AS WELL AS THE NEUROLOGIST MADE A FINAL DIAGNOSIS OF MALIGNANT HYPERTHERMIA SECONDARY TO RISPERIDONE. HOSPITAL RECORDS HAVE BEEN REQUESTED.							

JANSA14282(5)	USA regulatory authority	48yr M	Recovered Serious	Seizures Cerebral (08-MAY-1994) Extrapyramidal Disorder (08-MAY-1994) Urinary Incontinence (08-MAY-1994) Fever (08-MAY-1994) Blood Pressure High (08-MAY-1994) Spot Increased (08-MAY-1994) Uric Acid Blood Increased (08-MAY-1994) Cpk Increased (08-MAY-1994) Hyperglycemia (08-MAY-1994) Hypokalemia (11-MAY-1994)
tablet 3 mg - 3mg Event Description: FDA MISMATCH REPORT: PSYCHIATRIC INPATIENT ON RISPERIDONE 9 MG DAILY PRESENTED AT THE EMERGENCY ROOM WITH SEIZURES MANIFESTED BY "BASAL GANGLION DYSFUNCTION, JERKING MOVEMENTS OF LIMBS, INCONTINENCE, FEVER OF 102 F, PULSE 112, RESPIRATIONS 24, AND BLOOD PRESSURE 154/102". TWO BLOOD CULTURES PERFORMED IN THE EMERGENCY ROOM (ER) WERE NEGATIVE. PATIENT WAS ADMITTED TO THE INTENSIVE CARE UNIT. LUMBAR PUNCTURE SHOWED NO MONOCYTOSIS OR RED CELLS NOR ANYTHING SPECIFIC TO SUGGEST HERPES SIMPLEX ENCEPHALITIS. LABORATORY VALUES WERE ESSENTIALLY NORMAL. CHEST X-RAY, CT OF BRAIN, MRI OF CERVICAL AND THORACIC SPINE AND BRAIN WERE ALL NORMAL. EEG DOCUMENTED SEIZURE ACTIVITY. PARLODEL WAS UNSUCCESSFUL IN CONTROLLING PATIENT'S MOVEMENT DISORDER. RISPERIDONE WAS DISCONTINUED, AND PATIENT WAS TREATED WITH PHENYTOIN AND LORAZEPAM. PATIENT RECOVERED AND WAS DISCHARGED 18 DAYS LATER IN STABLE CONDITION.				Causality Per Reporter: probable Causality Per Company: probable Indications: Paranoid Type Schizophrenia

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Volume 15/Page 96

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R. 6262

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	28
Formul Strength-Unit dose (Therapy start date/end date)								
JANSA14314(1)								
USA health professional	30yr F	1 week(s) at onset	Recovered	Not Serious		Hypoglycaemia (Unknown)		
tablet 3 mg - 3mg (01-AUG-1994 / Unknown)							Causality Per Reporter: possible	
Event Description: AFTER ONE WEEK OF RISPERIDONE THERAPY (3 MG DAILY) PATIENT BECAME SYMPTOMATIC WITH DIZZINESS, CONFUSION, TREMORS, AND DIAPHORESIS. A THREE HOUR GLUCOSE TOLERANCE TEST REVEALED REACTIVE HYPOGLYCAEMIA. PATIENT WAS STARTED ON A SPECIAL DIET AND THE SYMPTOMS RESOLVED. SHE CONTINUES RISPERIDONE.							Causality Per Company: possible	
							Indications: Bipolar Disorder	
							Concomitant Diseases: Obesity	
JANSA14639(1)								
USA health professional	45yr F	13 week(s) at onset	No Change/Not Yet Subsidized	Not Serious		Hyperglycaemia (10-OCT-1994)		
tablet 3 mg - 3mg (10-JUL-1994 / Unknown)							Causality Per Reporter: doubtful	
							Causality Per Company: doubtful	
Event Description: NON-INSULIN DEPENDENT DIABETIC ON RISPERIDONE 6 MG DAILY FOR 3 MONTHS EXPERIENCED AN INCREASE IN FASTING BLOOD GLUCOSE (180 MG/DL) (BASELINE 88 MG/DL) ON ROUTINE TEST. PATIENT WAS BEING TREATED WITH GLIBENCLAMIDE FOR THE DIABETES BUT THAT HAS BEEN DISCONTINUED AND PATIENT PLACED ON NPH INSULIN (INTERMEDIATE ACTION). PHYSICIAN DOUBTS THE HYPERGLYCAEMIA IS DUE TO RISPERIDONE BUT TO NON-COMPLIANCE WITH DIET.							Indications: Unspecified Schizophrenia	
JANSA14670(1)								
USA health professional	34yr M		No Change/Not Yet Subsidized	Not Serious		Hyperglycaemia (Unknown)		
tablet 3 mg - 3mg (08-AUG-1994 / Unknown)							Thirst Excessive (Unknown)	
							Skin Dry (Unknown)	
							Taste Metallic (Unknown)	
Event Description: NON-DIABETIC PATIENT ON RISPERIDONE 6 MG DAILY FOR 2 MONTHS PRESENTED TO INTERNIST WITH POLYDIPSIA, DRY SKIN, AND A METALLIC TASTE. A FASTING GLUCOSE TEST WAS DONE AND BLOOD GLUCOSE WAS 555 MG/DL. FOLLOW-UP IN PROGRESS.							Causality Per Reporter: possible	
							Causality Per Company: possible	

14639ack 16JUN00

Ref.no.(vers.no.)	City	Prim. source	Age	Sex	Latency	Outcome	Reaction
							28
Formul Strength-Unit dose (Therapy start date/end date)							
Indications: Unspecified Schizophrenia							

JADSA14694(1)	USA health professional	45yr F	Recovered Not Serious	Diabetes Mellitus Aggravated (Unknown)
tablet - - -				Causality Per Reporter: possible
Event Description: AN INSULIN DEPENDENT DIABETIC PATIENT REQUIRED INCREASED DOSES OF INSULIN SINCE STARTING RISPERIDONE THERAPY. PATIENT'S GLUCOSE IS STABLE AT THIS TIME. FOLLOW UP IS IN PROGRESS.				Causality Per Company: doubtful Indications: Unspecified Schizophrenia

JADSA14725(5)	USA health professional	55yr F	Death Serious	Cardiac Arrest (07-OCT-1994) Efficacy, Lack Of (77-OCT-1994) Constipation (77-OCT-1994) Abdominal Pain (77-OCT-1994) Constipation Aggravated (77-OCT-1994) Acidosis Metabolic (77-OCT-1994) Apnoea (07-OCT-1994) Bradycardia (Unknown) Hypotension (Unknown) Sepsis (Unknown) Gastric Ulcer (Unknown)
tablet 2 mg - 2mg (21-SEP-1994 / 05-OCT-1994)				Causality Per Reporter: possible Causality Per Company: possible Indications: Schizo-Affective Type Schizophrenia Concomitant Diseases: Constipation; Irritable Colon; Leucocytosis of Uterus, unspecified
Event Description: PATIENT WAS STARTED ON RISPERIDONE 2 MG BID AND WAS SCHEDULED FOR A RETURN APPOINTMENT APPROXIMATELY THREE WEEKS LATER. REPORTER LATER LEARNED FROM A FAMILY MEMBER THE PATIENT HAD DISCONTINUED RISPERIDONE AFTER TWO WEEKS BECAUSE OF A LACK OF EFFECT (CONCOMITANT THIORIDAZINE AND AMITRIPTYLINE WERE CONTINUED). SHE THEN ADMITTED HERSELF TO THE HOSPITAL FOR A MEDICATION CHANGE. SHE REPORTEDLY "COLLAPSED AND DIED" IN THE HOSPITAL. DATE OF DEATH IS UNKNOWN. ADDITIONAL DETAILS SURROUNDING THE DEATH ARE NOT KNOWN AT THIS TIME. ADDITIONAL INFORMATION REQUESTED.				
F O L L O W - U P 27-OCT-94: PATIENT DID NOT ADMIT HERSELF FOR A MEDICATION CHANGE AS ORIGINALLY REPORTED. SHE PRESENTED TO THE EMERGENCY ROOM ON THE EVENING OF 05-OCT-94 WITH ABDOMINAL PAIN AND EXTREME CONSTIPATION. SHE WAS AFEBRILE. PATIENT HAD A HISTORY OF CHRONIC CONSTIPATION. LABORATORY STUDIES REVEALED METABOLIC ACIDOSIS. PATIENT REPORTEDLY RECEIVED ENEMAS FOR THE CONSTIPATION ON THE MORNING OF 08-OCT-94 AND WAS DOING WELL. LATER THE SAME DAY, SHE DEVELOPED SHORTNESS OF BREATH. IT IS UNKNOWN IF PATIENT RECEIVED ANY INTERVENTION OR TREATMENT FOR THE DYSPNOEA. SHE WENT INTO WITNESSED CARDIAC ARREST THE FOLLOWING DAY. THE RESULTS HAVE BEEN REQUESTED. PATIENT WAS CODED. SHE DIED ON 07-OCT-94; AUTOPSY REVEALED PULMONARY CONGESTION. DETAILS SURROUNDING THE PATIENT'S DEATH AS WELL AS DISCHARGE SUMMARY, HOSPITAL RECORDS, AND AUTOPSY REPORT HAVE BEEN REQUESTED.				
F O L L O W - U P 06-DEC-94: AUTOPSY WAS PERFORMED ON 09-OCT-94, TWO DAYS AFTER THE PATIENT DIED. THE POST-MORTEM RECORD STATES THE PATIENT'S CLINICAL DIAGNOSIS AT THE TIME OF HER DEATH INCLUDED "CONSTIPATION, SPASTIC COLON SECONDARY TO MEDICATIONS (UNSPECIFIED), STATUS POST				

1daback 16JUN00

Volume 15/Page 98

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JRP 00384086

D821.100

R. 6264

Ref.no.(vers.no.) City Prim. source Age Sex Latency Outcome Reaction 30
Seriousness

Formul Strength-Unit dose (Therapy start date/end date)

CARDIOPULMONARY ARREST WITH SUCCESSFUL RESUSCITATION, CARDIAC DYSRHYTHMIA (BRADYCARDIA, IDIOVENTRICULAR), HYPOTENSION, ADULT RESPIRATORY DISTRESS SYNDROME AND SEPSIS.
PROVISIONAL ANATOMIC DISEASE INCLUDED SEVERE PULMONARY EDEMA AND CONGESTION (LUNG WEIGHT 1650 GNS); OLD CALCIFIED HILAR LYMPH NODE WITH ADHESIONS OF THE RIGHT PLEURAL SPACE. THERE WAS ALSO ACUTE CONGESTION OF THE LIVER AND SPLEEN. THERE WAS MINIMAL PEDAL EDEMA. HYPERTROPHY OF THE MUSCULAR COAT OF THE COLON, ACUTE STRESS ULCER OF THE STOMACH AND LEIOMYOMATA OF THE UTERUS WERE ALSO FOUND. CAUSE OF DEATH WAS NOT SPECIFIED. DISCHARGE SUMMARY AND HOSPITAL RECORDS HAVE BEEN REQUESTED.

JAUSA14782(3) USA health 48yr F No Change/Not Yet Blood Sugar Increased (Unknown)
professional Subsidized
Not Serious Causality Per Reporter: possible

tablet 3 mg - 3mg (09-MAY-1994 / Unknown)

Causality Per Company: doubtful

Event Description: DIABETIC PATIENT INADEQUATELY CONTROLLED ON GLIBENCLAMIDE 20 MG DAILY THERAPY (GLUCOSE 180-200 MG/DL) IS EXPERIENCING INCREASED GLUCOSE LEVELS. THE DOSE OF GLIBENCLAMIDE WAS INCREASED TO 40 MG DAILY LAST MONTH BUT THE GLUCOSE LEVEL CONTINUES TO INCREASE (300 MG/DL) AT PRESENT. THE INCREASED GLUCOSE LEVELS MAY BE DUE TO POOR DIETARY COMPLIANCE BY PATIENT. A PHYSICIAN CONSULTATION IS SCHEDULED TO DISCUSS PATIENT'S CONDITION.
P O L L O W - U P (DEC.94); CONCOMITANT DRUGS ADDED.

Indications: Schizo-Affective Type Schizophrenia

JAUSA14884(1) USA health 04yr F 5 week(s) at onset Recovered Hypoglycemia (18-APR-1994)
professional Serious Hypotension (16-JUL-1994)
Syncope (77-JUL-1994)

tablet 3 mg - 2mg (02-MAR-1994 / 18-APR-1994)

Causality Per Reporter: possible

Causality Per Company: doubtful

Event Description: PSYCHIATRIC IN-PATIENT WITH HYPERTENSION AND NIDDM (WELL CONTROLLED BY 1500 CALORIE ADA DIET), BEGAN RISPERIDONE ON 02-MAR-94. APPROXIMATELY SEVEN WEEKS LATER, A FASTING BLOOD SUGAR (FBS) WAS 22 MG/DL. TWO HOURS LATER, IT ROSE TO 47 BUT THREE HOURS AFTER ONSET IT DECREASED TO 11 (VALUE CONFIRMED WITH REPEATUR). THE GLUCOSE LEVEL DIDN RISE TO 160 FOUR HOURS AFTER ONSET. EACH EPISODE OF HYPOGLYCAEMIA WAS TREATED WITH JUICE AND FOOD. PATIENT WAS ASYMPTOMATIC. ALL MEDICATIONS WERE HELD (RISPERIDONE, PAROXETINE, NIFEDIPINE (PROCARDIA XL), POTASSIUM CHLORIDE AND AMANTADINE) BUT ORAL NIFEDIPINE (10 MG) WAS ADMINISTERED. PATIENT WAS TRANSFERRED TO THE MEDICAL UNIT AND WAS GIVEN A SINGLE IV DOSE OF 50% DEXTROSE (50 ML) AFTER THE GLUCOSE DROPPED TO 44. INSULIN AND CATACHOLAMINE LEVELS WERE WITHIN NORMAL LIMITS. RISPERIDONE, PAROXETINE AND NIFEDIPINE (PROCARDIA XL) WERE SUSPECTED AS THE CAUSATIVE AGENTS FOR THE HYPOGLYCAEMIA. THE PATIENT WAS RETURNED TO THE PSYCHIATRIC UNIT AFTER EIGHT DAYS. OVER THE FOLLOWING THREE MONTHS THE PATIENT EXPERIENCED SPORADIC HYPOGLYCAEMIA WHICH WAS ASYMPTOMATIC EXCEPT FOR ONE EPISODE WHICH

Indications: Schizo-Affective Type Schizophrenia

Concomitant Diseases: Diabetes Mellitus Without Mention Of Complication

Company Remarks: The glucose and insulin concentrations do not match. Nutritional status (low weight) might be a factor.

1debaeck 18JUN00

Volume 15/Page 99

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D821.101

R. 6265

Ref.no. (verse.no.)	City	Prim. source	Age	Sex	Latency	Outcome	Reaction
						Seriousness	

Formal Strength-Unit dose (Therapy start date/end date)

WAS ACCOMPANIED BY HYPOTENSION AND SYNOPE AND HAD FOLLOWED A DOSE OF PER NIFEDIPINE. THE NIFEDIPINE WAS DISCONTINUED, THE ADA DIET WAS INCREASED TO 2000 CALORIES AND HALOPERIDOL (20 MG HS) WAS ADDED TO THE PATIENT'S THERAPY. THE EVENTS HAVE NOT RECURRENT. THE PATIENT CONTINUES TO BE MONITORED.

JANSA14963(1)	USA health professional	40yr F	Recovered	Serious	Ketoacidosis (Unknown) Polyuria (Unknown) Thirst Excessive (Unknown) Diabetes Mellitus Aggravated (Unknown)

tablet 3 mg - 3mg

Event Description: PATIENT ON RISPERIDONE 6 MG DAILY PRESENTED TO THE HOSPITAL. CEMATOSES, WITH A BLOOD SUGAR OF 1700 MG/DL, PH 7.01, SODIUM 177 MMOL/L AND WAS DIAGNOSED WITH DIABETIC KETOACIDOSIS. RISPERIDONE WAS DISCONTINUED AND PATIENT WAS TREATED WITH I.V. FLUID (REQUIRED 14 LITERS) AND INSULIN. THE PHYSICIAN FEELS THE PATIENT HAS PROBABLY BEEN AN UNDIAGNOSTIC DIABETIC FOR SOME TIME. THE PATIENT REPORTED SHE WAS DIABETIC DURING HER PREGNANCY SOME YEARS AGO. THE FAMILY REPORTED THE PATIENT HAD BEEN EXPERIENCING EXCESSIVE THIRST AND URINARY FREQUENCY FOR A LONG TIME BUT THEY WERE UNAWARE THESE WERE DIABETIC SYMPTOMS. THE PATIENT WAS ALSO ON A VERY POOR DIET. THE PATIENT RECOVERED, WAS DISCHARGED FROM THE HOSPITAL, AND IS NOW ON INSULIN THERAPY. THE PHYSICIAN FEELS THE PATIENT WOULD HAVE DEVELOPED THIS CONDITION WITHOUT RISPERIDONE DUE TO HER GENERAL PHYSICAL AND MEDICAL NEGLIGENCE.

Causality Per Reporter: doubtful

Causality Per Company: doubtful

Indications: Unspecified Schizophrenia

Concomitant Diseases: Polydipsia; Polyuria

JANSA14980(1)	USA health professional	32yr F	28 day(s) at onset	Recovered	Not Serious	Hyperglycaemia (26-SEP-1994) Vision Abnormal (30-AUG-1994)

tablet - - 12mg (01-JUN-1994 / 30-AUG-1994)
tablet - - 10mg (31-AUG-1994 / 26-SEP-1994)
tablet 4 mg - 4mg (27-SEP-1994 / Unknown)

Causality Per Reporter: possible

Causality Per Company: possible

Indications: Schizo-Affective Type Schizophrenia

Event Description: A NON-DIABETIC PATIENT ON RISPERIDONE 12 MG DAILY AND VALPROIC ACID EXPERIENCED VISUAL PROBLEMS (UNABLE TO FOCUS). THE DOSE OF RISPERIDONE WAS DECREASED TO 10 MG DAILY AND THE PATIENT RECOVERED. ON A ROUTINE BLOOD TEST INCREASED BLOOD GLUCOSE WAS NOTED 26-SEP-94 (238 MG/DL), 27-SEP-94 (180 MG/DL), 28-SEP-94 (182 MG/DL). PATIENT IS OTHERWISE ASYMPTOMATIC. THE DOSE OF RISPERIDONE WAS DECREASED ON 27-SEP-94 TO 6 MG DAILY AND GLIHECLAMIDE 2.5 MG DAILY WAS ADDED TO THE THERAPY. THE BLOOD GLUCOSE DECREASED TO 120 MG/DL ON 12-OCT-94. GLIHECLAMIDE WAS DISCONTINUED ON 17-OCT-94 AND SUBSEQUENT BLOOD GLUCOSE VALUES WERE 100-114 MG/DL. PATIENT CONTINUES ON RISPERIDONE 6 MG DAILY AND BLOOD GLUCOSE ON 3-NOV-94 WAS 110 MG/DL. PATIENT IS BEING TRANSFERRED TO A LONG TERM FACILITY IN PUERTO RICO FURTHER FOLLOW-UP NOT POSSIBLE.

JANSA15192(1)	USA health professional	40yr M	0 day(s) at onset	Recovered	Not Serious	Hypoglycaemia (27-OCT-1994) Light-Headed Feeling (27-OCT-1994)

tablet 1 mg - 1mg (15-MAY-1994 / 14-JUL-1994)

Volume 15/ Page 100

Confidential/Produced in Litigation Pursuant to Protective Order

JRRP 00384088

D821.102

R. 6266

tablet 2 mg - 2mg (15-JUL-1994 / 28-OCT-1994)

Causality Per Reporter: probable

Ref.no.(vers.no.) Cty Prim. source Age Sex Latency

Outcome
Seriousness

Reaction

32

Formal Strength-Unit dose (Therapy start date/end date)

tablet 1 mg - 3mg (27-OCT-1994 / 12-NOV-1994)

tablet 2 mg - 2mg (12-NOV-1994 / Unknown)

Causality Per Company: doubtful

Event Description: AN AIDS PATIENT ON RISPERIDONE THERAPY EXPERIENCED HYPOGLYCAEMIA. ON 1-MAY-94 PRIOR TO STARTING RISPERIDONE THE PATIENT'S GLUCOSE WAS 80 MG/DL. AFTER STARTING RISPERIDONE ON 15-MAY-94 THE GLUCOSE LEVEL DECREASED AS FOLLOWS: 31-MAY-94 GLUCOSE 77 MG/DL, 15-AUG-94 GLUCOSE 74 MG/DL, 28-SEP-94 GLUCOSE 65 MG/DL, AND ON 27-OCT-94 THE GLUCOSE WAS 44 MG/DL, AT WHICH TIME THE PATIENT WAS COMPLAINING OF LIGHtheadedness. THE PATIENT WAS GIVEN COOKIES AND JUICE AND THE REPEAT GLUCOSE ON 27-OCT-94 WAS 57 MG/DL. THE DOSE OF RISPERIDONE WAS DECREASED TO 3 MG DAILY AND THE PATIENT IS GIVEN JUICE WITH EACH DOSE. ON 1-NOV-94 THE GLUCOSE WAS 60 MG/DL AND CONTINUED TO IMPROVE. ON 12-NOV-94 GLUCOSE WAS 78 MG/DL AND THE DOSE OF RISPERIDONE WAS INCREASED TO 4 MG DAILY. THE GLUCOSE ON 15-NOV-94 WAS 79 MG/DL AND INCREASED TO 80 MG/DL ON 17-NOV-94. THE PATIENT WAS RECOVERED AND WILL CONTINUE ON THE RISPERIDONE 4 MG DAILY AND WILL ALSO CONTINUE TAKING EACH DOSE WITH JUICE.

Indications: Unspecified Schizophrenia

Company Remarks: Bacterial infection is a differential diagnosis for hypoglycaemia as are the disease and the co-medication.

JAUSA15252(1)

USA health
professional

25yr F 4 week(s) at onset

Recovered
Not Serious

Diabetes Mellitus Aggravated (10-NOV-1994)

Causality Per Reporter: possible

tablet 1 mg - 1mg (06-OCT-1994 / Unknown)

Event Description: DIABETIC PATIENT ON RISPERIDONE 1 MG DAILY FOR 6 WEEKS IS EXPERIENCING AN INCREASE IN HER FASTING BLOOD GLUCOSE (200 MG/DL). THE PATIENT'S BASELINE VALUE IS 120 MG/DL. THE DOSE OF GLIBENCLAMIDE WAS INCREASED AND THE PATIENT RECOVERED.

Causality Per Company: doubtful

Indications: Unspecified Schizophrenia

JAUSA15347(1)

USA health
professional

65yr M 13 day(s) at onset

Recovered
Not Serious

Diabetes Mellitus Aggravated (10-NOV-1994)

Causality Per Reporter: possible

tablet 3 mg - 3mg (28-OCT-1994 / Unknown)

Event Description: DIABETIC PATIENT ON RISPERIDONE 6 MG DAILY EXPERIENCED AN INCREASE IN BLOOD GLUCOSE (NOS). THE DOSE OF INSULIN WAS INCREASED AND THE PATIENT RECOVERED.

Causality Per Company: doubtful

Indications: Unspecified Schizophrenia

JADA15517(1)

USA patient/consent 31yr M 5 week(s) at onset

No Change/Not Yet
Subsided
Not Serious

Accommodation Abnormal (05-DEC-1994)
Blood Sugar Increased (05-DEC-1994)
Appetite Increased (24-NOV-1994)

Volume 15/Page 101

Confidential/Produced in Litigation Pursuant to Protective Order

JJRP 00384089

D821.103

R. 6267

tablet 2 mg - 2mg (31-OCT-1994 / Unknown)

Ref.no.(vers.no.)	Qty	Prin. source	Age	Sex	Latency	Outcome Seriousness	Reaction	
								33

Formul Strength-Unit dose (Therapy start date/end date)

CAUSALITY PER COMPANY: POSSIBLE

Event Description: CONSUMER REPORTS HIS NON DIABETIC SON, ON RISPERIDONE 4 MG DAILY, IS EXPERIENCING ABNORMAL VISUAL ACCOMODATION. THE PATIENT'S BLOOD SUGAR HAS INCREASED (NOS) DUE TO NON-COMPLIANCE WITH DIET AND EXCESSIVE EATING. ADDITIONAL INFORMATION FROM PHYSICIAN DENIED.

Indications: Unspecified Schizophrenia

CAUSALITY PER REPORTER: POSSIBLE

JANUS15530(1)	USA health professional	67yr F	4 day(s) at onset	Recovered Not Serious	Diabetes Mellitus Aggravated (05-DEC-1994) Vertigo (05-DEC-1994)

tablet 3 mg - 3mg (01-DEC-1994 / 07-DEC-1994)

Event Description: DIABETIC PATIENT ON RISPERIDONE 8 MU DAILY EXPERIENCED VERTIGO. THE PATIENT ALSO PRESENTED WITH A FASTING BLOOD SUGAR OF 400 MG/DL. RISPERIDONE WAS DISCONTINUED AND BOTH THE VERTIGO AND THE HYPERGLYCAEMIA RESOLVED. PHYSICIAN FEELS THE PATIENT'S NON-COMPLIANCE WITH HER DIET CONTRIBUTED TO THESE EVENTS.

CAUSALITY PER REPORTER: POSSIBLE

CAUSALITY PER COMPANY: DOUBTFUL

Indications: Unspecified Schizophrenia

Concomitant Diseases: Diabetes Mellitus Without Mention Of Complication

CAUSALITY PER REPORTER: PROBABLE

JANUS15399(3)	USA regulatory authority	49yr F	14 day(s) at onset	Recovered Serious	Ketoacidosis (01-JUN-1994) Diabetes Mellitus Aggravated (01-JUN-1994) Hallucination (01-JUN-1994) Tachycardia (01-JUN-1994)

tablet 1 mg - 1mg (18-MAY-1994 / 07-JUN-1994)

Event Description: FDA MEDWATCH REPORT:

TWO WEEKS AFTER BEGINNING RISPERIDONE, PATIENT WITH NON-INSULIN DEPENDENT DIABETES MELLITUS WAS HOSPITALIZED FOR DIABETIC KETOACIDOSIS. ADMISSION LABS: GLUCOSE WAS 498. SODIUM WAS 128 AND HEART RATE WAS 122. SHE ALSO PRESENTED WITH HALLUCINATIONS WHICH THE REPORTER STATES MAY BE DUE TO THE PATIENT'S BIPOLAR AFFECTIVE DISORDER. RISPERIDONE WAS DISCONTINUED. IV THERAPY WITH NORMAL SALINE, BICARBONATE AND INSULIN WAS ADMINISTERED AND THE PATIENT RECOVERED, HOWEVER, SHE NOW REQUIRES DAILY INSULIN THERAPY.

F O L L O W - U P 13-JAN-95:

REPORTER STATES THAT PRIOR TO THE EVENT, THE PATIENT WAS WELL-CONTROLLED ON GLIBENCLAMIDE BUT OUTPATIENT FASTING BLOOD SUGARS ARE NOT AVAILABLE. DURING HOSPITALIZATION, SERUM GLUCOSE LEVELS RANGED FROM 368 TO 498. RISPERIDONE WAS DISCONTINUED ON 07-JUN-94. POST-RISPERIDONE GLUCOSE VALUES ARE NOT AVAILABLE. PATIENT'S PHYSICIAN FEELS RISPERIDONE

CAUSALITY PER REPORTER: PROBABLE

CAUSALITY PER COMPANY: DOUBTFUL

Indications: Bipolar Disorder; Unspecified Psychosis

Concomitant Diseases: Obesity

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Volume 15/Page 102

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JJP 00384090
D821.104

R. 6268

Ref.no.(vers.no.)	Cty	Pris. source	Age	Sex	Latency	Outcome Seriousness	Reaction	34

Formul Strength-Unit dose (Therapy start date/end date)

CONTRIBUTED TO HER LOSS OF DIABETIC CONTROL. GLIBENCLAMIDE WAS DISCONTINUED ON 02-JUN-94
AND INSULIN THERAPY WAS INSTITUTED ON 01-JUN-94.

JAUSA18114(1)	USA health professional	56yr F	0 day(s) at onset	Recovered Serious	Coma (21-JAN-1995) Suicide Attempt (21-JAN-1995) Overdose Effect (21-JAN-1995) Hyponatremia (21-JAN-1995) Diabetes Mellitus Aggravated (21-JAN-1995)
tablet - - - (18-APR-1994 / 20-JAN-1995)					
tablet 3 mg - 180mg (21-JAN-1995 / 21-JAN-1995)					

Event Description: PATIENT TAKING RISPERIDONE FOR APPROXIMATELY NINE MONTHS WAS FOUND 21-JAN-95, COMATOSE WITH SPONTANEOUS RESPIRATIONS AND A PULSE. A FAMILY MEMBER ESTIMATED THE PATIENT HAD INGESTED APPROXIMATELY SIXTY-3 MG TABLETS OF RISPERIDONE IN A SUICIDE ATTEMPT. SHE HAS A HISTORY OF PRIOR ATTEMPTS. PATIENT RECEIVED CHARCOAL AND GASTRIC LAVAGE. AN ECG WAS NORMAL WITHOUT ARRHYTHMIAS OR QT PROLONGATION. CHEM SCREEN ABNORMALITIES INCLUDED A SODIUM OF 129 AND GLUCOSE 400. PATIENT WAS NON-KETOTIC. SHE IS A NON-INSULIN DEPENDENT DIABETIC AND TAKES GLIBENCLAMIDE. AN IV DRIP OF INSULIN WAS STARTED THEN CHANGED TO THE SUBCUTANEOUS ROUTE. THE PATIENT RECOVERED AND THE PHYSICIAN DOES NOT FEEL THE INSULIN WILL BE NEEDED LONG-TERM.

Causality Per Reporter: possible

Causality Per Company: possible

Company Remarks: REPORTEDLY THE COMA SEEMED TO BE CAUSED BY THE HYPERGLYCAEMIA.

JAUSA18398(1)	USA health professional	55yr M	No Change/Not Yet Subsided Not Serious	Blood Sugar Increased (Unknown) Polyuria (Unknown) Thirst Excessive (Unknown) Fecal Incontinence (Unknown) Urine Incontinence (Unknown)
tablet 3 mg - 3mg (18-SEP-1994 / Unknown)				

Event Description: PATIENT ON RISPERIDONE 6 MG DAILY AND POLYPHARMACY EXPERIENCED AN INCREASE IN BLOOD GLUCOSE (HbG). THE PATIENT IS ALSO EXPERIENCING POLYURIA, POLYDIPSIA, URINARY AND FECAL INCONTINENCE. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

Causality Per Reporter: possible

Causality Per Company: doubtful

Indications: Schizo-Affective Type Schizophrenia

JAUSA18483(3)	USA health professional	68yr M	1 day(s) at onset	Death Serious	Neuroleptic Malignant Syndrome (21-FEB-1995) Renal Failure Acute (21-FEB-1995) Hypoglycemia (17-FEB-1995) Cardiac Arrest (21-FEB-1995)
tablet 1 mg - 1mg (16-FEB-1995 / 17-FEB-1995)					

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Volume 15/Page 103

JRP 00384091
D821.105
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R. 6269

Ref.no.(varn.no.) Cty Priu. source Age Sex Latency Outcome Reaction 35
Seriousness

Formul Strength Unit dose (Therapy start date/end date)

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Event Description: PATIENT BEGAN RISPERIDONE (1 MG BID) AND WAS HOSPITALIZED THE FOLLOWING DAY WITH A DIAGNOSIS OF NMS. PEAK CPK VALUE WAS REPORTED AS 78,000. PATIENT REQUIRED DIALYSIS AFTER DEVELOPING ACUTE RENAL FAILURE ASSOCIATED WITH MYOGLOBINURIA. HE DIED THE FOLLOWING MORNING. PATIENT HAS A HISTORY OF NMS ASSOCIATED WITH HALOPERIDOL TWO TO THREE YEARS AGO. PRIOR TO RISPERIDONE, HE HAD NOT RECEIVED A NEUROLEPTIC FOR "QUITE SOME TIME." ADDITIONAL INFORMATION HAS BEEN REQUESTED FROM THE ATTENDING PHYSICIAN.
F O L L O W - O P (25-FEB-95):
PATIENT WITH MENTAL RETARDATION STARTED RISPERIDONE 16-FEB-95 AT 1 MG BID AND RECEIVED ONLY THREE DOSES. HE WAS HOSPITALIZED THE FOLLOWING DAY (17-FEB-95) FOR INCREASED AGITATION AND "UNMANAGEABILITY." HE THEN DEVELOPED A FEVER, TACHYCARDIA, TACHYPNOEA, HYPOTENSION "BECAME ILL" AND WAS TRANSFERRED TO ANOTHER HOSPITAL. INITIAL IMPRESSION WAS PNEUMONIA BUT CHANGED TO NMS AFTER DISCOVERY OF ELEVATED CPK AND PRESENCE OF MYOGLOBIN IN THE URINE. ADDITIONAL ABNORMAL LABS INCLUDED ELEVATED LIVER FUNCTION TESTS: ELEVATED BUN, CREATININE, PHOSPHORUS AND URIC ACID. CPK PEAKED AT 78,250 ON 18-FEB. THE NB FRACTION WAS ELEVATED BUT REMAINED LESS THAN 5.6% OF THE TOTAL CPK. IV FIBROSEIDE (40 MG) AND IV MANNITOL (25 G) WERE GIVEN. THERE WAS NO RESPONSE TO DIURETIC MEDICATIONS AND PATIENT BECAME OLIGURIC. OXYGEN WAS ADMINISTERED BY MASK. CPK DECREASED TO 12,980 ON 19-FEB AND 12,020 ON 20-FEB. BLOOD CULTURES DRAWN ON 17-FEB SHOWED NO GROWTH AFTER FIVE DAYS. IV FLUIDS WERE DECREASED TO 20 ML/HR ON 20-FEB BECAUSE OF THE DEVELOPMENT OF ANURIA. A CENTRAL VENOUS LINE WAS INSERTED FOR DIALYSIS. PATIENT DEVELOPED A PNEUMOTHORAX AND HEMOTHORAX. A CHEST TUBE WAS INSERTED BUT HAD COMPLICATIONS FROM THE PROCEDURE WITH SIGNIFICANT BLEEDING FROM THE SITE. HAEMOGLOBIN AND HAEMATOCRIT DECREASED (14.4/44.7 TO 10.8/31.8); TWO UNITS OF BLOOD WERE REQUIRED TO REPLACE BLOOD LOSS FROM THE CHEST TUBE SITE. HAEMODIALYSIS WAS CARRIED OUT FOR APPROXIMATELY ONE AND ONE-HALF HOURS ON 20-FEB BUT ADEQUATE FLUID COULD NOT BE REMOVED DUE TO LOW BP. NO FURTHER ATTEMPTS AT DIALYSIS WERE MADE AS PER THE FAMILY'S WISHES. PATIENT CONTINUED TO BE ANURIC. HE THEN DEVELOPED BRADYCARDIA AND SIGNIFICANT HYPOTENSION. AT 0624 ON 21-FEB HE WENT INTO CARDIOPULMONARY ARREST AND DIED. AN AUTOPSY WAS NOT PERFORMED. CAUSE OF DEATH IS STATED TO BE RENAL FAILURE SECONDARY TO MYOGLOBINURIA SECONDARY TO NMS.

Apnoea (21-FEB-1995)
Bradycardia (21-FEB-1995)
Hypotension (21-FEB-1995)
Liver Function Tests Abnormal Nos (17-FEB-1995)
Acidosis Metabolic (17-FEB-1995)
Tachypnoea (17-FEB-1995)
Agitation (17-FEB-1995)
Condition Aggravated (17-FEB-1995)
Anuria (20-FEB-1995)
Haemoglobin Decreased (20-FEB-1995)

Causality Per Reporter: possible

Causality Per Company: probable

Indications: Unspecified Schizophrenia

Concomitant Diseases: Oligophrenia; Agitation

Company Remarks: ALTHOUGH NMS WAS REPORTED BY THE REPORTER, THE DIAGNOSTIC CRITERIA ARE NOT MET IN THE DESCRIPTION.

JAUSA16853(1) USA health 16yr F 2 day(s) at onset Recovered
professional Not Serious
tablet 1 mg - 1mg (18-FEB-1995 / 20-FEB-1995)
tablet 1 mg - .5mg (21-FEB-1995 / Unknown)

Hypoglycaemia (20-FEB-1995)
Light-Headed Feeling (18-FEB-1995)
Headache (18-FEB-1995)
Nausea (18-FEB-1995)

Event Description: PATIENT, HOSPITALIZED TO INITIATE ANTIPSYCHOTIC THERAPY, STARTED RISPERIDONE 1 MG DAILY ON 18-FEB-95. THE PATIENT EXPERIENCED NAUSEA, HEADACHE AND A LIGHT-HEADED FEELING. NOW FASTING BLOOD SUGAR PERFORMED ON 20-FEB-95 WAS 21 MG/DL (PATIENT BASELINE 108 MG/DL). THE PATIENT WAS GIVEN ORANGE JUICE WITH SUGAR IN IT AND THE BLOOD SUGAR ONE HOUR LATER WAS 61 MG/DL. THE PATIENT WAS GIVEN ORANGE JUICE, SUGAR, AND SMALL AMOUNTS OF FOOD EVERY TWO HOURS THROUGHOUT THE DAY AND NOW FASTING BLOOD SUGAR PERFORMED THE NEXT MORNING WAS 90 MG/DL. A CONSULTATION WITH THE ENDOCRINOLOGIST ON 21-

Causality Per Reporter: possible

Causality Per Company: possible

Indications: Depressive Disorder, Not Elsewhere Classified; Unspecified Psychosis

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Volume 15/Page 104

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JJRP 00384092

R. 6270

Ref.no. (vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction

Formul Strength-Unit dose (Therapy start date/end date)
FEB-95 CONCLUDED THE DOSE OF RISPERIDONE SHOULD BE DECREASED TO 0.5 MG DAILY. THE PATIENT CONTINUES ON RISPERIDONE 0.5 MG DAILY AND HYPOGLYCEMIC DIET AND NO FURTHER EPISODES OF HYPOGLYCEMIA HAVE OCCURRED. HOSPITALIZATION WAS NOT PROLONGED BY THIS EPISODE OF HYPOGLYCEMIA.

JANSA16856(3)	USA health professional	40yr M	No Change/Not Yet Subsidized	Diabetes Mellitus (31-DEC-1994)
				Causality Per Reporter: doubtful
tablet - - 6mg (Unknown / 31-DEC-1994)				
tablet - - 4mg (01-JAN-1995 / Unknown)				Causality Per Company: doubtful

Indications: Unspecified Schizophrenia
Event Description: PATIENT ON RISPERIDONE 0.5 MG DAILY DEVELOPED DIABETES MELLITUS. GLIPIZIDE WAS ADDED TO THE THERAPY AND THE BLOOD GLUCOSE DECREASED FROM 500 MG/DL TO 168 MG/DL. THE DOSE OF RISPERIDONE WAS DECREASED TO 4 MG/DAILY AND PATIENT WILL BE SEEN BY AN ENDOCRINOLOGIST. ADDITIONAL INFORMATION HAS BEEN REQUESTED.
F O L L O W - U P 15-MAY-95:
PHYSICIAN PROVIDES MINIMAL INFORMATION IN FOLLOW-UP, INDICATING "THIS PROVED A FALSE ALARM. MY PATIENT'S DIABETES IS CERTAINLY BASED ON HIS GENES AS IT IS FAMILIAL."

JANSA16748(6)	USA health professional	35yr M	8 day(s) at onset	No Change/Not Yet Subsidized Serious	Ketoacidosis (14-MAR-1995) Diabetes Mellitus (14-MAR-1995) Leukocytosis (14-MAR-1995) Amylase Increased (19-MAR-1995) Tachycardia (19-MAR-1995) Palpitation (19-MAR-1995) Tachypnea (19-MAR-1995) Nausea (06-MAR-1995)
tablet 1 mg - 1mg (06-MAR-1995 / 07-MAR-1995)					
tablet 1 mg - 1mg (08-MAR-1995 / 09-MAR-1995)					
tablet - - 3mg (10-MAR-1995 / 18-MAR-1995)					
Event Description: THIS 35-YEAR-OLD MALE PSYCHIATRIC INPATIENT PRESENTED WITH NAUSEA AND VOMITING ON 14-MAR-95, EIGHT DAYS AFTER BEGINNING RISPERIDONE. HE WAS TITRATED TO 3 MG DAILY OVER THREE DAYS. AN UNSPECIFIED ANTIEMETIC WAS PRESCRIBED WITHOUT SUCCESS. HE WAS TRANSFERRED TO AN ACUTE CARE HOSPITAL ON 19-MAR-95 WITH CONFUSION, NAUSEA, VOMITING, TACHYCARDIA, PALPITATIONS AND TACHYPNEA. ABNORMAL LAB VALUES INCLUDED AMYLASE 877, GLUCOSE 1009 AND WBC 22,000. A DIAGNOSIS OF PANCREATITIS WAS MADE AND RISPERIDONE WAS DISCONTINUED. PATIENT WAS TREATED WITH IV HYDRATION AND IV INSULIN. HE REMAINS IN THE ICU. RISK FACTORS FOR PANCREATITIS INCLUDE A HISTORY OF DRUG ABUSE (HEROIN, PCP, COCAINE AND METHAMPHETAMINE). HISTORY OF ALCOHOL ABUSE IS UNKNOWN. PATIENT IS A RESIDENT IN A PRISON FOR THE CRIMINALLY INSANE; REPORTER STATES PATIENT HAS NOT TO HER KNOWLEDGE HAD ACCESS TO ILLEGAL DRUGS OR ALCOHOL. REPORTER FEELS THE PANCREATITIS IS SECONDARY TO RISPERIDONE TREATMENT. ADDITIONAL INFORMATION INCLUDING MORE EXTENSIVE PATIENT HISTORY AND					
				Causality Per Reporter: doubtful	
				Causality Per Company: possible	
				Indications: Unspecified Schizophrenia; Unspecified Psychosis	
				Concomitant Diseases: Obesity	

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Volume 15/Page 105

Confidential/Produced in Litigation Pursuant to Protective Order
JJRP 00384093
D821.107

R. 6271

Ref.no. (vers.no.) Ctry Prim. source Age Sex Latency Outcome Reaction
 Seriousness

Formul Strength Unit dose (Therapy start date/end date)
 DISCHARGE SUMMARY HAVE BEEN REQUESTED.

FOI LOW - U P 25-APR-95:
 HOSPITAL PHARM.D. REPORTS PATIENT WAS DIAGNOSED AND TREATED FOR DIABETIC KETOACIDOSIS, NOT PANCREATITIS AS MENTIONED IN THE INITIAL REPORT. HE HAS NO HISTORY OF DIABETES; A RANDOM SERUM GLUCOSE FROM 26-SEP-84 WAS 60. HOWEVER, HE HAD GAINED 30 POUNDS FROM SEP-84 TO MAR-85. THERE IS NO FAMILY HISTORY OF DIABETES. PATIENT BEGAN VOMITING ON 17-MAR AND REPORTED FEELING NAUSEOUS SINCE BEGINNING RISPERIDONE ON 08-MAR. ABNORMAL ADMISSION LABS FROM 10-MAR-85 INCLUDE GLUCOSE 1004, CO2 11, BUN 23, AND CREATININE 1.8. PATIENT WAS TRANSFERRED TO THE ICU AND HEPAT LAB WORK AFTER INSULIN REVEALED GLUCOSE 740, SODIUM 154 AND BICARBONATE 8.1. PATIENT WAS RETURNED TO THE STATE HOSPITAL ON 23-MAR ON AN INSULIN REGIMEN AND DIABETIC DIET. DOXEPIN (50 MG HS) WAS ADDED FOR PRE-EXISTING INSOMNIA. CURRENT INSULIN REQUIREMENT INCLUDES NPH (40 UNITS) AND REGULAR (20 UNITS) IN THE AM AND NPH (20 UNITS) IN THE PM. RECENT SERUM GLUCOSE LEVELS ON 04-APR-85 AND 18-APR-85 WERE 152 AND 131 RESPECTIVELY. REPORTER STATES HOUSE STAFF PHYSICIAN AT THIS STATE HOSPITAL ARE CONCERNED ABOUT PATIENTS SEQUESTERING CANDY AND HIGH CALORIC FOOD ITEMS IN THEIR BED AREAS WHICH ARE NOT CONTROLLED BY STAFF. THEY ALSO FELT THAT RISPERIDONE WAS NOT A CAUSALLY RELATED AGENT TO THE DIABETIC KETOACIDOSIS.

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JAUSA1685(1) USA patient/consum 28yr M 14 day(s) at onset Recovered Diabetes Mellitus (15-MAR-1995)
 or Not Serious Weight Increase (15-APR-1994)

tablet 3 mg - 3mg (15-APR-1994 / 01-DEC-1994)
 tablet 3 mg - 3mg (01-MAR-1995 / Unknown) Causality Per Company: possible

Indications: Unspecified Schizophrenia

Event Description: PATIENT ON RISPERIDONE 6 MG DAILY FOR EIGHT MONTHS GAINED 50 POUNDS. RISPERIDONE WAS DISCONTINUED AND CLOZAPINE WAS INITIATED. PATIENT STOPPED GAINING WEIGHT AFTER RISPERIDONE WAS DISCONTINUED. THE PATIENT WAS ON CLOZAPINE FOR THREE MONTHS BUT DID NOT LIKE THE BLOOD TESTS AND REQUESTED TO GO BACK ON RISPERIDONE. PATIENT WAS RESTARTED ON RISPERIDONE THE DAY AFTER CLOZAPINE WAS DISCONTINUED AND TWO WEEKS LATER THE PATIENT WAS DIAGNOSED WITH DIABETES (BLOOD SUGAR 450 MG/DL). THE PATIENT WAS TREATED WITH NPH AND REGULAR INSULIN AND BLOOD SUGAR DECREASED TO 189 MG/DL. PATIENT CONTINUES ON RISPERIDONE 6 MG DAILY AND THE DIABETES IS BEING CONTROLLED WITH INSULIN. REQUEST FOR ADDITIONAL INFORMATION FROM PHYSICIAN DENIED.

Company Remarks: NO DIRECT RELATION BETWEEN DRUG AND DIABETES MELLITUS IS SHOWN.

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JAUSA1685(1) USA patient/consum 26yr M 12 month(s) at onset Unknown Diabetes Mellitus (10-MAR-1995)
 or Serious

tablet . . . (15-MAR-1994 / Unknown) Dyspnea (18-MAR-1995)
 Tachypnea (16-MAR-1995)
 Vomiting (15-MAR-1995)
 Nausea (16-MAR-1995)
 Thirst (18-MAR-1995)

Event Description: CONSUMER REPORTS HER BROTHER WAS ADMITTED ON 10-MAR-95 WITH DYSPNEA,

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Volume 15/Page 106

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JJRP 00384094

D821.108

R. 6272

Ref.no.(vers.no.) Cty Prim. source Age Sex Latency Outcome Seriousness Reaction 38

Formul Strength-Unit dose (Therapy start date/end date)

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TACHYPNEA, POLYDIPSIA, NAUSEA AND VOMITING. HE HAD BEEN TAKING RISPERIDONE FOR APPROXIMATELY ONE YEAR. A SERUM GLUCOSE WAS REPORTED AS ELEVATED (VALUE UNSPECIFIED). PATIENT WAS DIAGNOSED WITH DIABETES AND TREATED WITH INSULIN IN THE ICU. HE HAS NO HISTORY OF DIABETES. ADDITIONAL INFORMATION HAS BEEN REQUESTED FROM THE REPORTER. PHYSICIAN CONTACT DENIED.

Causality Per Reporter: possible

Causality Per Company: possible

Indications: Unspecified Schizophrenia

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JAUSA16888(1) USA health professional

F

No Change/Not Yet Subsidized
Not Serious

Hyperglycemia (Unknown)
Galactorrhea (Unknown)
Breast Enlargement (Unknown)

tablet - - -

Causality Per Reporter: possible

Event Description: PATIENT IS EXPERIENCING GALACTORRHEA, BREAST ENLARGEMENT AND HYPERGLYCEMIA WHILE TAKING RISPERIDONE. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

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JAUSA17311(1) USA health professional

34yr F 0 week(s) at onset

Recovered
Not Serious

Hyperglycemia (01-APR-1995)

Causality Per Reporter: probable

tablet - - 4mg (14-FEB-1995 / Unknown)

Causality Per Company: possible

Event Description: PATIENT ON RISPERIDONE 4 MG DAILY EXPERIENCED HYPERGLYCEMIA 6 WEEKS AFTER STARTING RISPERIDONE THERAPY. PATIENT HAS NO FAMILY HISTORY OF DIABETES. THE PATIENT'S BLOOD SUGAR WAS NORMAL (NGS) WHILE HOSPITALIZED TO INITIATE RISPERIDONE. PATIENT RETURNED IN 6 WEEKS FOR FOLLOW-UP VISIT AND HER BLOOD SUGAR WAS 600 MG/DL. PATIENT IS BEING TREATED WITH INSULIN AND HER BLOOD SUGAR HAS RETURNED TO NORMAL. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

Indications: Schizo-Affective Type Schizophrenia

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JAUSA17334(1) USA health professional

M

No Change/Not Yet Subsidized
Not Serious

Blood Sugar Decreased (Unknown)

Causality Per Reporter: possible

tablet - - -

Causality Per Company: possible

Idexbaeck 18JUN00

Volume 15/Page 107

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JJRP 00384095
D821.109

R. 6273

Ref.no.(vers.no.)	Ctry	Prim. source	Age	Sex	Latency	Outcome	Reaction
						Seriousness	

Formul Strength-Unit dose (Therapy start date/end date)

Event Description: A PHYSICIAN REPORTS THAT HER PATIENT HAS EXPERIENCED PROGRESSIVELY DECREASED BLOOD SUGARS SINCE BEGINNING RISPERIDONE THERAPY ABOUT ONE MONTH AGO (VALUES NOT CURRENTLY AVAILABLE). ADDITIONAL INFORMATION HAS BEEN REQUESTED.

Indications: Unspecified Schizophrenia

JAUSA17388(1)	USA health professional	40yr M	9 month(s) at onset	Death	Serious	Enbolism Pulmonary (02-MAY-1995) Ketoacidosis (01-MAY-1995) Diabetes Mellitus (Unknown) Appetite Decreased (27-APR-1995) Thirst Excessive (17-APR-1995) Polyuria (28-APR-1995) Urinary Incontinence (01-MAY-1995)

tablet . . . (01-MAR-1994 / 01-AUG-1994)

tablet 3 mg - 3mg (02-AUG-1994 / Unknown)

Event Description: SECOND OF TWO PATIENTS. A FORTY-YEAR-OLD AFRICAN-AMERICAN MALE RESIDING IN A GROUP HOME WAS ADMITTED TO THE ICU ON 01-MAY-95 IN DIABETIC KETOACIDOSIS (DKA). HE WAS CONSCIOUS AND VOMITING. PATIENT HAD STARTED RISPERIDONE ON 01-MAR-94 AND HAD BEEN TAKING 6 MG DAILY SINCE 02-AUG-94. HIS DIET IS REPORTED TO HAVE BEEN WELL BALANCED WITH A DECREASE IN APPETITE FOUR DAYS PRIOR TO ADMISSION (PTA). THERE HAD BEEN NO RECENT CHANGES IN WEIGHT OR VISION. PATIENT HAD NO KNOWN HISTORY OF DIABETES BUT HAD COMPLAINED OF INCREASED THIRST TWO WEEKS PTA WITH POLYURIA THREE DAYS PTA. HE WAS INCONTINENT OF URINE ON ADMISSION. THERE IS NO KNOWN FAMILY HISTORY OF DM. RANDOM SERUM GLUCOSE LEVELS FROM THE PRECEDING YEAR RANGED FROM 100 TO 120. A RANDOM GLUCOSE ON 27-FEB-95 WAS 110. ABNORMAL LABS ON ADMISSION INCLUDED SERUM GLUCOSE 1489, BICARBONATE 0, HEMOGLOBIN A1C 13.1, CREATININE 3.4, BUN 55, URINE KETONES 15 MG/DL (SEVERAL HOURS AFTER ADMISSION; AFTER ONE LITER OF URINARY OUTPUT). TOTAL CHOLESTEROL 358, CGT 90 (PRE-EXISTING), MAGNESIUM 2.5, CALCIUM 10.5 AND PHOSPHORUS 1.3. THE ELEVATED CREATININE IS THOUGHT TO BE FALSELY ELEVATED IN PART TO THE INTERFERENCE OF KETONES AND PRESENCE OF DERYORATION. THE ELEVATED CHOLESTEROL IS ATTRIBUTED IN PART TO THE DKA. A BASELINE CHOLESTEROL IS NOT AVAILABLE FOR COMPARISON. BASELINE RENAL FUNCTION IS REPORTED TO HAVE BEEN WITHIN NORMAL LIMITS. ABC SHOWED PH 7.17, PCO2 18, PO2 98, BICARBONATE 8.7 AND O2 SATURATION 90%. A DRUG SCREEN AND EKG WERE NEGATIVE. URINE AND BLOOD CULTURES SHOWED NO GROWTH. PATIENT RECEIVED BETWEEN 1-2 LITERS OF FLUID IN THE ER AND 4.5 ADDITIONAL LITERS IN THE ICU. TREATMENT ALSO INCLUDED IV INSULIN (20 UNITS NORMAL AND 8 UNITS REGULAR IN THE AM; 8 UNITS NORMAL AND 6 UNITS REGULAR IN THE PM), MAGNESIUM AND PO SKIN WALK TO REPLISH SERUM PHOSPHORUS. THE FOLLOWING DAY (02-MAY) PATIENT'S CONDITION HAD IMPROVED. HE WAS AMBULATORY AND ALERT AND ORIENTED TO TIME, PLACE AND PERSON. HE WAS TRANSFERRED OUT OF ICU TO A MEDICAL UNIT AND PLACED IN BED. FIVE TO TEN MINUTES LATER PATIENT WAS FOUND ASYSTOLIC WITH FIXED AND DILATED PUPILS. RESUSCITATION EFFORTS WERE UNSUCCESSFUL AND PATIENT WAS PRONOUNCED DEAD. AN AUTOPSY WAS NOT PERFORMED. THE CAUSE OF DEATH LISTED ON THE DEATH CERTIFICATE IS PULMONARY THROMBO-EMBOLUS. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

Causality For Reporter: possible

Causality For Company: possible

Indications: Unspecified Schizophrenia

Concomitant Diseases:

JAUSA17400(1)	USA health professional	28yr M		Recovered	Serious	Ketoacidosis (18-MAR-1996) Diabetes Mellitus (18-MAR-1996)

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Volume 15/Page 108

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JRP 00384096

D821.110

R. 6274

Ref.no.(vers.no.) Cty Prim. source Age Sex Latency Outcomes Reaction 40
 Seriousness
 Formul Strength-Unit dose (Therapy start date/end date)
 tablet 3 mg - 2mg
 Event Description: FIRST OF TWO PATIENTS. TWENTY-EIGHT YEAR-OLD MALE WITHOUT KNOWN HISTORY OF DIABETES, PRESENTED TO THE EMERGENCY ROOM ON 16-MAR-95 IN DIABETIC KETOACIDOSIS (DKA). THERE IS NO FAMILY HISTORY OF DIABETES. PATIENT HAD COMPLAINED OF FEELING WEAK AND TIRED FOR A FEW DAYS PRIOR TO ADMISSION. SERUM GLUCOSE ON ADMISSION WAS 475 WITH A SERUM BICARBONATE OF 6 MEQ/L. PATIENT WAS TREATED WITH IV FLUIDS AND INSULIN. HE RECOVERED AND WAS DISCHARGED ON 21-MAR. ADDITIONAL INFORMATION REGARDING RISPERIDONE THERAPY DATES AS WELL AS PAST MEDICAL HISTORY AND DISCHARGE SUMMARY HAVE BEEN REQUESTED.
 Fatigue (27-MAR-1995)
 Weakness Generalized (13-MAR-1995)
 Causality Per Reporter: possible
 Causality Per Company: possible
 Indications: Unspecified Schizophrenia

JANS17530(3) USA health 31yr F 8 week(s) at onset No Change/Not Yet Subsidized Serious
 professional
 tablet - - 3mg (15-MAR-1995 / Unknown)
 Event Description: NEWLY DIAGNOSED PATIENT (PSYCHOSIS AND DEPRESSION) WAS PLACED ON RISPERIDONE WITH CONCOMITANT LITHIUM AND BENZOTROPINE IN APRIL 1995. THE BEGINNING OF MAY 1995 THE PATIENT IS REPORTED TO HAVE DEVELOPED POLYDIPSIA, POLYURIA AND BLURRED VISION. SYMPTOMS PERSISTED AND ON 15-MAY-95 THE PATIENT WAS ADMIITTED TO THE HOSPITAL WITH "STABLE" NONKETOTIC HYPERGLYCEMIC-HYPEROSMOLAR COMA. BLOOD GLUCOSE ON ADMISSION WAS 875. PATIENT WAS TREATED WITH IV FLUIDS AND SLIDING SCALE INSULIN THERAPY FOR A FEW DAYS, THEN PLACED ON ORAL GLIBENCLAMIDE THERAPY. DISCHARGE EXPECTED ON 17-MAY-95. PATIENT'S BLOOD GLUCOSE LEVELS ARE CONTROLLED, OTHER SYMPTOMS REPORTEDLY RESOLVED. DIAGNOSIS BY ENDOCRINOLOGICAL WORK-UP IS NEW ONSET DIABETES MELLITUS, RISPERIDONE CONTINUES, LITHIUM WAS DISCONTINUED ON ADMISSION AND IS THE SUSPECTED CAUSATIVE AGENT. PATIENT ALSO HAS A FAMILY HISTORY OF TYPE II DIABETES MELLITUS. ADDITIONAL INFORMATION INCLUDING ENDOCRINE CONSULTATION REPORT HAS BEEN REQUESTED.
 F O L L O W U P (JUN95): ON 19-MAY-95 FOLLOW-UP GLUCOSE WAS 484 AND THE DOSE OF GLIBENCLAMIDE HAS INCREASED TO 6 MG/DAY. ON 20-MAY-95 GLUCOSE WAS 484 AND GLIBENCLAMIDE WAS INCREASED TO 10 MG/DAY. ADDITIONAL INFORMATION INDICATES PATIENT WAS RESTARTED AS AN OUTPATIENT ON RISPERIDONE (DATE NOS).
 Coma Diabetic (15-MAY-1995)
 Plasma Osmolality Increased (15-MAY-1995)
 Polyuria (01-MAY-1995)
 Thirst Excessive (01-MAY-1995)
 Vision Blurred (01-MAY-1995)
 Diaphoresis (01-MAY-1995)
 Causality Per Reporter: doubtful
 Causality Per Company: possible
 Indications: Unspecified Psychosis
 Concomitant Diseases: Obesity

JANS17614(3) USA health 41yr M 12 day(s) at onset Recovered Serious
 professional
 tablet 1 mg - 1mg (11-MAY-1995 / 23-MAY-1995)
 Event Description: PATIENT, ON RISPERIDONE 6 MG DAILY FOR TWO WEEKS AND NO PREVIOUS
 Hyperglycemia (23-MAY-1995)
 Hypoxia (23-MAY-1995)
 Confusion (23-MAY-1995)
 Vision Blurred (23-MAY-1995)
 Polyuria (23-MAY-1995)
 Thirst Excessive (23-MAY-1995)

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Volume 15/Page 109

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 JJP 00384097
 D821.111

R. 6275

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	41
Formul Strength-Unit dose (Therapy start date/end date) ===== HISTORY OF DIABETES. PRESENTED TO THE HOSPITAL WITH CONFUSION, HYPERGLYCEMIA (GLUCOSE 543 mg/dL), BLURRED VISION, URINARY FREQUENCY AND EXCESSIVE THIRST. PATIENT WAS ADMITTED TO THE HOSPITAL, INSULIN WAS INITIATED, AND RISPERIDONE WAS DISCONTINUED. THE SERUM GLUCOSE IS INCREASING AND ALL OTHER SYMPTOMS HAVE RESOLVED. ADDITIONAL INFORMATION HAS BEEN REQUESTED. CAUSALITY PER REPORTER: possible ===== F O L L O W - U P 16-AUG-95: PHYSICIAN REPORTS PATIENT WAS ADMITTED TO THE HOSPITAL WITH A BLOOD SUGAR OF 425, POLYURIA, INCREASED THIRST, BLURRED VISION AND WEIGHT LOSS. CBC AND CHEM PROFILE WERE NORMAL. RENAL PROFILE WAS NORMAL. CHEST X-RAY WAS NORMAL. RESTING ECG WAS NORMAL. ARTERIAL BLOOD GASES FAILED TO DEMONSTRATE ACIDOSIS. PATIENT HAS HYPOXIC (UNSPECIFIED) THOUGHT TO BE SECONDARY TO HEAVY CIGARETTE SMOKING. THE PATIENT WAS REHYDRATED, RISPERIDONE WAS DISCONTINUED AND HUMULIN 10/30 20 UNITS DAILY WAS INITIATED. THE PATIENT WAS DISCHARGED WITH A BLOOD SUGAR OF 199. ON FOLLOW-UP EXAMINATION ONE WEEK AFTER HOSPITAL DISCHARGE THE PATIENT'S BLOOD SUGAR WAS 199. THE DOSE OF INSULIN WAS INCREASED TO .24 UNITS DAILY. ON HIS NEXT OFFICE VISIT THREE WEEKS LATER HIS BLOOD SUGAR WAS 182. ONE WEEK LATER A FASTING BLOOD SUGAR WAS PERFORMED AND WAS 104. PATIENT CONTINUES TO DO WELL. CAUSALITY PER COMPANY: possible Indications: Unspecified Schizophrenia Concomitant Diseases: Diaphragmatic Hernia Without Mention Of Obstruction Or Gangrene; Bipolar Affective Disorder, Mixed; Pharyngitis ===== JAUSA17744(3) USA health 42yr F 16 week(s) at onset No Change/Not Yet Subeided Not Serious Hyperglycaemia (07-APR-1995) Galactorrhoea (07-APR-1995) Cauality Per Reporter: possible tablet 1 mg - 1mg (15-DEC-1994 / Unknown) Event Description: NON-INSULIN DEPENDENT DIABETIC PATIENT EXPERIENCED HYPERGLYCEMIA (XOS) AFTER 2 MONTHS ON RISPERIDONE 2 MG DAILY WHICH RESOLVED WITHOUT INTERVENTION. PRESENTLY, THE PATIENT IS EXPERIENCING GALACTORRHOEA IN ONE BREAST UPON PALPATING. MAMMOGRAM WAS PERFORMED BUT RESULTS ARE NOT YET AVAILABLE. NO SERUM PROLACTIN LEVEL PERFORMED. ADDITIONAL INFORMATION HAS BEEN REQUESTED. F O L L O W - U P 03-AUG-96: NURSE REPORTS PROLACTIN LEVEL WAS PERFORMED BUT THE PROLACTIN LEVEL WAS NOT ELEVATED. Cauality Per Company: doubtful Indications: Schizo-Affective Type Schizophrenia Concomitant Diseases: Oligophrenia ===== JAUSA17767(1) USA health M 21 week(s) at onset Recovered Not Serious Diabetes Mellitus Aggravated (03-OCT-1994) Cauality Per Reporter: doubtful tablet . . . (06-MAY-1994 / Unknown) Event Description: FIRST OF FOUR PATIENTS. STABILIZED DIABETIC PATIENT WITH NORMAL SERUM GLUCOSE FOR 4 1/2 YEARS PRIOR TO STARTING RISPERIDONE, EXPERIENCED INCREASED BLOOD SUGAR (159 mg/dL) 6 MONTHS AFTER STARTING RISPERIDONE. REPORTER DOUBTS THIS WAS CAUSED BY RISPERIDONE. ADDITIONAL INFORMATION IS NOT EXPECTED. Cauality Per Company: doubtful Concomitant Diseases: Diabetes Mellitus Without Mention Of Complication								

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Volume 15/Page 110

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JRP 00384098
D821.112

R. 6276

Ref.no.(vers.no.) Cty Prim. source Age Sex Latency Outcome Reaction 42
Seriousness
Formul Strength-Unit dose (Therapy start date/end date)
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JAUSA17769(1) USA health N 3 month(s) at onset No Change/Not Yet Diabetes Mellitus Aggravated (Unknown)
professional Subsidized Weight Increase (Unknown)
Not Serious

tablet - - - Causality Per Reporter: doubtful

Event Description: SECOND OF FOUR PATIENTS. DIABETIC PATIENT EXPERIENCED INCREASED
GLUCOSE (HOS) 3 MONTHS AFTER STARTING RISPERIDONE THERAPY. FASTING BLOOD SUGAR WAS
PERFORMED AND WAS WITHIN NORMAL LIMITS. THE PATIENT HAS ALSO GAINED 100 LBS. IT IS
UNKNOWN HOW MUCH OF THIS WEIGHT GAIN OCCURRED AFTER STARTING RISPERIDONE. REPORTER
DOUBTS RISPERIDONE IS RESPONSIBLE FOR THESE EVENTS. ADDITIONAL INFORMATION IS NOT
EXPECTED. Causality Per Company: doubtful

Concomitant Diseases: Diabetes Mellitus Without Mention Of
Complication

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JAUSA17771(2) USA health M 21 week(s) at onset No Change/Not Yet Diabetes Mellitus Aggravated (24-DEC-1994)
professional Subsidized Weight Increase (01-APR-1994)
Not Serious

tablet 2 mg - 2mg (27-JUL-1994 / Unknown) Causality Per Reporter: not related

Event Description: THIRD OF FOUR PATIENTS. DIABETIC PATIENT ON RISPERIDONE 4 MG DAILY
EXPERIENCED INCREASED RANDOM GLUCOSE (123 MG/DL) ON 24-DEC-94 FIVE MONTHS AFTER STARTING
RISPERIDONE. ON 29-DEC-95 PRIOR TO STARTING RISPERIDONE BLOOD GLUCOSE WAS 82 MG/DL. THE
PATIENT ALSO GAINED 100 LBS. OVER THE LAST THIRTEEN MONTHS. A FASTING BLOOD SUGAR
PERFORMED ON 01-FEB-95 WAS 83 MG/DL WITHOUT ANY INTERVENTION. REPORTER DOES NOT BELIEVE
THESE EVENTS ARE RELATED TO RISPERIDONE. ADDITIONAL INFORMATION IS NOT EXPECTED. Causality Per Company: doubtful

Concomitant Diseases: Depressive Disorder, Not Elsewhere
Classified; Diabetes Mellitus Without Mention Of
Complication

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JAUSA17772(3) USA health M 1 day(s) at onset Recovered Diabetes Mellitus Aggravated (01-FEB-1995)
professional Serious

tablet - - - (31-JAN-1995 / Unknown) Causality Per Reporter: not related

Event Description: FOURTH OF FOUR PATIENTS. DIABETIC PATIENT ON RISPERIDONE AND
HALOPERIDOL THERAPY EXPERIENCED INCREASED BLOOD GLUCOSE (465 MG/DL) ONE DAY AFTER
STARTING RISPERIDONE. THE PATIENT WAS HOSPITALIZED TO START RISPERIDONE AND NO GLUCOSE
Causality Per Company: doubtful

Concomitant Diseases: Diabetes Mellitus Without Mention Of
Complication

1dbsack 18JUN90

Volume 15/Page 111

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JJRP 00384099
D821.113

R. 6277

Ref.no. (Para.no.)	City	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	43

Formal Strength-Unit dose (Therapy start date/end date)
 #####

TESTING WAS DONE ON ADMISSION. REPORTER BELIEVES THE HYPERGLYCEMIA WAS PROBABLY PRESENT PRIOR TO STARTING RISPERIDONE. THE PATIENT WAS TREATED WITH INSULIN AND BLOOD SUGAR WAS 138 MG/DL THREE WEEKS LATER. PATIENT'S BODY WEIGHT IS WITHIN NORMAL LIMITS. ADDITIONAL INFORMATION IS NOT EXPECTED.

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JANSA17975(6)	USA regulatory authority	78yr M	14 day(s) at onset	Recovered Serious	Unconsciousness (28-MAY-1995) Bradycardia (28-MAY-1995) Hyperglycemia (28-MAY-1995) Condition Aggravated (28-MAY-1995) Speech Disorder (28-MAY-1995) Blood Pressure Increased (28-MAY-1995)

tablet - - 1mg (23-MAY-1995 / 26-MAY-1995)

Event Description: FDA MEDWATCH REPORT: AFTER THREE DAYS OF RISPERIDONE, PATIENT WAS TRANSFERRED FROM THE NURSING HOME TO THE EMERGENCY ROOM WITH CHIEF COMPLAINT OF UNRESPONSIVENESS, BRADYCARDIA AND HYPERGLYCEMIA (NOT OTHERWISE SPECIFIED). PATIENT WAS ADMITTED TO THE HOSPITAL. INTERVENTIONS NOT SPECIFIED. RISPERIDONE WAS THE NEWEST ADDITION TO THE PATIENT'S POLYPHARMACY. REPORTER INDICATES REACTIONS ABATED AFTER RISPERIDONE WAS DISCONTINUED. ADDITIONAL INFORMATION HAS BEEN REQUESTED. INDICATION AND PRODUCT LOT NUMBER FOR RISPERIDONE ARE UNKNOWN.

CAUSALITY PER COMPANY: POSSIBLE

INDICATIONS: UNSPECIFIED PSYCHOSIS; AGITATION

FOLLOW-UP 13-FEB-96:

PHARMACIST REPORTS PATIENT HAD AN ADVERSE EPISODE AT THE NURSING HOME. PATIENT EXPERIENCED ALTERED MENTAL STATUS, BRADYCARDIA (54BPM), DIFFICULTY IN SPEAKING, AND BECAME UNRESPONSIVE. THE PATIENT'S BLOOD PRESSURE WAS 130/70 MMHG. THE PATIENT WAS TRANSFERRED TO THE EMERGENCY ROOM BUT HAD REMAINED CONSCIOUSNESS AND THE HEART RATE HAD STABILIZED (68BPM) WITH NO INTERVENTIONS. BY THE TIME HE ARRIVED AT THE HOSPITAL. IN THE EMERGENCY ROOM THE BLOOD PRESSURE WAS 168/98 MMHG, GLUCOSE WAS 136 MG/DL, CBC AND CHEM SCREEN WERE WITHIN NORMAL RANGE. DRUG SCREEN WAS NEGATIVE. THE PATIENT WAS ADMITTED TO THE HOSPITAL FOR EXACERBATION OF AGITATION. RISPERIDONE WAS DISCONTINUED AND THE PATIENT WAS TREATED WITH HALOPERIDOL 1MG DAILY. THE NEXT MORNING THE PATIENT WAS ALERT AND DISCHARGED BACK TO THE NURSING HOME. NO ADDITIONAL INFORMATION EXPECTED.

CONCOMITANT DISEASES: ALZHEIMER'S DISEASE; CAD; ARTHRITIS

COMPANY REMARKS: ALTHOUGH RISPERIDONE TABLETS CONTAIN MAIZE STARCH, THE POSSIBILITY OF ALLERGIC REACTION(S) IS NOT DENIABLE IN THIS CASE.

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JANSA18451(1)	USA health professional	33yr F	8 day(s) at onset	Recovered Serious	Hypoglycemia (24-JUL-1995) Dizziness (24-JUL-1995) Weakness Generalized (24-JUL-1995)

tablet - - 1mg (18-JUL-1995 / 24-JUL-1995)

Event Description: INSULIN-DEPENDENT DIABETIC HAD AN ORAL HYPOLYCEMIC AGENT (METFORMIN) ADDED TO HER THERAPY TWO WEEKS AGO AND HER BLOOD SUGAR WAS STABLE AT THAT TIME. ONE WEEK LATER RISPERIDONE 1 MG DAILY WAS STARTED AND AFTER ONE WEEK THE PATIENT PRESENTED AT THE EMERGENCY ROOM DIZZY AND WEAK. THE PATIENT WAS ADMITTED TO THE INTENSIVE CARE UNIT WITH A BLOOD GLUCOSE OF 43. CANNY, CEREAL AND JUICE WERE GIVEN TO THE PATIENT BUT THE BLOOD GLUCOSE ONLY INCREASED TO 63. SIX VIALS OF GLUCOSE 10% WERE NEEDED TO STABILIZE THE PATIENT. RISPERIDONE WAS DISCONTINUED. AFTER FURTHER INVESTIGATION, THE ENDOCRINOLOGIST REALIZED METFORMIN IS NOT INDICATED FOR INSULIN DEPENDENT DIABETES. METFORMIN WAS

CAUSALITY PER REPORTER: NOT RELATED

CAUSALITY PER COMPANY: POSSIBLE

INDICATIONS: UNSPECIFIED SCHIZOPHRENIA

COMPANY REMARKS: A DETERIORATION OF HYPOLYCAEMIA THAT IS

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Volume 15/ Page 112

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JJRP 00384100

D821.114

R. 6278

Ref.no.(verse.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	44
Formul Strength-Unit dose (Therapy start date/end date) DISCONTINUED AND THE INSULIN DOSE WAS ADJUSTED. THE ENDOCRINOLOGIST BELIEVES THE MORE DIFFICULT TO TREAT, IS KNOWN FROM THE COMBINED HYPOGLYCEMIA WAS DUE TO METFORMIN AND NOT RISPERIDONE. THE PSYCHIATRIST IS PLANNING TO METFORMIN TREATMENT; PROBABLY BY THE INDUCTION OF LACTIC RESTART RISPERIDONE. REQUEST FOR ADDITIONAL INFORMATION DECLINED. ACID ACIDOSIS.								
JAUSA19128(1) USA health 13yr F Recovered Glycosuria (Unknown) professional Not Serious Hyperglycaemia (Unknown) tablet --- 4mg (15-AUG-1995 / Unknown) Event Description: THIRTEEN-YEAR-OLD PATIENT ON RISPERIDONE EXPERIENCED 3+ GLUCOSE IN HER URINE ON A ROUTINE URINALYSIS. A 2 HOUR POST PRANDIAL GLUCOSE TOLERANCE TEST WAS 214 MG/DL. RISPERIDONE WAS DISCONTINUED AND SEVERAL FOLLOW-UP GLUCOSE TESTS WERE NORMAL. PATIENT'S GLUCOSE WILL CONTINUE TO BE MONITORED. REQUEST FOR ADDITIONAL INFORMATION DECLINED. Causality Per Reporter: possible Causality Per Company: probable Indications: Unspecified Psychosis Concomitant Diseases: Depressive Disorder, Not Elsewhere Classified								
JAUSA19142(1) USA health 18yr M 15 week(s) at onset No Change/Not Yet Subsidized Diabetes Mellitus Aggravated (01-SEP-1995) professional Serious Sedation Excessive (Unknown) Efficacy, Lack Of (Unknown) tablet --- 4mg (15-MAY-1995 / Unknown) tablet --- 10mg (01-SEP-1995 / Unknown) tablet --- 4mg (Unknown / 01-SEP-1995) tablet --- 8mg Causality Per Reporter: possible Causality Per Company: doubtful Indications: Schiz-Affective Type Schizophrenia Event Description: NURSE REPORTS ADOLESCENT PATIENT EXPERIENCED AGGRAVATION OF HIS DIABETES (GLUCOSE = 300 TO 400'S) AND EXCESSIVE SEDATION WHILE ON RISPERIDONE. THE PATIENT STARTED ON RISPERIDONE FOUR MONTHS AGO AT FOUR MG/DAY. THE DOSE WAS INCREASED TO SIX MG/DAY DUE TO CONTINUED AUDITORY HALLUCINATIONS HOWEVER HE EXPERIENCED EXCESSIVE SEDATION. THE DOSE WAS REDUCED TO FOUR MG/DAY AND THE SEDATION ABATED. AT THIS TIME THE PATIENT WAS HOSPITALIZED DUE TO THE AUDITORY HALLUCINATIONS. THE DOSE WAS SUBSEQUENTLY INCREASED TO TEN MG/DAY TWO WEEKS AGO. THE EXCESSIVE SEDATION DID NOT RETURN, HOWEVER THE GLUCOSE LEVELS ROSE TO OVER 300 DURING THE LATE AFTERNOON AND OVER 200 IN THE EARLY MORNING. THE INCREASED GLUCOSE HAS BEEN CONTROLLED VIA CHANGE IN DIET, EXERCISE AND INSULIN DOSE. THE AUDITORY HALLUCINATIONS PERSIST. NO ADDITIONAL INFORMATION IS EXPECTED.								

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Volume 15/Page 113

JJRP 00384101

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D821.115

R. 6279

Ref.no.(vers.no.)	City	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction
Paraul Strength-Unit dose (Therapy start date/and date) =====							
JANSA18361(2)	USA	health professional				Unknown Not Serious	Hyperglycaemia (Unknown) Causality Per Reporter: possible
tablet . . . Event Description: PHYSICIAN REPORTS PATIENT EXPERIENCED HYPERGLYCAEMIA WHILE ON RISPERIDONE. ADDITIONAL INFORMATION REQUESTED. THE INFORMATION AVAILABLE ON THIS CASE IS VERY SKETCHY; NO FURTHER DETAILS ARE EXPECTED (AND CASE HAS BEEN CLOSED). =====							
JANSA18648(1)	USA	health professional	53yr F		2 day(s) at onset	Death Serious	Sudden Death (27-JUL-1995) Hyperglycaemia (Unknown) Tachypnoea (Unknown) Causality Per Reporter: possible Causality Per Company: possible Indications: Paranoid Type Schizophrenia Concomitant Diseases:
tablet 4 mg - 4mg (25-OCT-1994 / 25-JUL-1995) tablet . . . 8mg (25-JUL-1995 / 27-JUL-1995) Event Description: 53-YEAR-OLD FEMALE, WITH SCHIZOPHRENIA, TYPE II DIABETES MELLITUS AND OBESITY (171.6 LBS) WAS STARTED ON RISPERIDONE 4 MG BID WHILE HOSPITALIZED IN OCT-94. HER MOST RECENT PHYSICAL EXAM WAS ON 13-JUL-95. BLOOD PRESSURE AT THAT TIME WAS 148/80, HEART RATE 94 AND REGULAR, RESPIRATORY RATE 24 BREATHS/MIN. THE EXAM REVEALED VERY DRY SKIN OF LOWER EXTREMITIES AND WAS OTHERWISE UNREMARKABLE. PATIENT'S BLOOD SUGARS WERE NOTED TO FLUCTUATE BETWEEN 160 AND 240 MG/DL. FOR REASONS NOT SPECIFIED, RISPERIDONE WAS INCREASED FROM 4 MG BID TO 8 MG DAILY ON 28-JUL-95. THE PATIENT WAS FOUND DEAD IN HER APARTMENT 27-JUL-95. AN AUTOPSY WAS NOT PERFORMED. ACCORDING TO THE CORONER, THE "PATIENT DIED FROM NATURAL CAUSE-PROBABLE WT." DETAILS ARE LIMITED AT THIS TIME. ADDITIONAL INFORMATION HAS BEEN REQUESTED. =====							
JANSA20189(1)	USA	health professional	56yr M		2 day(s) at onset	No Change/Not Yet Subsided Serious	Convulsions (19-NOV-1995) Myoclonus (19-NOV-1995) Hypoglycaemia (08-NOV-1995) Causality Per Reporter: possible Causality Per Company: possible Indications: Unspecified Schizophrenia
tablet . . . (08-NOV-1995 / 19-NOV-1995) tablet . . . 4mg (17-NOV-1995 / 19-NOV-1995) Event Description: PATIENT WAS STARTED ON RISPERIDONE AND EXPERIENCED HYPOGLYCAEMIA (NOS) IMMEDIATELY WHICH RESOLVED WITH THE PATIENT DRINKING COLA. THE DOSE OF RISPERIDONE WAS TITRATED TO 4 MG DAILY OVER 8 DAYS. THREE DAYS AFTER STARTING RISPERIDONE 4 MG DAILY, THE PATIENT EXPERIENCED MYOCLONIC MOVEMENTS WHICH PROCEEDED TO A GENERALIZED SEIZURE. THE PATIENT WAS HOSPITALIZED AND RISPERIDONE WAS DISCONTINUED. PHENYTOIN AND LORAZEPAM							

1debaeck 16JUN00

Ref.no.(vers.no.)	Ccy	Prin. source	Age	Sex	Latency	Outcome Seriousness	Reaction	46
Formul Strength-Unit dose (Therapy start date/end date) WERE INITIATED. THE PATIENT RECOVERED FROM THE SEIZURE, BUT THE MYOCLONIC MOVEMENTS CONTINUED. ELECTROENCEPHALOGRAPH WAS NEGATIVE EXCEPT FOR "NON-FOCAL GENERALIZED SLOWING". MRI AND CT SCANS WERE UNREMARKABLE. TEMPERATURE, CHEM PANEL AND ELECTROLYTES WERE NORMAL. REQUEST FOR ADDITIONAL INFORMATION DECLINED.								
JAUSA20238(4) USA health 27yr M 21 month(s) at onset Recovered Serious Ketacidosis (29-NOV-1995) Adrenal Cortex Activity Increased (20-NOV-1995) Diabetes Mellitus (29-NOV-1995) tablet 2 mg - 2mg (15-FEB-1994 / Unknown) Event Description: PATIENT WITH NO PREVIOUS OR FAMILY HISTORY OF DIABETES DEVELOPED NEW ONSET DIABETES AND KETOACIDOSIS WHILE ON RISPERIDONE. PATIENT WAS HOSPITALIZED AND THE KETOACIDOSIS RESOLVED WITHIN 24-HOURS. INSULIN WAS INITIATED AND THE PATIENT RECOVERED BUT REMAINED IN THE HOSPITAL FOR FOUR DAYS FOR DIABETIC EDUCATION. PATIENT REMAINS STABLE ON INSULIN THERAPY. RISPERIDONE CONTINUED UNINTERRUPTED. ADDITIONAL INFORMATION RECEIVED FROM THE PHYSICIAN STATES A 24-HOUR CORTISOL TEST WAS 2X NORMAL LIMITS. PHYSICIAN IS NOW CONSIDERING CUSHING'S SYNDROME AS PART OF THE DIFFERENTIAL DIAGNOSIS AND FURTHER STUDIES ARE BEING PERFORMED. ADDITIONAL INFORMATION HAS BEEN REQUESTED. FOLLOW-UP 11-APR-98: PHYSICIAN REPORTS AFTER RISPERIDONE WAS DISCONTINUED, THE PATIENT'S INSULIN REQUIREMENTS DECREASED AND HE IS CURRENTLY OFF INSULIN WITH NORMOGLYCEMIA. Causality Per Reporter: possible Causality Per Company: possible Indications: Unspecified Psychosis Concomitant Diseases: Anxiety States								
JAUSA20260(1) USA health 60yr F 8 month(s) at onset Recovered Not Serious Diabetes Mellitus Aggravated (15-NOV-1995) tablet - - 8mg (15-MAY-1995 / Unknown) tablet - - 10mg (15-NOV-1995 / Unknown) Event Description: INSULIN DEPENDENT DIABETIC EXPERIENCED AN AGGRAVATION OF HER DIABETES AFTER STARTING RISPERIDONE 10 MG DAILY. THE PATIENT DID NOT EXPERIENCE ANY INCREASE IN BLOOD SUGAR WHILE ON RISPERIDONE 6 MG DAILY. THE PATIENT'S INSULIN DOSE WAS INCREASED AND SHE RECOVERED. REQUEST FOR ADDITIONAL INFORMATION DECLINED. Causality Per Reporter: possible Causality Per Company: doubtful Indications: Schizo-Affective Type Schizophrenia								
JAUSA20419(4) USA health 25yr M Recovered Serious Cardiac Arrest (01-MAY-1995) Respiratory Failure (01-MAY-1995) Encephalopathy (02-MAY-1995) GI Hemorrhage (Unknown) Ventricular Fibrillation Paroxysm (01-MAY-1995) Tachycardia Ventricular (01-MAY-1995) tablet 1 mg - 1mg (01-AUG-1994 / 01-MAR-1995) tablet 1 mg - 1.5mg (01-MAR-1995 / 28-APR-1995)								

1debneek 18JUN00

Volume 15/ Page 115

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JJRP 00384103
D821.117

R. 6281

Ref.no.(vers.no.) Cty Prim. source Age Sex Latency Outcome Reaction 47
 Seriousness

Formal Strength-Unit dose (Therapy start date/and date)

Event Description: 25-YEAR-OLD MALE WITH A QUESTIONABLE HISTORY OF TOURETTE'S SYNDROME, BEGAN RISPERIDONE IN AUGUST, 1994. ACCORDING TO THE REPORTER, NO MARKED IMPROVEMENT WAS OBSERVED BUT THE PATIENT CONTINUED THERAPY. HIS CONDITION GRADUALLY DETERIORATED AND BECAME UNSTABLE (UNSPECIFIED) SO RISPERIDONE WAS INCREASED TO 3 MG DAILY. SHORTLY AFTER THE DOSE INCREASE, THE PATIENT BEGAN TO EXPERIENCE INCREASED SOMNOLENCE AND INTERMITTENT NAUSEA WHICH WAS FELT TO BE DRUG RELATED. ABOUT MID-MAY 1995, THE PATIENT DEVELOPED TENDER GYNecomastia. HIS NAUSEA WORSENEO, BEGAN VOMITING AND WAS UNABLE TO TOLERATE NORMAL QUANTITIES OF LIQUIDS OR SOLID FOOD. A SHORT WHILE LATER HE EXPERIENCED "VIOLENT RETCHING" ON SEVERAL OCCASIONS FOR WHICH HE TREATED HIMSELF WITH AN OVER-THE-COUNTER STOMACH REMEDY (PEPITO-BISMOL), EXCEEDING DOSAGE RECOMMENDATIONS FOR FOUR DAYS, ACCORDING TO FAMILY MEMBERS. HE ALSO TOOK AN UNSPECIFIED AMOUNT OF PROCHLORPERAZINE. ON THE MORNING OF 25-MAY-95, THE PATIENT DEVELOPED SEVERE AND PERSISTENT HICUPS. AS THE DAY PROCEEDED, HE BEGAN TO EXPERIENCE INCREASING FATIGUE, DIFFICULTY WALKING DUE TO FALLS AND PARASTHESIA OF THE HANDS AND FEET. LATER THAT DAY, THE PATIENT WAS DISCOVERED UNCONSCIOUS BY HIS MOTHER. EMS WAS SUMMONED TO THE SCENE IMMEDIATELY. THIS PATIENT WAS UNRESPONSIVE, RESPIRATIONS SHALLOW, AND EXTREMITIES RIGIDLY EXTENDED. FINGER STICK DETERMINATION INDICATED A GLUCOSE OF 70 MG/DL. UPON ARRIVAL IN THE EMERGENCY ROOM, HE WENT INTO CARDIOPULMONARY ARREST. SUBSEQUENTLY HE WAS INTUBATED AND A DOPAMINE DRIP WAS STARTED. HIS VITAL SIGNS STABILIZED, BUT THE PATIENT DEVELOPED SEVERE ANIONIC ENCEPHALOPATHY WITHOUT SEIZURES. HE WAS ADMITTED TO THE HOSPITAL WITH A DIAGNOSIS OF CORTICADRENAL INSUFFICIENCY. SERUM CORTISOL LEVEL WAS MEASURED AT 2 PM (POST RESUSCITATION) AND WAS 2 MG/DL. ELECTROLYTES WERE ALTERED REVEALING A SODIUM OF 114 MEQ/L AND CHLORIDE 81 MEQ/L. RENAL FUNCTION TESTS SHOWED BUN OF 47 MG/DL AND CREATININE 2.4 MG/DL. REPEAT BLOOD GLUCOSE DETERMINED BY LAB ANALYSIS WAS 28 MG/DL. THE PATIENT DEVELOPED REFRACTORY VENTRICULAR TACHYCARDIA SECONDARY TO METABOLIC ABNORMALITIES WHICH RESPONDED TO 30 MINUTES OF CARDIOPULMONARY RESUSCITATION. WHILE IN THE EMERGENCY ROOM, BASELINE HEMOGLOBIN VALUE DROPPED FROM 15 GM/DL TO 8 GM/DL; BLEEDING WAS VERIFIED WITH A NASOGASTRIC TUBE WHICH WHEN ASPIRATED INITIALLY RESEMBLED "OLD BLOOD." COAGULATION STUDIES WERE PERFORMED INDICATING PROTHROMBIN TIME OF 19.9 SECONDS, PARTIAL THROMBOPLASTIN TIME 76 SECONDS, AND FIBRINOGEN OF 280 MG/DL WITH NORMAL FIBRIN SPLIT PRODUCTS. LIVER ENZYMES WERE ALSO ELEVATED (NOS). A CT SCAN OF THE HEAD INDICATED THE ABSENCE OF INTRACRANIAL BLEEDING; CT SCAN OF THE LUNGS INDICATED DIFFUSE PULMONARY EDEMA. INITIAL ECHOCARDIOGRAM PERFORMED INDICATED MILD LEFT DEPRESSSED VENTRICULAR FUNCTION WITH HYPOKINESIA NOTED ON VENTRICULOGAM. SUBSEQUENT ECHO'S OBTAINED AT VARIABLE INTERVALS DURING THE PATIENT'S HOSPITALIZATIONS SHOWED IMPROVED VENTRICULAR FUNCTION. MEDICAL INTERVENTION CONSISTED MAINLY OF IV FLUIDS, TOTAL PARENTAL NUTRITION, RESPIRATORY ASSISTANCE AND SUPPORTIVE MEASURES. THE PATIENT'S CONDITION SLOWLY AND GRADUALLY IMPROVED. HE COMPLETELY RECOVERED WITHOUT SEQUELAE AND WAS DISCHARGED FROM THE HOSPITAL APPROXIMATELY ONE MONTH AFTER ADMISSION. FINAL DISCHARGE DIAGNOSIS INCLUDE:

1. STATUS POST CARDIAC/RESPIRATORY ARREST
2. STATUS POST ASPIRATION WITH INTUBATION; RESPIRATORY DISTRESS SYNDROME
3. RESOLVED ANEMIA SECONDARY TO MALNOURISHMENT AND GI BLEED
4. RESOLVED MILD GI BLEED
5. VENTRICULAR TACHYCARDIA WITH SUBSEQUENT EPISODES OF NON-SUSTAINED VENTRICULAR TACHYCARDIA

Causality Per Reporter: possible

Causality Per Company: possible

Indications: Tourette

Concomitant Diseases: Asthma; Unspecified Protein-Calorie Malnutrition; Other And Unspecified Mitral Valve Diseases

Company Remarks: THE EVENTS OCCURRED AFTER DISCONTINUATION OF RISPERIDONE.

1dbaeck 16JUN00

Volume 15/Page 116

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 D821.118

R. 6282

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	48

Formal Strength-Unit dose (Therapy start date/end date)

6. RESOLVED DEPRESSED LEFT VENTRICULAR FUNCTION

7. HYPOLIC BRAIN INJURY - LARGELY RESOLVED; NO DIFFERENCE FROM BASELINE

8. RESOLVED LACTIC ACIDOSIS ON ADMISSION

9. RESOLVED TRANSIENT RHEUMYOLYSIS

10. RESOLVED COAGULOPATHY OF UNKNOWN ETIOLOGY

11. RESOLVED INCREASED LIVER ENZYME STUDIES SECONDARY TO RESUSCITATIVE MEASURES

12. RESOLVED DECREASED SERUM OSMOLALITY AND HYPONATREMIA

13. RESOLVED RENAL INSUFFICIENCY WITH NORMALIZED RENAL FUNCTION

14. RESOLVED HYPOLYCEMIA

15. NORMALIZED HYPOCHOLESTEROLEMIA

16. NORMALIZED DECREASED SERUM PROTEIN AND ALBUMIN

ADDITIONAL INFORMATION HAS BEEN REQUESTED.

POLLOD - OP (23-JAN-96) RISPERIDONE WAS DISCONTINUED ON 26-APR-95. THE PATIENT BECAME CRITICALLY ILL ON 1-MAY-95 IN CONTRAST TO 25-MAY-95. WHEN THE ENT'S ARRIVED THEY DESCRIBED THE PATIENT AS HAVING HYPOTENSION WITH A REGULAR PULSE WHICH LATER DEGENERATED TO MONOPHASIC VENTRICULAR TACHYCARDIA, VENTRICULAR FIBRILLATION, UNSPECIFIED BRADYCARDIA, AND ULTIMATELY ASYSTOLE. IT WAS FELT THAT THIS SERIES OF EVENTS WAS ATTRIBUTED TO HIS POOR ORAL INTAKE AND NOT MEDICATION RELATED. NUMEROUS LABORATORY VALUES WERE ABNORMAL ON ADMISSION AS NOTED PREVIOUSLY. AN ECHOCARDIOGRAM DONE ON 2-MAY-95 DEMONSTRATED MILD MITRAL AND TRICUSPID REGURGITATION, MITRAL VALVE PROLAPSE, AND DIMINISHED EJECTION FRACTION (-40%). IT WAS THOUGHT THAT THIS FINDING SUGGESTED CONGESTIVE HEART FAILURE AND THE PATIENT WAS TREATED WITH DIGOXIN AND CAPTOPRIL. ON 2-MAY-95 HE WAS EVALUATED BY A NEUROLOGIST AND FOUND TO HAVE AN ABNORMAL EEG DEMONSTRATING "MILD GENERALIZED SLOWING". SUBSEQUENTLY, A CARDIAC CATHETERIZATION WAS PERFORMED BECAUSE OF PERSISTENT VENTRICULAR FIBRILLATION WHICH SHOWED AN EJECTION FRACTION OF 60%, APICAL HYPOKINESIS, AND NORMAL CORONARY ARTERIES. FOLLOW-UP ECHOCARDIOGRAM ON 22-MAY-95 SHOWED AN EJECTION FRACTION OF -50%. THE PATIENT NEVER DEMONSTRATED FEVER OR RIGIDITY. IT WAS THOUGHT THAT THE PATIENT EXPERIENCED RHEUMYOLYSIS (MARKEDLY ELEVATED CPK LEVELS) WHICH OCCURRED FOLLOWING CARDIAC ARREST AND RESOLVED ON 7-MAY-95. SCOT, SCPT, AND LDH WERE ELEVATED ON ADMISSION AND PEAKED ON DAY TWO OF HOSPITALIZATION. THE PATIENT CONTINUED TO EXPERIENCE NON-SUSTAINED VENTRICULAR TACHYCARDIA AND HAS LATER TRANSFERRED TO ANOTHER HOSPITAL FOR ELECTROPHYSIOLOGY STUDIES. VENTRICULAR ARRHYTHMIAS WERE NOT INDUCIBLE USING ELECTROPHYSIOLOGICAL STIMULI. THE REPORTER DOES NOT ATTRIBUTE THE CARDIAC ARREST OR EVENT OCCURRING AFTERWARD TO RISPERIDONE THERAPY.

6. RESOLVED DEPRESSED LEFT VENTRICULAR FUNCTION

JANSA20807 (7)	USA literature	73yr F	Recovered Serious	Neuroleptic Malignant Syndrome (08-AUG-1995) Thrombophlebitis (08-AUG-1995) Dehydration (08-AUG-1995) Diabetes Mellitus Aggravated (08-AUG-1995) Hypovolemia (08-AUG-1995)

tablet 1 mg - .5mg (Unknown / 08-AUG-1995)

Event Description: 73-YEAR-OLD BLACK FEMALE EXPERIENCED KES WHILE ON RISPERIDONE 0.5 MG TWICE DAILY. PATIENT WAS HOSPITALIZED WITH ADMITTING DIAGNOSES OF KES, DEHYDRATION, AND HYPOLYCEMIA. ON ADMISSION PATIENT DEMONSTRATED GENERALIZED MUSCULAR RIGIDITY.

Causality Per Reporter: probable

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Volume 15/Page 117

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JJRP 00384105

D821.119

R. 6283

Ref.no.(vars.no.)	Cty	Pris. source	Age	Sex	Latency	Outcome	Reaction	48
						Seriousness		

Formul Strength-Unit dose (Therapy start date/end date)

COGNITIVE FUNCTIONING OF THE UPPER EXTREMITIES, DECREASED MENTAL STATUS, RESPONDED ONLY TO PAINFUL STIMULI, TEMPERATURE OF 38.4 DEGREES CELSIUS, BLOOD PRESSURE OF 168/100 AND HEART RATE OF 118 BPM. AN ECG REVEALED NO ACUTE ST CHANGES. A CT OF THE HEAD REVEALED ENLARGEMENT OF THE VENTRICLES AND FOCI CONSISTENT WITH AGE. DANTROLENE 75 MG IV Q8H, BROMOCRIPTINE 2.5 MG TID, AND CEFTRIAXONE 1 GRAM Q12H WERE INITIATED. VITAL SIGNS RETURNED TO NORMAL AFTER 12 HOURS. CEFTRIAXONE WAS DISCONTINUED. BROMOCRIPTINE WAS STOPPED ON DAY 2 AND DANTROLENE ON DAY 5. PATIENT WAS NOTED TO HAVE RIGHT UPPER ARM EDema WITH LOSS OF PULSE. UROKINASE WAS INFUSED INTO RIGHT BRACHIAL ARTERY TO TREAT THROMBUS IN RIGHT AXILLA. COURSE WAS COMPLICATED BY HYPOPERFUSION. PATIENT WAS DISCHARGED 30-AUG-95 WITH DECREASED MENTAL STATUS SECONDARY TO IHS. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

CAUSALITY Per Company: probable

Indications: Desantia

Concomitant Diseases: Cad; Hypertension; Copd; Cva; Alzheimer's Disease

FOLLOW UP: ADDITIONAL INFORMATION RECEIVED 18-MAR-98 REVEALED PATIENT THEN DEVELOPED A COMPARTMENT SYNDROME OF THE RIGHT UPPER EXTREMITY WHICH REQUIRED A FASCIOTOMY ON 11-AUG-95 WITH DELAYED AND SUBSEQUENT CLOSURE ON 15-AUG-95. TWO DAYS LATER (NINE DAYS AFTER RISPERIDONE WAS DISCONTINUED) PATIENT DEVELOPED AN UPPER GI BLEED WITH ASSOCIATED ANEMIA, SECONDARY TO THE UROKINASE INFUSION. IV RANITIDINE WAS STARTED; TWO UNITS OF PACKED RBC'S WERE ALSO GIVEN. A LEFT PLEURAL EFFUSION WAS ALSO DIAGNOSED AT THIS TIME; THE PNEUMONIA WAS TREATED SUCCESSFULLY WITH NEBULIZERS, OXYGEN AND IV TIMENTIN(R). THE PATIENT WAS ALSO TREATED WITH IV VANCOMYCIN FOR DEVELOPMENT OF LINE SEPSIS. PATIENT WAS TRANSFERRED FROM THE MEDICAL ICU TO THE GENERAL MEDICAL FLOOR WITH STABLE BUT DECREASED MENTAL STATUS COMPARED TO HER PRE-ADMISSION BASELINE. THOUGHT BY THE REPORTER TO BE SECONDARY TO THE INITIAL DIAGNOSIS OF IHS AND THE PATIENT'S STAY IN THE ICU. SHE RECOVERED AND WAS DISCHARGED TO A NURSING HOME IN STABLE CONDITION.

FOLLOW UP (JUN97): ARTICLE WAS PUBLISHED IN PHARMACOTHERAPY 17 (3) p. 617-621, 1997. BY P.P. GLEASON ET AL. (LJID:M125718)

FIRST PATIENT OF ELIGIT. ADDITIONAL INFORMATION RECEIVED NOTES THAT THE PATIENT'S PREVIOUS MEDICATIONS EXCEPT FOR NITROGLYCERIN PATCHES WERE DISCONTINUED. TREATMENT WAS BEGUN WITH NORMAL SALINE FOR RESUSCITATION TO TREAT SEVERE DEHYDRATION AND HYPOVOLAEMIA. TWELVE HOURS LATER ALL VITAL SIGNS HAD RETURNED TO NORMAL AND THE PATIENT HAD DEEPERESCED. MUSCULAR RIGIDITY AND COGNITIVE IMPROVED, BUT COGNITIVE FUNCTIONING REMAINED UNCHANGED. HER HOSPITAL COURSE WAS ALSO COMPLICATED BY A GI BLEED REQUIRING TRANSFUSION. ON DISCHARGE THE WOMAN WAS STABLE AND HER MENTAL STATUS WAS AT BASELINE (ALERT, EASILY AROUSED AND ORIENTED TO NAME). ADDITIONAL LABORATORY FINDINGS, VITAL SIGNS AND CONCOMITANT DISEASES WERE ADDED TO THIS REPORT.

JANSA21202(3)	USA health professional	29yr M	17 month(s) at onset	Recovered Serious	Hypoglycaemia (15-DEC-1995) Glycosuria (15-DEC-1995)	Caasality Per Reporter: possible
tablet 2 mg - Zag (15-JUL-1994 / 15-DEC-1995)						
Event Description: MALE PATIENT IN HIS THIRTIES WAS HOSPITALIZED WITH NEW ONSET OF DIABETES MELLITUS THREE TO FOUR DAYS AFTER STARTING RISPERIDONE. IT IS UNKNOWN IF PATIENT WAS SYMPTOMATIC PRIOR TO INITIATION OF RISPERIDONE THERAPY OR IF HE HAS A FAMILY HISTORY OF DIABETES. RISPERIDONE HAS BEEN DISCONTINUED AND THE PATIENT IS REPORTED TO BE DOING "BETTER." DETAILS REGARDING THE CASE ARE NOT AVAILABLE AT THIS TIME. ADDITIONAL					Caasality Per Company: possible	Indications: Unspecified Schizophrenia

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Volume 15/Page 118

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D821.120
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R. 6284

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	50

Formul Strength-Unit dose (Therapy start date/end date)

=====

INFORMATION HAS BEEN REQUESTED FROM THE PHYSICIAN.

F O L L O W - U P 15-MAY-86:

PHYSICIAN REPORTS THE PATIENT EXPERIENCED ELEVATED BLOOD AND URINE GLUCOSE ON A ROUTINE EXAMINATION BY HIS FAMILY PHYSICIAN. THE PATIENT WAS HOSPITALIZED BRIEFLY AND RISPERIDONE WAS DISCONTINUED. THE PATIENT RAPIDLY RECOVERED AFTER RISPERIDONE WAS DISCONTINUED. ADDITIONAL INFORMATION IS NOT EXPECTED.

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JAUSA21243(1)	USA health professional	42yr F	No Change/Not Yet Subsided Not Serious	Pain Right Upper Quadrant (15-NOV-1985) Hyperglycaemia (14-JAN-1986) Tachycardia (14-JAN-1986) Nausea (15-NOV-1985) Hypercholesterolaemia (14-JAN-1986) Hepatic Function Abnormal (14-JAN-1986)

tablet 3 mg - 3mg (15-JAN-1986 / Unknown)

Event Description: PATIENT ON RISPERIDONE EXPERIENCED NAUSEA AND MILD PAIN IN RIGHT UPPER QUADRANT IN NOV-85. THE PAIN CONTINUED AND THE PATIENT WAS SEEN IN THE EMERGENCY ROOM 14-JAN-86 AND APPENDICITIS AND GALL BLADDER WERE RULED OUT. LIVER FUNCTION TESTS WERE PERFORMED AND SGOT WAS 105 U/L, SGPT 103 U/L, SGCT 126 U/L, CHOLESTEROL 265 MG/DL, GLUCOSE WAS 230 MG/DL. EKG SHOWED SINUS TACHYCARDIA 101 BPM. THE PATIENT HAS NO HISTORY OF LIVER PROBLEMS, ALCOHOL ABUSE OR DIABETES. REQUEST FOR ADDITIONAL INFORMATION FROM PHYSICIAN DENIED. REPORTER WILL CONTACT US WITH ADDITIONAL INFORMATION WHEN AVAILABLE.

Causality Per Reporter: possible

Causality Per Company: possible

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JAUSA21308(1)	USA health professional	64yr M 0 day(s) at onset	No Change/Not Yet Subsided Not Serious	Diabetes Mellitus Aggravated (77-JAN-1990) Causality Per Reporter: possible

tablet 1 mg - 1mg (15-OCT-1985 / 31-DEC-1985)

tablet 2 mg - 2mg (01-JAN-1986 / Unknown)

Causality Per Company: possible

Event Description: PATIENT WITH WELL CONTROLLED IDDM EXPERIENCED AN INCREASE IN HIS FASTING SERUM GLUCOSE LEVELS (170'S) AFTER INCREASING HIS RISPERIDONE DOSE FROM 2 TO 4 MG DAILY. THE INSULIN DOSE WAS ADJUSTED BUT THE FASTING GLUCOSE LEVELS HAVE REMAINED ELEVATED. A GLYCOSYLATED HEMOGLOBIN HAS NOT BEEN DRAWN. ADDITIONAL INFORMATION IS NOT EXPECTED.

Indications: Unspecified Schizophrenia

Concomitant Diseases: Adenoma, Prostate

=====

JAUSA21548(1)	USA health professional	32yr M 9 month(s) at onset	No Change/Not Yet Subsided Not Serious	Diabetes Mellitus (01-FEB-1986) Patechiae (30-JAN-1986) Echymosis (30-JAN-1986)

1debneck 16JUN00

Volume 15/ Page 119

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D821.121

R. 6285

Ref.no.(vero.no.)	Ctry	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	51
Formul Strength-Unit dose (Therapy start date/end date)								
Infection Tbc (01-FEB-1996)								
tablet - - 3mg (04-APR-1996 / 01-FEB-1996)								
Event Description: PHARMACIST REPORTS A 32-YEAR-OLD MALE PATIENT, KNOWN TO ABUSE DRUGS AND ALCOHOL, WHO HAD BEEN ON RISPERIDONE (3 MG TWICE DAILY) SINCE APRIL 4, 1995. HE EXPERIENCED ECCHYMOSES AND PRURITIA ON HIS UPPER ARMS AND LEGS BEGINNING JANUARY 30, 1996 AND LASTING TWO DAYS. HIS PSYCHIATRIST DISCONTINUED RISPERIDONE ON FEBRUARY 1, 1996, SUSPECTING THROMBOCYTOPENIA, BUT A PLATELET COUNT PERFORMED FEBRUARY 1, 1996 WAS WITHIN NORMAL LIMITS. A TUBERCULIN SKIN TEST WAS POSITIVE, THROUGH THE PATIENT WAS ASYMPTOMATIC. GLUCOSE WAS ELEVATED AT 281 (NON-FASTING). HE HAD BEEN RECENTLY DIAGNOSED WITH DIABETES MELLITUS. ADDITIONAL INFORMATION IS NOT EXPECTED.							Causality Per Company: doubtful	
Indications: Unspecified Schizophrenia								
JANSA21557(1) USA health 50yr M 6 week(s) at onset Unknown Diabetes Mellitus Aggravated (Unknown)								
professional Not Serious							Causality Per Reporter: possible	
tablet - - 3mg								
Event Description: PHYSICIAN REPORTS A 50-YEAR-OLD MALE PATIENT WITH PRE-EXISTING INSULIN DEPENDENT DIABETES MELLITUS EXPERIENCED AN AGGRAVATION OF HIS CONDITION SIX WEEKS AFTER STARTING RISPERIDONE, 6 MG DAILY. HE WAS WELL CONTROLLED PRIOR TO STARTING RISPERIDONE AND NOW IS DIFFICULT TO MANAGE. ADDITIONAL INFORMATION HAS BEEN REQUESTED.							Causality Per Company: doubtful	
Indications: Unspecified Schizophrenia								
JANSA21847(1) USA health 60yr M 7 day(s) at onset No Change/Not Yet Subsidized Diabetes Mellitus (20-MAR-1996)								
professional Not Serious							Polyuria (20-MAR-1996)	
tablet - - 3mg (13-MAR-1996 / 22-MAR-1996)								
Event Description: PHYSICIAN REPORTS A 60-YEAR-OLD NEGROID MALE PATIENT WITH A HISTORY OF ALCOHOLISM EXPERIENCED POLYURIA ONE WEEK AFTER STARTING ON RISPERIDONE. CONCOMITANT MAXIDEX(R) WAS DISCONTINUED BUT POLYURIA PERSISTED. THE PATIENT HAD NO HISTORY OF HYPERGLYCEMIA AND NO FAMILY HISTORY OF DIABETES MELLITUS. URINE DIPSTICK ON 20-MAR-96 REVEALED 4+ KETONES, AND HIS BLOOD GLUCOSE WAS 697. DIAGNOSIS OF DIABETES MELLITUS WAS CONFIRMED AND INSULIN THERAPY WAS STARTED. RISPERIDONE AND ISOMAXIDEX WERE DISCONTINUED ON 22-MAR-96. FASTING GLUCOSE WAS STILL ELEVATED AT 234 ON 25-MAR-96. ADDITIONAL INFORMATION IS NOT EXPECTED.							Causality Per Company: doubtful	
Indications: Unspecified Schizophrenia								
JANSA22283(1) USA patient/consum 46yr M 0 day(s) at onset Recovered Hypoglycemia (10-APR-1996)								
at Not Serious							Tiredness (10-APR-1996)	

1debneek 16JUN00

Volume 15/Page 120

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 D821.122

R. 6286

Ref.no. (verse.no.)	Cty	Prin. source	Age	Sex	Latency	Outcome Seriousness	Reaction	52
Form: Strength-Unit dose (Therapy start date/end date) =====								
							Shaking (10-APR-1996)	
tablet 1 mg - 1mg (08-APR-1996 / 08-APR-1996) tablet - - 2mg (08-APR-1996 / 09-APR-1996) tablet - - 3mg (10-APR-1996 / 10-APR-1996)							Causality Per Company: possible	
tablet - - 4.5mg (11-APR-1996 / Unknown)							Indications: Unspecified Schizophrenia	
Event Description: A 46-YEAR-OLD MALE CONSUMER WITH 100M EXPERIENCED TIREDNESS, SHAKINESS, AND HYPOGLYCEMIA BY THE THIRD DAY OF RISPERIDONE THERAPY. RISPERIDONE DOSE WAS DECREASED FROM 8 MG DAILY TO 4.5 MG DAILY WITH IMPROVEMENT IN TIREDNESS. A HOME BLOOD GLUCOSE TEST MEASUREMENT REVEALED A GLUCOSE OF 76. THE CONSUMER DID NOT TAKE HIS LATE AFTERNOON DOSE OF INSULIN BUT HE ATE A SNACK AND FELT BETTER. RISPERIDONE CONTINUES. ADDITIONAL INFORMATION IS NOT EXPECTED.								
=====								
JAUSA22346(3)	USA health professional	44yr M	18 month(s)	at onset	No Change/Not Yet Scheduled	Diabetes Mellitus Aggravated (01-MAR-1996)	Causality Per Reporter: doubtful	
tablet - - 9mg (22-OCT-1994 / Unknown)							Causality Per Company: doubtful	
Event Description: PHYSICIAN REPORTS A PATIENT ON RISPERIDONE FOR APPROXIMATELY 1 1/2 YEARS WHO WAS HOSPITALIZED FOR EXACERBATION OF PREVIOUSLY STABLE DIABETES MELLITUS. SERUM GLUCOSE EXCEEDED 300 MG/DL. CONCOMITANT MEDICATIONS INCLUDE AN UNSPECIFIED ORAL HYPOGLYCEMIC AGENT AND PAROXETINE. PATIENT IS ASYMPTOMATIC FOR SIGNS OF INFECTION. RESULTS OF THE MEDICAL WORK-UP ARE PENDING. ADDITIONAL INFORMATION HAS BEEN REQUESTED. FOLLOW UP (MAY96): THE 'UNSPECIFIED ORAL HYPOGLYCAEMIA AGENT' WAS INSULIN (IN).								
=====								
JAUSA22608(1)	USA health professional, c	adul F	7 day(s)	at onset	Recovered Not Serious	Hyperglycemia (22-APR-1996)	Causality Per Reporter: possible	
tablet 1 mg - 4mg (15-APR-1996 / 22-APR-1996)							Causality Per Company: doubtful	
Event Description: PATIENT ON RISPERIDONE 4 MG DAILY FOR ONE WEEK PRESENTED WITH HYPERGLYCAEMIA (MG) ON ROUTINE BLOOD STUDIES. RISPERIDONE WAS DISCONTINUED, AND PATIENT TREATED WITH AN ORAL HYPOGLYCEMIC AGENT (MG). THE SERUM GLUCOSE LEVEL HAS RETURNED TO NORMAL. PHYSICIAN WILL DISCONTINUE THE HYPOGLYCEMIC MEDICATION IN THE NEXT FEW DAYS. ADDITIONAL INFORMATION WILL BE PROVIDED BY PHYSICIAN WHEN AVAILABLE.								
=====								
JAUSA23378(2)	USA health professional				Unknown Not Serious	Blood Sugar Increased (Unknown)	Causality Per Reporter: possible	

Volume 15/ Page 121

tablet - - -
 Ref.no.(vers.no.) Cty Prim. source Age Sex Latency Outcomes Reaction 53
 Seriousness
 Formu Strength Unit dose (Therapy start date/end date)
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Event Description: PATIENT ON RISPERIDONE EXPERIENCED INCREASED BLOOD SUGAR (NOS). Causality Per Company: doubtful
 ADDITIONAL INFORMATION HAS BEEN REQUESTED.
 THE INFORMATION AVAILABLE ON THIS CASE IS VERY SKETCHY; NO FURTHER DETAILS ARE EXPECTED
 (AND CASE HAS BEEN CLOSED).

JANS23848(5) USA health 17yr F No Change/Not Yet Subsidized Hyperglycaemia (Unknown) Twitching (Unknown) Fatigue (Unknown) Headache (Unknown)
 Not Serious

tablet - - 1mg (03-JUL-1995 / Unknown)

Event Description: THIS FEMALE PATIENT HAS BEEN TAKING RISPERIDONE AND CHLORTHIAZIDE FOR AN UNKNOWN PERIOD OF TIME. SHE HAD "DIABETES MELLITUS" YEARS AGO THAT WAS CONTROLLED WITH DIET. AT AN UNKNOWN DATE A GLUCOSE TOLERANCE TEST WAS DONE AND SHE HAD A NORMAL RESPONSE AT THE LAST FACILITY. RECENTLY HER NONFASTING GLUCOSE INCREASED TO 200-300 MG/DL AND SHE REPORTED FATIGUE AND HEADACHE. IT IS NOT KNOWN WHETHER THERE IS A FAMILY HISTORY OF DIABETES MELLITUS. SHE IS PRESENTLY OBSE. PSYCHIATRIST PLANS TO DISCONTINUE BOTH MEDICATIONS SIMULTANEOUSLY.
 F O L L O W U P (SEP96): BENZOTRIPINE WAS ADDED FOR TWITCHING WHICH IMPROVED. RISPERIDONE AND BUSPIRONE CONTINUE. VALPROATE SODIUM AND CLONAZEPAM ARE BEING TITRATED DOWN TO DISCONTINUATION.
 Causality Per Reporter: possible
 Causality Per Company: doubtful
 Concomitant Diseases: Obesity

JANS23758(1) USA health M No Change/Not Yet Subsidized Hypoglycemia (Unknown) Weight Decrease (Unknown)
 Not Serious

tablet 1 mg - 1mg

Event Description: PHYSICIAN REPORTS PATIENT ON RISPERIDONE THERAPY IS EXPERIENCING HYPOLYCAEMIA AND WEIGHT LOSS. ADDITIONAL INFORMATION REQUESTED.
 Causality Per Reporter: possible
 Causality Per Company: possible

JANS23833(1) USA health F Unknown Serious Diabetes Mellitus (Unknown)
 Causality Per Reporter: possible

tablet - - -

Event Description: PHYSICIAN REPORTS A PATIENT ON RISPERIDONE EXPERIENCING DIABETES
 Causality Per Company: possible

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Volume 15/ Page 122

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JRP 00384110

D821.124

R. 6288

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	34

Formul Strength-Unit dose (Therapy start date/end date)

MELLITUS. ADDITIONAL INFORMATION REQUESTED.

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JAUSA23877(1)	USA health professional	62yr F	Recovered Serious	Hypoglycaemia (24-JUL-1996)
tablet 2 mg - 2mg (Unknown / 24-JUL-1996)				Causality Per Reporter: possible
Event Description: THIS PATIENT IS A 62-YEAR-OLD OBESE FEMALE WHO IS CURRENTLY TAKING RISPERIDONE, HALOPERIDOL, BENZTROPINE AND AN UNKNOWN FOURTH DRUG. SHE HAS NO DIABETIC HISTORY, BUT DOES HAVE HYPOTHYROIDISM. ON 24 JULY 1996, SHE EXPERIENCED HYPOLYCEMIA SEVERE ENOUGH TO REQUIRE TREATMENT WITH DEXTROSE AND OVERNIGHT HOSPITALIZATION FOR OBSERVATION. SHE "RECOVERED WELL" AND WAS DISCHARGED. RISPERIDONE WAS DISCONTINUED ON 24-JUL-96. ADDITIONAL INFORMATION HAS BEEN REQUESTED.				Causality Per Company: possible Indications: Other Unknown And Unspecified Cause Of Morbidity Or Mortality Concomitant Diseases: Obesity; Hypothyroidism

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JAUSA23665(1)	USA health professional	35yr F	Unknown Not Serious	Hypoglycaemia (Unknown)
tablet - .5mg tablet 1 mg - 1mg				Causality Per Reporter: probable
Event Description: PHYSICIAN REPORTS A FEMALE INSULIN DEPENDENT DIABETIC (ADULT ONSET) PATIENT WHO EXPERIENCED AN EPISODE OF HYPOGLYCEMIA WHILE ON RISPERIDONE (1MG). BLOOD SUGAR PRIOR TO THE START OF RISPERIDONE (1MG) WAS 300 AND DROPPED TO 60 AFTER THE START OF RISPERIDONE THERAPY. THE PATIENT WAS TAKING 100 UNITS OF INSULIN PRIOR TO THE START OF RISPERIDONE. ADDITIONAL INFORMATION REQUESTED.				Causality Per Company: possible Company Remarks: A 40-UNIT DAILY DOSE OF INSULINE IS MORE PHYSIOLOGICAL.

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JAUSA24010(1)	USA patient/consum er	28yr M	8 week(s) at onset No Change/Not Yet Subsided Not Serious	Diabetes Mellitus (??-JUL-1996) Hyperglycaemia (??-JUL-1996) Thirst Excessive (Unknown) Polyuria (Unknown) Otitis Media (??-JUL-1996)
tablet 4 mg - 4mg (01-JUN-1996 / Unknown)				Causality Per Company: doubtful
Event Description: CONSUMER REPORTS HER OVERWEIGHT SON HAS BEEN TAKING ANTIPSYCHOTICS SINCE 1989 FOR "NERVOUS BREAKDOWNS." AROUND JUNE 1996, PATIENT WAS SWITCHED FROM HALOPERIDOL TO RISPERIDONE. APPROXIMATELY TWO MONTHS LATER, HE STARTED TO EXPERIENCE				

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Volume 15/Page 123

JJRP 00384111

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D821.125

R. 6289

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome	Reaction	65
						Seriousness		

Formal Strength-Unit dose (Therapy start date/end date)

SYMPTOMS OF HYPERGLYCEMIA (POLYDIPSIA AND POLYURIA). GLIPIZIDE WAS STARTED FOR DIAGNOSIS CONCOMITANT DISEASE: Obesity OF DIABETES MELLITUS AND SYMPTOMS RESOLVED. PATIENT'S MOTHER HAS DIABETES MELLITUS. DURING JULY 1996, HE EXPERIENCED OTITIS MEDIA AND TOOK SIMTAR(R). HYPERGLYCEMIC SYMPTOMS HAVE RETURNED DURING THE BEGINNING OF AUGUST 1996; FASTING BLOOD GLUCOSE WAS 180 MG/DL ON 12-AUG-96. NO FURTHER INFORMATION ANTICIPATED.

JAUSA24223(1)	USA patient/consum	38yr M		No Change/Not Yet Subsidized	Hyperglycemia (Unknown)
				Not Serious	Irritability (77-NOV-1995)
					Drowsiness (77-JUN-1996)
					Therapeutic Response Decreased (77-NOV-1995)
					Emotional Withdrawal (77-JUN-1996)

tablet 1 mg - 1mg (15-SEP-1995 / 15-AUG-1996)
tablet 2 mg - 2mg (16-AUG-1996 / Unknown)

Event Description: A DIABETIC MALE CONSUMER WITH ANXIETY AND MENTAL DISTURBANCES HAS BEEN EXPERIENCING IRRITABILITY AND HYPERGLYCEMIA WHILE ON RISPERIDONE THERAPY. HE ADMITTED BEING ARGUMENTATIVE AND CRABBY SINCE NOV-95. THE PATIENT REPORTED BEING BROWSY AND SOCIALLY WITHDRAWN SINCE VENLAFEXINE THERAPY WAS INITIATED IN JUN-96. ON 16-AUG-96, THE DOSE OF RISPERIDONE WAS RAISED FROM 1 TO 2 MG BID. PATIENT HAS NOT RECOVERED FROM SYMPTOMS AT THE TIME OF THIS REPORT (21-AUG-96). ADDITIONAL INFORMATION IS NOT EXPECTED.

Causality Per Company: possible
Indications: Mental Disturbance; Anxiety States

JAUSA24343(1)	USA health professional	23yr F		Recovered Serious	Diabetes Mellitus (Unknown)
					Eurexia (Unknown)

tablet -- 8mg (31-AUG-1994 / Unknown)
tablet ---

Event Description: THIRD OF FOUR PATIENTS. NURSE REPORTS A 23-YEAR-OLD FEMALE ON 8 MG OF RISPERIDONE EXPERIENCED EUREXIS. SHE WAS DIAGNOSED WITH DIABETES MELLITUS AND IS PRESENTLY CONTROLLED WITH ORAL HYPOLYCEMICS. RISPERIDONE DOSE HAS BEEN DECREASED (NOS). NO ADDITIONAL INFORMATION IS EXPECTED.

Causality Per Company: doubtful
Indications: Unspecified Schizophrenia

Concomitant Diseases: Obesity

JAUSA24344(1)	USA health professional	32yr M	7 month(s) at onset	Recovered Serious	Diabetes Mellitus (16-JAN-1996)
					Eurexia (15-JAN-1996)

tablet 3 mg - 3mg (15-JUN-1996 / 15-JAN-1996)

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Volume 15/Page 124

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JJRP 00384112
D821.126

R. 6290

Ref.no. (vers.no.)	Cty	Pris. source	Age	Sex	Latency	Outcome Seriousness	Reaction	56

Formul Strength-Unit dose (Therapy start date/end date)

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Event Description: FOURTH OF FOUR PATIENTS. NURSE REPORTS A MALE PATIENT ON 6 MG OF RISPERIDONE FOR APPROXIMATELY SIX MONTHS EXPERIENCED ENOPRESIS. HE WAS DIAGNOSED WITH DIABETES AND IS NOW TAKING AN ORAL HYPOLYCEMIC AGENT (XOS). RISPERIDONE WAS DISCONTINUED. NO ADDITIONAL INFORMATION IS EXPECTED.

Causality Per Reporter: possible

Causality Per Company: doubtful

Indications: Paranoid Type Schizophrenia

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JAUSA24447(3)	USA health professional	30yr F	8 week(s) at onset	Recovered Serious	Ketoacidosis (15-MAY-1998) Diabetes Mellitus Precipitated (Unknown)

tablet - - 1mg (04-APR-1998 / 01-MAY-1998)
tablet - - 2mg (02-MAY-1998 / 07-MAY-1998)
tablet - - 3mg (08-MAY-1998 / 15-MAY-1998)

Causality Per Reporter: probable

Causality Per Company: doubtful

Indications: Unspecified Psychosis

Concomitant Diseases: Profound Mental Retardation; Deaf Mutism

Event Description: PATIENT WITH SEVERE MENTAL RETARDATION WAS STARTED ON RISPERIDONE ON 04-APR-98 AT 1 MG DAILY AND WAS TITRATED TO 3 MG DAILY BY 02-MAY-98. ON 15-MAY-98 THE PATIENT WAS TAKEN TO THE EMERGENCY ROOM WHERE SHE WAS DIAGNOSED WITH KETOACIDOSIS AND ADMITTED TO THE HOSPITAL FOR TREATMENT. THE PHYSICIAN DOES NOT BELIEVE THAT THE PATIENT OR HER FAMILY HAVE A HISTORY OF DIABETES. RISPERIDONE WAS DISCONTINUED ON ADMISSION. KETOACIDOSIS DID RESOLVE AND THE PATIENT WAS DISCHARGED ON 22-MAY-98. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

7-OCT-98 FOLLOW UP:

DISCHARGE SUMMARY RECEIVED WHICH REVEALED INFORMATION SURROUNDING THE PATIENT'S HOSPITALIZATION. THE PATIENT WAS SEEN IN THE DOCTOR'S OFFICE PRIOR TO ADMISSION. RISPERIDONE WAS STOPPED ON ADMISSION TO THE HOSPITAL. THE PATIENT'S BLOOD GLUCOSE WAS 429 AND URINALYSIS REVEALED A SPECIFIC GRAVITY OF 1.02, PH OF 6.04, 4+GLUCOSE AND 4+KETONES. THE PATIENT'S BLOOD GAS RESULTS ON ADMISSION WERE: PH = 7.248, PCO2= 13, PO2= 108, BICARB= 4.8. RESPIRATORY RATE RANGED BETWEEN 40-50. INSULIN WAS ADMINISTERED BOTH IV AND SUBCUTANEOUSLY. BLOOD GLUCOSE DECREASED TO 234. INSULIN THERAPY CONTINUED AND BY 20-OCT-98 THE BLOOD GLUCOSE HAD DECREASED TO 159. THE PATIENT WAS DISCHARGED. INSULIN (SLIDING SCALE COVERAGE) WAS PRESCRIBED. NO ADDITIONAL INFORMATION IS EXPECTED.

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JAUSA24498(1)	USA health professional	20yr M	No Change/Not Yet Subsidized Serious	Pancreatitis (24-JAN-1998) Epigastric Food-Related Pain (24-JAN-1998) Nausea (24-JAN-1998) Leukocytosis (24-JAN-1998) Amylase Increased (24-JAN-1998) Hyperglycaemia (24-JAN-1998)

tablet - - - (02-JAN-1998 / 28-JAN-1998)

Event Description: PATIENT WAS HOSPITALIZED ON 24-JAN-98 AFTER HE DEVELOPED MDU.

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Volume 15/Page 125

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JRP 00384113

D821.127

R. 6291

Ref.no. (vwr.no.) Ctry Prim. source Age Sex Latency Outcome Reaction 57
Seriousness

Formul Strength/Unit dose (Therapy start date/end date)

EPIGASTRIC PAIN ASSOCIATED WITH NAUSEA. HE HAD STARTED RISPERIDONE APPROXIMATELY THREE WEEKS PRIOR (DOSE UNSPECIFIED). ABNORMAL LAB VALUES INCLUDED LEUKOCYTOSIS (NOS), ELEVATED AMYLASE (867) AND HYPERGLYCEMIA (FBS 190-260). DIAGNOSIS OF PANCREATITIS WAS MADE. TREATMENT INCLUDED DISCONTINUATION OF RISPERIDONE, IV FLUIDS, TPN, SUCTION, SLIDING SCALE INSULIN AND IMIPENEM. PATIENT IS OBESE AND HAS A HISTORY OF BINGE DRINKING. ALTHOUGH NO ALCOHOL HAD BEEN CONSUMED WITHIN ONE MONTH OF ADMISSION. NO OTHER RISK FACTORS ARE KNOWN. PATIENT RECOVERED. ADDITIONAL INFORMATION IS NOT EXPECTED.

Causality Per Reporter: possible

Causality Per Company: possible

Indications: Unspecified Schizophrenia

Concomitant Diseases: Obesity

Company Remarks: ALCOHOLIC PANCREATITIS IS LESS POSSIBLE. THE EPIGASTRIC PAIN MIGHT HAVE BEEN DUE TO ULCER THAT BROKE THROUGH.

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JANSA24890(1) USA health 8yr M
professional

Recovered
Serious

Hyperglycemia (Unknown)
Diarrhoea (Unknown)
Glycosuria (Unknown)

tablet -- 2mg (15-JUN-1998 / Unknown)

Event Description: PHYSICIAN REPORTS AN 8-YEAR-OLD MALE PATIENT ON RISPERIDONE, 2 MG/DAILY, WAS EXPERIENCING DIARRHEA FOR SEVERAL DAYS AND WAS HOSPITALIZED. ON ROUTINE ADMISSION SCREENING THE PATIENT'S BLOOD GLUCOSE WAS HIGH AND GLUCOSE WAS ALSO FOUND IN THE URINE. INTRAVENOUS FLUIDS WERE ADMINISTERED AND THE EVENTS RESOLVED. RISPERIDONE THERAPY CONTINUES. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

Causality Per Reporter: possible

Causality Per Company: possible

Indications: Tourette

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JANSA24893(1) USA health 48yr M 2 month(s) at onset
professional

Unknown
Serious

Diabetes Mellitus Aggravated (15-AUG-1998)

tablet -- 8mg (15-AUG-1998 / 01-OCT-1998)

Causality Per Company: possible

Event Description: PHARMACIST REPORTS A 45-YEAR-OLD MALE (DIABETIC) WHO EXPERIENCED A BLOOD SUGAR INCREASE WHEN HE WAS STARTED ON RISPERIDONE (8MG DAILY), ON 15-AUG-98. BLOOD SUGAR MONITORING WAS DONE BY PATIENT AND SPECIFIC RESULTS UNKNOWN. RISPERIDONE WAS DISCONTINUED 01-OCT-98. OUTCOME UNKNOWN. NO ADDITIONAL INFORMATION EXPECTED.

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JANSA24894(1) USA health 51yr M
professional

Death
Serious

Renal Failure Acute (20-OCT-1998)
Diabetes Mellitus Aggravated (18-OCT-1998)
Appetite Absent (17-OCT-1998)

Volume 15/Page 126

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JJRP 00384114

D821.128

R. 6292

tablet 1 mg - 1mg (09-OCT-1998 / 13-OCT-1998)
Ref.no. (Vers.no.) City Pris. source Age Sex Latency Outcome
Seriousness Reaction 58
Formul. Strength-Unit dose (Therapy start date/end date)
tablet 1 mg - .5mg (14-OCT-1998 / 15-OCT-1998)

Event Description: PSYCHIATRIST REPORTS A 61-YEAR-OLD MALE PATIENT WITH IDDM AND HISTORY OF CVA'S (1992 AND JUL-96) WHO PRESENTED WITH AGITATION AND AGGRESSION IN EARLY OCT-98. RISPERIDONE WAS STARTED ON 08-OCT-98 AT 1 MG BID. PATIENT HAD NO PRIOR PSYCHIATRIC HISTORY. THE PATIENT'S CONDITION WORSENER OVER THE NEXT COUPLE OF DAYS AND HE DEVELOPED APATHY, WEAKNESS AND URINARY AND FECAL INCONTINENCE. RISPERIDONE DOSE WAS DECREASED TO 0.5 MG BID DAILY WITHOUT IMPROVEMENT. A NEUROLOGY CONSULT FELT THE PATIENT'S EVENTS HAD A NEUROLOGICAL ETIOLOGY AS OPPOSED TO A PSYCHIATRIC OR PHARMACOLOGICAL ETIOLOGY. A CT OF THE BRAIN WAS PERFORMED BUT THE RESULTS ARE NOT KNOWN BY THE REPORTER. RISPERIDONE WAS DISCONTINUED ON 15-OCT-98. TWO DAYS LATER THE PATIENT BEGAN TO REFUSE FLUIDS AND FOOD; HIS URINARY OUTPUT DECREASED AND TUB FEEDINGS WERE INITIATED. BUN AND CREATININE VALUES ARE NOT AVAILABLE; BASELINE VALUES ARE NOT KNOWN BY REPORTER. ON THE EVENING OF 19-OCT-98 PATIENT EXPERIENCED MODERATE SWEATING WITHOUT A FEVER OR CHEST PAIN. A GLUCOSE BY FINGERSTICK WAS ELEVATED (240). HE DIED AT HOME THE FOLLOWING DAY. AN AUTOPSY WAS NOT PERFORMED. REPORTER STATES CAUSE OF DEATH TO BE RENAL FAILURE, UNRELATED TO RISPERIDONE THERAPY. ADDITIONAL INFORMATION INCLUDING A COPY OF THE DEATH CERTIFICATE HAS BEEN REQUESTED.

Urinary Incontinence (??-OCT-1998)
Fecal Incontinence (??-OCT-1998)
Weakness Generalized (??-OCT-1998)
Apathy (??-OCT-1998)
Causality Per Reporter: not related
Causality Per Company: doubtful
Indications: Explosive Personality Disorder
Concomitant Diseases: Homiparesis; Aphasia

JAUSA25008(6) USA literature 48yr M 15 day(s) at onset Recovered
Serious
tablet 1 mg - 1mg (04-AUG-1998 / Unknown)
tablet - - 3mg (Unknown / 19-SEP-1998)

Event Description: PHARMACIST REPORTS A 60-YEAR-OLD MALE PATIENT HAD TAKEN RISPERIDONE 8 MG/DAILY FOR APPROXIMATELY TWO WEEKS. THE PATIENT "WAS FOUND IN HIS APARTMENT" AND HOSPITALIZED. IT IS UNKNOWN IF HE WAS UNCONSCIOUS. THE REPORTER INDICATES THE PATIENT HAD EXPERIENCED SEIZURES (UNWITNESSED); HIS SODIUM WAS LOW ON ADMISSION TO THE HOSPITAL. ADDITIONAL INFORMATION HAS BEEN REQUESTED.
F O L L O W U P (DEC98):
PHYSICIAN REPORTS A 49-YEAR-OLD MALE PATIENT PRESENTED IN THE EMERGENCY ROOM AFTER HAVING A GENERALIZED SEIZURE. THE PATIENT'S SODIUM WAS 114 MEQ/L. ON 22-SEP-98 HE WAS CYANOTIC AND REQUIRED INTUBATION. THE EKG REVEALED A LEFT BUNDLE BRANCH BLOCK WITH ST ELEVATION. THE CHEST X-RAY REVEALED BILATERAL INFILTRATES. THE PATIENT'S BLOOD SUGAR WAS 174. THE PATIENT WAS ADMITTED TO THE ICU WITH THE DIAGNOSIS OF HYPONATREMIA, GENERALIZED SEIZURES, ASPIRATION PNEUMONIA AND A POSSIBLE ANTERIOR WALL MYOCARDIAL INFARCTION. FOLLOWING ADMISSION TO THE ICU THE PATIENT'S SODIUM FELL TO 110 MEQ/L. HE WAS TREATED WITH HYPERTONIC SALINE AND THE SODIUM CORRECTED TO 120 MEQ/L. THE PATIENT ALSO DEVELOPED ACUTE RHABDOMYOLYSIS; CPK WAS 100,000. THE PATIENT WAS TREATED WITH 5% DEXTROSE IN WATER WITH 2 AMPOLLES OF SODIUM BICARBONATE AND 25 GMS OF MANNITOL. THE FLUID OUTPUT WAS MANAGED WITH FURSEMIDE AND INTRAVENOUS FLUIDS. THE SODIUM SLOWLY INCREASED TO 125 MEQ/L THEN TO 135 MEQ/L. THE RHABDOMYOLYSIS CLEARED WITHIN SIX DAYS. DURING THE COURSE OF HIS HOSPITALIZATION HE DEVELOPED CELLULITIS OF THE RIGHT LOWER EXTREMITY. THE PATIENT WAS

Rhabdomyolysis (18-AUG-1998)
Pneumonia (18-AUG-1998)
Myocardial Infarction (18-AUG-1998)
Seizures Cerebral (18-AUG-1998)
Hyperglycaemia (18-AUG-1998)
Bundle Branch Block (Unknown)
Cellulitis (Unknown)
Sinus (18-AUG-1998)
Cyanosis (18-AUG-1998)
Causality Per Reporter: probable
Causality Per Company: possible
Indications: Unspecified Psychosis
Concomitant Diseases: Functional And Undiagnosed Cardiac
Murmurs; Paraneoplastic Type Schizophrenia

Idoback 18JUN00

Volume 15/Page 127

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JJRP 00384115
D821.129

R. 6293

Ref.no.(vers.no.) Cty Prim. source Age Sex Latency Outcome Reaction 68
Seriousness

Formul Strength-Unit dose (Therapy start date/end date)

DISCHARGED. IT WAS REPORTED THAT THE CELLULITIS WAS IMPROVING WHEN THE PATIENT WAS SEEN BY THE DOCTOR ON A FOLLOW UP VISIT. ADDITIONAL INFORMATION IS NOT EXPECTED.

F O L L O W U P (22-DEC-97):

THIS CASE REPORT WAS PUBLISHED IN THE ANNUALS OF CLINICAL PSYCHIATRY, VOL.9, NO.3, 1997, P 181-183. ON 04-AUG-98 THE PATIENT WAS HOSPITALIZED FOR AN ACUTE EPISODE OF PARANOID SCHIZOPHRENIA. HE HAD A HISTORY OF BEING TREATED WITH NEUROLEPTICS SINCE 1989. EXAMINATION DID NOT INDICATE ANY MAJOR PHYSICAL ILLNESS OR ANY EVIDENCE OF POLYDIPSIA. THE SODIUM WAS 136 MEQ/L AND THE URINE AND DRUG SCREEN WERE BOTH NEGATIVE. HE WAS STARTED ON RISPERIDONE 1 MG TWICE DAILY WHICH WAS INCREASED TO 8 MG TWICE DAILY. HE WAS NOT ON ANY CONCOMITANT MEDICATION. HE WAS DISCHARGED ON 12-AUG-98. SEVEN DAYS LATER HE WAS ADMITTED TO THE EMERGENCY ROOM FOLLOWING A SEIZURE. HE WAS FOUND TO BE HYPONATRAEMIC (114 MEQ/L) AND WAS CYANOTIC. AN ECG REVEALED A LEFT BUNDLE BRANCH BLOCK AND ST ELEVATION. A CHEST FILM INDICATED BILATERAL INFILTRATES, POTASSIUM WAS 4.1 MEQ/L, CHLORIDE WAS 107 MEQ/L, BUN WAS 8, CREATININE WAS 0.7, WITH A BLOOD SUGAR OF 174 MG%. HE WAS ADMITTED TO THE INTENSIVE CARE UNIT AND WAS DIAGNOSED WITH HYPONATRAEMIA, GENERAL SEIZURES, (ANOTHER SEIZURE OCCURRED IN THE EMERGENCY ROOM) AND POSSIBLE ASPIRATION PNEUMONIA WITH A POSSIBLE ANTERIOR MYOCARDIAL INFARCTION. FOLLOWING ADMISSION TO THE INTENSIVE CARE UNIT, THE SODIUM DROPPED TO 110 MEQ/L. HE WAS TREATED WITH HYPERTONIC SALINE AND THE SODIUM CORRECTED TO 130 MEQ/L. THE SODIUM SLOWLY ROSE TO 136 MEQ/L. HE DEVELOPED ACUTE RABDOMYOLYSIS WITH A CPK OF 100,000. THE RABDOMYOLYSIS CLEARED IN SIX DAYS BUT DURING THE HOSPITALIZATION HE DEVELOPED CELLULITIS OF HIS LEFT LOWER EXTREMITY. HE STABILIZED AND WAS TRANSFERRED BACK TO THE MENTAL HEALTH CENTER WHERE HE RECEIVED HALOPERIDOL AND A REPEAT SODIUM WAS 137 MEQ/L. THE PHYSICIAN ASSURES THAT THE MECHANISM OF SICKLE WAS RESPONSIBLE FOR THE CLINICAL PICTURE.

ADDITIONAL INFORMATION 28-MAR-99:

IT HAS BEEN

DETERMINED THAT REFNO-49764 IS A DUPLICATE OF REFNO-51151. INFORMATION FROM REFNO-49764 HAS BEEN MERGED INTO REFNO-51151 AND REFNO-49764 WILL BE NEUTRALIZED FROM JANSSEN DRUG SAFETY DATABASE.

JAUSA25075(1)	USA health professional	75yr F	No Change/Not Yet Subsidied Not Serious	Hypoglycaemia (25-OCT-1996) Causality Per Reporter: possible
tablet	2mg (03-OCT-1996 / Unknown)			Causality Per Company: possible

Event Description: PHARMACIST REPORTS A 75-YEAR-OLD CONSUMER HAS EXPERIENCED A DECREASED BLOOD SUGAR WHILE ON RISPERIDONE 2 MG DAILY. THE ROUTINE BLOOD SUGAR WAS DRAWN ON 25-OCT-98 AND THE RESULTS WERE 38. BASELINE WAS NOT AVAILABLE. THE PATIENT HAS DIABETES AND IS ON ROUTINE BLOOD SUGAR COVERAGE. RISPERIDONE THERAPY CONTINUES. NO ADDITIONAL INFORMATION IS EXPECTED.	Indications: Bipolar Disorder Concomitant Diseases: Hypertension

JAUSA25080(2)	USA health professional	Unknown Not Serious	Blood Sugar Increased (Unknown) Causality Per Company: possible
tablet			

Volume 15/Page 128

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D821.130

JRP 00384116

R. 6294

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	60

Formul Strength Unit dose (Therapy start date/end date)

Event Description: PHARMACIST REPORTS A PATIENT WHO EXPERIENCED AN INCREASE IN BLOOD SUGAR LEVELS WHILE BEING TREATED WITH RISPERIDONE.
THE INFORMATION AVAILABLE ON THIS CASE IS VERY SKETCHY; NO FURTHER DETAILS ARE EXPECTED (AND CASE HAS BEEN CLOSED).

JAUSA25083(1)	USA health professional	63yr F	1 day(s) at onset	No Change/Not Yet Subsided Not Serious	Diabetes Mellitus Aggravated (04-NOV-1998) Causality Per Reporter: probable

tablet 1 mg - .5mg (03-NOV-1998 / Unknown)

Causality Per Company: possible

Event Description: PHARMACIST REPORTS AN 83-YEAR-OLD FEMALE DIABETIC PATIENT WHO EXPERIENCED AN INCREASE IN BLOOD SUGAR LEVELS (800+ IN MORNINGS) ONE DAY AFTER STARTING RISPERIDONE (0.5 MG / TWICE DAILY). ADDITIONAL INFORMATION HAS BEEN REQUESTED.

Indications: Alzheimer's Disease

JAUSA25088(1)	USA health professional	89yr F	No Change/Not Yet Subsided Serious	Diabetes Mellitus (Unknown) Liver Function Tests Abnormal Mos (Unknown)

tablet - - 4mg (15-JUL-1998 / Unknown)

Causality Per Reporter: possible

Event Description: PHYSICIAN REPORTS A 39-YEAR-OLD FEMALE PATIENT ON RISPERIDONE 4 MG DAILY, IS EXPERIENCING AN INCREASED BLOOD SUGAR AND LIVER FUNCTION TESTS. THE PATIENT WAS ADMITTED TO A PSYCHIATRIC FACILITY FOR MANAGEMENT OF HER DEPRESSION AND THE ABNORMAL RESULTS WERE DISCOVERED ON ROUTINE ADMISSION SCREENING. THE PATIENT'S BLOOD SUGAR WAS 600 PRIOR TO THE ADMINISTRATION OF CLIBENCLAMIDE. THE BLOOD SUGAR THEN DECREASED TO 81. THE PATIENT HAS A HISTORY OF SUBSTANCE ABUSE, BOTH ALCOHOL AND COCAINE, HOWEVER HAS NOT HAD AN ELEVATION OF HER LIVER ENZYMES IN THE PAST. RISPERIDONE THERAPY CONTINUES. THE PHYSICIAN PLANS TO STOP ALL MEDICATIONS AND WILL REPEAT THE LAB WORK IN ONE MONTH. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

Causality Per Company: possible

Indications: Depressive Disorder, Not Elsewhere Classified

Company Remarks: PATIENT'S BLOOD SUGAR BEFORE RISPERIDONE IS UNKNOWN. BESIDES SHE HAS A FAMILY HISTORY OF DIABETES.

JAUSA25108(1)	USA health professional	25yr M	8 month(s) at onset	No Change/Not Yet Subsided Serious	Ketacidosis (02-NOV-1998) Diabetes Mellitus (02-NOV-1998) Neuroleptic Malignant Syndrome (02-NOV-1998) Hepatic Enzymes Increased (02-NOV-1998) Respiratory Distress (02-NOV-1998)

tablet - - 4.5mg (15-FEB-1998 / 03-NOV-1998)

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Volume 15/Page 129

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JJRP 00384117

D821.131

R. 6295

Ref.no.(vers.no.) Ccy Prim. source Age Sex Latency Outcome Reaction 61
Seriousness

Formal Strength/Unit dose (Therapy start date/end date)

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Event Description: 25-YEAR-OLD FEMALE PATIENT ON RISPERIDONE SINCE 15-FEB-98 WAS ADMITTED TO THE HOSPITAL ON 2-NOV-98 WITH SIGNS OF NMS (LOW-GRADE FEVER, MUSCLE RIGIDITY, TREMORS, ELEVATED BLOOD PRESSURE AND ELEVATED HEART RATE). ABNORMAL LAB VALUES INCLUDED ELEVATED CPK (3000), INCREASED BLOOD SUGAR (1424) AND ELEVATED LIVER FUNCTION TESTS. A HEPATITIS PROFILE WAS NOT PERFORMED; THERE IS NO HISTORY OF DRUG OR ALCOHOL ABUSE. ON ADMISSION AN INSULIN DRIP WAS STARTED AND THE BLOOD SUGAR DECREASED TO 200. THERE IS NO PAST MEDICAL OR FAMILY HISTORY OF DIABETES; THE PATIENT DENIED POLYURIA, POLYDIPSIA AND POLYPHAGIA PRIOR TO ADMISSION. RISPERIDONE WAS DISCONTINUED ON 3-NOV-98. ON 5-NOV-98 THE PATIENT SHOWED SIGNS OF RESPIRATORY DISTRESS, WAS INTUBATED AND PLACED ON A RESPIRATOR. THE REPORTER INDICATES THE DECREASED RESPIRATORY STATUS WAS DUE TO THE DIABETIC KETOACIDOSIS. SINCE INTUBATION THE PATIENT SEEMS MORE ALERT. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

Causality Per Reporter: probable
Causality Per Company: doubtful
Indications: Unspecified Schizophrenia
Concomitant Diseases: Obesity

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JAUSA25307(1) USA health 35yr F 2 day(s) at onset No Change/Not Yet Subsidized Diabotom Mellitus Aggravated (18-SEP-1998)
professional Not Serious Causality Per Reporter: probable

tablet 1 mg - 1mg (17-SEP-1998 / 14-OCT-1998)
tablet 1 mg - 1mg (14-OCT-1998 / 28-OCT-1998)

Causality Per Company: possible

tablet 1 mg - .5mg (28-OCT-1998 / Unknown)

Indications: Hallucinations

Event Description: NURSE REPORTS A DIABETIC PATIENT WHO EXPERIENCED AN INCREASE IN BLOOD SUGAR (405 IN A.M.) ON 18-SEP-98 AFTER BEING TREATED WITH RISPERIDONE (2MG DAILY) FOR TWO DAYS. PATIENT REMAINS ON RISPERIDONE WITH CONTINUED ELEVATED BLOOD SUGARS (ABOVE 300). DOSAGE ADJUSTMENTS HAVE BEEN MADE TO CONTROL THE HALLUCINATIONS. ADJUSTMENTS (NOS) IN INSULIN THERAPY WERE MADE ON 11-NOV-98 IN AN EFFORT TO CONTROL BLOOD SUGARS. NO ADDITIONAL INFORMATION EXPECTED.

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JAUSA25424(2) USA health Recovered Gait Abnormal (11-NOV-1998);
professional Not Serious Vomiting (11-NOV-1998)
Sedation Excessive (Unknown)
Hyperglycemia (11-NOV-1998)
Nausea (11-NOV-1998)
tablet - - - (16-JUL-1998 / 31-OCT-1998)
tablet - - 4mg (01-NOV-1998 / 04-NOV-1998)

Event Description: PHARMACIST REPORTS A MALE PATIENT WHOSE DOSE OF RISPERIDONE WAS INCREASED TO 4 MG DAILY ON 1-NOV-98 AND DISCONTINUED ON 4-NOV-98. ON THE EVENING OF 11-NOV-98 THE PATIENT BEGAN TO EXPERIENCE AN ABNORMAL GAIT. THIS WAS DISCOVERED WHEN THE PATIENT WAS OBSERVED STUMBLING IN THE HALLWAY. THE PATIENT ALSO PRESENTED WITH NAUSEA

Causality Per Reporter: possible

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Volume 15/Page 130

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JRP 00384118
D821.132

R. 6296

Ref.no.(vers.no.)	Cty	Prim..source	Age	Sex	Latency	Outcome Seriousness	Reaction	62

Formul Strength-Unit dose (Therapy start date/end date)

AND VOMITING. AN INTRAVENOUS WAS STARTED TO ADMINISTER FLUIDS AND ALSO A FOLEY CATHETER TO MONITOR HIS URINE OUTPUT. THE PATIENT THEN FELL INTO A VERY DEEP SLEEP. THE PATIENT'S BLOOD SUGAR ON THE MORNING OF THE EVENT WAS 200 (FASTING). THE PATIENT AWOK THE NEXT MORNING. EVENTS RESOLVED. NO ADDITIONAL INFORMATION IS EXPECTED.

Indications: Unspecified Schizophrenia

Causality Per Company: possible

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JANSA25463(1)	USA health professional	16yr F	No Change/Not Yet Subsided Not Serious	Hyperglycaemia (Unknown) Causality Per Reporter: possible

tablet -- 4mg (15-MAY-1996 / Unknown)

Causality Per Company: possible

Event Description: PHYSICIAN REPORTS A 16-YEAR-OLD FEMALE PATIENT ON RISPERIDONE 4 MG DAILY HAS EXPERIENCED AN INCREASE IN BLOOD SUGAR. THE PATIENT'S FASTING BLOOD SUGAR WAS 300. THERE IS NO HISTORY OF DIABETES. BASELINE BLOOD SUGAR WAS WITHIN NORMAL LIMITS. EVALUATION IS ONGOING. ADDITIONAL INFORMATION WILL BE PROVIDED WHEN IT BECOMES AVAILABLE.

Indications: Explosive Personality Disorder

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JANSA25496(1)	USA patient/consum er	71yr M	No Change/Not Yet Subsided Not Serious	Diabetes Mellitus Aggravated (Unknown) Delusion (Unknown)

tablet -- 1mg (20-SEP-1996 / Unknown)

Causality Per Reporter: not related

Event Description: CONSUMER REPORTS HER 71-YEAR-OLD HUSBAND WITH NIDON EXPERIENCED ELEVATED SERUM GLUCOSE (215) AND DELUSIONS DURING TREATMENT WITH RISPERIDONE (1 MG DAILY). RISPERIDONE AND CONCOMITANT GLIBENCLAMIDE AND Cimetidine WERE DISCONTINUED WITHOUT IMPROVEMENT. RISPERIDONE AND GLIBENCLAMIDE WERE THEN RESTARTED; REPEAT GLUCOSE WAS 151. GLIBENCLAMIDE DOSE HAS BEEN INCREASED AND SERUM GLUCOSE WILL BE MONITORED. ADDITIONAL INFORMATION WILL BE PROVIDED WHEN IT BECOMES AVAILABLE.

Causality Per Company: possible

Indications: Delusions

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JANSA25565(1)	USA patient/consum er	40yr F	No Change/Not Yet Subsided Not Serious	Diabetes Mellitus (Unknown) Feeling Strange (Unknown)

tablet -- 8mg (30-SEP-1996 / Unknown)

Causality Per Company: possible

Indications: Schizo-Affective Type Schizophrenia

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Volume 15/Page 131

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JJRP 00384119
D821.133

R. 6297

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction

Formul Strength-Unit dose (Therapy start date/end date)
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Event Description: CONSUMER REPORTS HER DAUGHTER HAS BEEN ON RISPERIDONE SINCE 30-SEPT-99 AND ON ROUTINE TESTING WAS FOUND TO HAVE INCREASED BLOOD SUGAR (BS). THE DIABETES IS DIST CONTROLLED AND HER BLOOD SUGAR WILL BE MONITORED. THE PATIENT IS OBSE AND WAS STARTED ON DEXEPFLURAMINE. THE PATIENT BEGAN FEELING STRANGE AND DEXEPFLURAMINE WAS DISCONTINUED 3 DAYS LATER. THE EVENT RESOLVED ONCE DEXEPFLURAMINE WAS DISCONTINUED. RISPERIDONE THERAPY CONTINUES. ADDITIONAL INFORMATION IS NOT EXPECTED.

JANSA25627(1)	USA health professional	M	No Change/Not Yet Subsided Serious	Ketoacidosis (Unknown) Neuroleptic Malignant Syndrome (Unknown) Diabetes Mellitus (Unknown) Depression (Unknown)

tablet -- 5mg (16-OCT-1999 / Unknown)
Event Description: PHYSICIAN REPORTS A MALE PATIENT ON RISPERIDONE HAD EXPERIENCED A DEPRESSIVE EPISODE AND WAS ADMITTED TO THE PSYCHIATRIC WING OF THE HOSPITAL. THE PATIENT HAS DEVELOPED DIABETES MELLITUS SINCE THE START OF RISPERIDONE. THERE IS NO PREVIOUS HISTORY OF DIABETES KNOWN TO THIS REPORTER. ON APPROXIMATELY 8-DEC-99 THE PATIENT'S FASTING BLOOD SUGAR WAS OVER 1,000. IT WAS DETERMINED THAT THE PATIENT WAS EXPERIENCING KETOACIDOSIS. THE PATIENT WAS TRANSFERRED TO THE INTENSIVE CARE UNIT OF THE HOSPITAL. AN INSULIN DRIP WAS STARTED. THE PATIENT'S BLOOD SUGAR HAS DECREASED TO 300. THE DIAGNOSIS OF NEUROLEPTIC MALIGNANT SYNDROME WAS ALSO MADE BASED ON AN ELEVATED TEMPERATURE (107 F) AND INCREASED CPK (NUS). DANTROLENE WAS GIVEN WITHOUT RESOLVE. THE PATIENT REMAINS HOSPITALIZED ON A RESPIRATOR. ADDITIONAL INFORMATION SURROUNDING THIS EVENT HAS BEEN REQUESTED.
Causality Per Reporter: probable
Causality Per Company: possible
Indications: Bipolar Disorder

JANSA26210(1)	USA health professional	34yr M	No Change/Not Yet Subsided Serious	Ketoacidosis (29-DEC-1999) Hyperglycaemia (20-DEC-1999) Renal Failure Acute (77-DEC-1999) Pancreatitis (77-DEC-1999) Rhabdomyolysis (77-DEC-1999)

tablet -- 6mg (30-NOV-1999 / Unknown)
Event Description: PHYSICIAN REPORTS A MALE PATIENT WITHOUT PREVIOUS KNOWN HISTORY OF DIABETES WHO WAS ADMITTED TO THE ICU WITH DIABETIC KETOACIDOSIS, RENAL AND PANCREATIC FAILURE, APPROXIMATELY ONE MONTH AFTER STARTING RISPERIDONE. THERAPY WAS INITIATED IN LATE NOV-99 AND SLOWLY TITRATED TO 8 MG DAILY OVER A ONE MONTH PERIOD. CONCOMITANT MEDICATIONS INCLUDE DEPAKOT FOR HIS BIPOLAR DISEASE. PATIENT HAS ALSO DEVELOPED RABDOMYOLYSIS. THERE IS NO KNOWN HISTORY OF ALCOHOL OR DRUG ABUSE; THERE IS A FAMILY HISTORY OF DIABETES. RISPERIDONE WAS DISCONTINUED ON ADMISSION; HE HAS NOT YET RECOVERED. ADDITIONAL INFORMATION INCLUDING BASELINE FASTING SERUM GLUCOSE AND DISCHARGE SUMMARY HAS BEEN REQUESTED.
Causality Per Reporter: possible
Causality Per Company: doubtful
Indications: Bipolar Disorder

JANSA26646(1)	USA health professional	18yr M	8 month(s) at onset No Change/Not Yet Subsided Not Serious	Diabetes Mellitus (Unknown) Causality Per Company: doubtful

Volume 15/ Page 132

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JRP 00384120
D821.134

R. 6298

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	64									
Formal Strength-Unit dose (Therapy start date/end date)																	
<table border="1"> <tr> <td>tablet</td> <td>---</td> <td>(15-JUL-1993 / Unknown)</td> <td></td> <td></td> <td></td> <td></td> <td>Indications: Explosive Personality Disorder</td> <td></td> </tr> </table>									tablet	---	(15-JUL-1993 / Unknown)					Indications: Explosive Personality Disorder	
tablet	---	(15-JUL-1993 / Unknown)					Indications: Explosive Personality Disorder										

Concomitant Diseases: Oligophrenia

Event Description: A PEDIATRIC ENDOCRINOLOGIST REPORTS THAT A CONSUMER DEVELOPED DIABETES MELLITUS FOLLOWING 6 MONTHS OF RISPERIDONE TREATMENT. ADDITIONAL INFORMATION IS NOT EXPECTED.

JANSA26688(1)	USA health professional	23yr M	No Change/Not Yet Subdued Serious	Ketacidosis (Unknown) Diabetes Mellitus (Unknown)
tablet	---			Causality Per Company: doubtful

Indications: Unspecified Schizophrenia

Event Description: PHYSICIAN REPORTS THAT HIS PATIENT WAS HOSPITALIZED WITH KETOACIDOSIS AND WAS DIAGNOSED WITH DIABETES MELLITUS AFTER RECENTLY STARTING ON RISPERIDONE.

JANSA28741(3)	USA health professional	30yr F	8 month(s) at onset	No Change/Not Yet Subdued Not Serious	Blood Sugar Increased (10-JAN-1995) Causality Per Reporter: possible
tablet	---	3mg (16-MAR-1994 / 15-APR-1994)			
tablet	---	6mg (16-APR-1994 / 17-JUL-1995)			Causality Per Company: possible

Indications: Unspecified Schizophrenia

Event Description: PHYSICIAN REPORTS A FEMALE PATIENT ON RISPERIDONE HAS EXPERIENCED AN INCREASE IN BLOOD SUGAR. THIS WAS IDENTIFIED ON ROUTINE SCREENING. THE PATIENT'S BLOOD SUGAR WAS 425. RISPERIDONE THERAPY HAS BEEN DISCONTINUED. ADDITIONAL INFORMATION IS NOT EXPECTED.

Concomitant Diseases: Obesity; Hypertriglycerid; Haemoglobin Decreased; Nonspecific Elevation Of Levels Of Transaminase Or Lactic Acid Dehydrogenase (Ldh)

JANSA28788(1)	USA patient/consumer	14yr F	Recovered Not Serious	Hypoglycaemia (Unknown) Dizziness (Unknown) Drowsiness (Unknown)
tablet	---	3.5mg		

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Volume 15/Page 133

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 JJRP 00384121
 D821.135

R. 6299

Ref.no. (vers.no.)	Cty	Pris. source	Age	Sex	Latency	Outcome Seriousness	Reaction	85
Formal Strength-Unit dose (Therapy start date/end date)								
Event Description: A MOTHER REPORTS THAT HER DAUGHTER BECAME HYPOGLYCAEMIC FOLLOWING THE USE OF RISPERIDONE FOR 10 DAYS. THIS ADOLESCENT USED RISPERIDONE FOR 1 1/2 YEARS WITHOUT ANY ADVERSE EFFECTS. SHE WAS EXPERIENCING DROWSINESS DURING THE DAY AND THE RISPERIDONE DOSING SCHEDULE WAS CHANGED FROM 1 MG A.M., 1 MG P.M., AND 1.5 MG HS TO 1 MG AM AND 2.5 MG AT HS. TWO DAYS AFTER THE CHANGE, SHE BECAME HYPOGLYCAEMIC AND WAS TREATED WITH INTRAVENOUS FLUIDS IN AN EMERGENCY ROOM. THE DOSING SCHEDULE WAS RESUMED TO 3 DIVIDED DOSES DAILY AND FURTHER EPISODES HAVE NOT OCCURRED.								
JANSA28991(1)	USA	patient/consum	40yr	F		No Change/Not Yet Subsidized Not Serious	Blood Sugar Increased (Unknown) Confusion (Unknown)	Causality Per Company: doubtful
tablet 6 mg - 6mg (15-MAR-1994 / Unknown)							Causality Per Company: possible	
Event Description: A PATIENT REPORTS THAT SHE EXPERIENCED AN ELEVATED GLUCOSE AFTER 3 YEARS OF RISPERIDONE THERAPY. SHE ALSO REPORTS THAT SHE IS EXPERIENCING CONFUSION. ADDITIONAL INFORMATION IS NOT EXPECTED.							Indications: Other Unknown And Unspecified Cause Of Morbidity Or Mortality	
JANSA27389(3)	USA	health professional				Unknown Not Serious	Diabetes Mellitus (Unknown)	Causality Per Company: doubtful
tablet - - -								
Event Description: PHARMACIST REPORTS PATIENT EXPERIENCING DIABETES MELLITUS WHILE ON RISPERIDONE. UNABLE TO OBTAIN FURTHER INFORMATION.								
JANSA27428(1)	USA	health professional	42yr	M		No Change/Not Yet Subsidized Not Serious	Blood Sugar Increased (Unknown)	Causality Per Reporter: possible
tablet - - 6mg							Causality Per Company: possible	
Event Description: PHARMACIST REPORTS 42-YEAR-OLD MALE PATIENT (TWO OF TWO PATIENTS) EXPERIENCING INCREASED BLOOD SUGAR WHILE ON RISPERIDONE. PATIENT HAS NO FAMILY HISTORY OF DIABETES AND DOES NOT COMPLAIN OF POLYDIPSIA OR POLYURIA. PATIENT RESIDES IN MENTAL WARD OF CORRECTIONAL FACILITY. ON AN ANNUAL EXAM, PHYSICIAN DISCOVERED FASTING BLOOD GLUCOSE							Indications: Unspecified Schizophrenia Concomitant Diseases: Depressive Disorder, Not Elsewhere Classified	

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Volume 15/ Page 134

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JJRP 00384122

D821.136

R. 6300

Ref.no.(vars.no.) Cty Prix. source Age Sex Latency Outcome Reaction 86
Seriousness
Formul. Strength-Unit dose (Therapy start date/end date)
OF 680 MG/L (NO BASELINE VALUE AVAILABLE). RISPERIDONE THERAPY CONTINUES. NO ADDITIONAL
INFORMATION IS EXPECTED.

JANSA27441(1) USA health 37yr M No Change/Not Yet Blood Sugar Increased (Unknown)
professional Subsidied Akathisia (Unknown)
Not Serious Tremor (Unknown)

tablet . . . 4mg

Event Description: PHARMACIST REPORTS 37-YEAR-OLD PATIENT (ONE OF TWO PATIENTS)
EXPERIENCING INCREASED BLOOD GLUCOSE WHILE ON RISPERIDONE. PATIENT ALSO EXPERIENCED
AKATHISIA AND HAND TREMORS FOR WHICH HE WAS TREATED WITH DIPHEHYDRAMINE AND THE EVENTS
RESOLVED. PHARMACIST EXPLAINED THAT THESE MOVEMENT DISORDERS OCCURRED WHEN THE
RISPERIDONE DOSE WAS INCREASED TO GREATER THAN 6 MG/DAY. PATIENT RESIDES IN MENTAL
CORRECTIONAL FACILITY. RECENT LAB WORK REVEALED FASTING BLOOD SUGARS RANGING FROM 300-400
MG/DL WHILE RECEIVING INSULIN THERAPY. PATIENT DOES NOT HAVE A FAMILY HISTORY OF DIABETES
AND DOES NOT COMPLAIN OF POLYDIPSIA OR POLYURIA. PATIENT HAS HYPERCHOLESTEROLAEMIA FOR
WHICH HE IS BEING TREATED THROUGH DIET MODIFICATION. PATIENT'S RISPERIDONE THERAPY HAS
BEEN TAPERED DOWN FROM 10 MG/DAY TO 4 MG/DAY WHICH HE IS CURRENTLY RECEIVING. PHYSICIAN
PLANS TO DISCONTINUE RISPERIDONE THERAPY. NO ADDITIONAL INFORMATION IS EXPECTED.

Causality Per Reporter: possible

Causality Per Company: possible

Indications: Unspecified Schizophrenia

Concomitant Diseases: Hypercholesterolaemia

JANSA27702(11) USA health 50yr F No Change/Not Yet Multiple Sclerosis Aggravated (Unknown)
professional Subsidied Constipation (??-OCT-1998)
Serious Gait Abnormal (??-OCT-1998)
Faecal Incontinence (??-OCT-1998)
Muscle Rigidity (??-OCT-1998)
Chest Pain (??-OCT-1998)
Parosmia (??-OCT-1998)
Numbness Localized (Unknown)
Breathing Difficult (Unknown)
Pain (Unknown)
Neuropathy (Unknown)
Diabetes Mellitus (Unknown)

solution . . . (15-FEB-1998 / 15-OCT-1998)

Event Description: A CONSUMER REPORTS THAT SHE EXPERIENCED RIGIDITY DESCRIBED AS A "TIGHT
VISE AROUND HER UPPER LEGS AND TRUNK". SHE IS UNABLE TO WALK WELL AND MUST STOP TO SIT
BEFORE FALLING. THERE ARE TIMES WHEN SHE IS UNABLE TO WALK AT ALL. SHE HAS BEEN USING
RISPERIDONE FOR ELEVEN MONTHS AND ALSO EXPERIENCES CONSTIPATION, WHICH IS RELIEVED BY
MILK OF MAGNESIA, WHICH SOMETIMES CAUSES INCONTINENCE. ADDITIONAL INFORMATION WAS
RECEIVED BY CONSUMER. SHE WAS ORIGINALLY ON RISPERIDONE FOR APPROXIMATELY 8 MONTHS WHEN
THE EVENTS OCCURRED. RISPERIDONE WAS DISCONTINUED AND OLANZAPINE AND HALOPERIDOL WERE
USED BUT SHE EXPERIENCED THE SAME EVENTS. RISPERIDONE WAS RESTARTED AND THE EVENTS
RECURRED. THE PATIENT STATES THAT HER PHYSICIAN FEELS THAT HER SYMPTOMS ARE PSYCHOSOMATIC
AND NOT DRUG RELATED.

F O L L O W U P:

ON 03-JUL-97 PATIENT REPORTS THAT HER SYMPTOMS PERSIST AND HER DOCTORS DO NOT BELIEVE SHE
IS EXPERIENCING ANY PROBLEMS. ON 14-JUL-97 HER ADVOCATE REPORTED THAT THE PATIENT'S
PHYSICIAN HAS NOT RECORDED THAT SHE HAS EXPERIENCED ANY ADVERSE EVENTS WITH RISPERIDONE
USE. HE HAS TOLD THE ADVOCATE THAT THE EVENTS THE PATIENT DESCRIBES ARE NOT IN THE

Causality Per Company: doubtful

Indications: Unspecified Psychosis

Concomitant Diseases: Schizo-Affective Type Schizophrenia;
Diabetes Mellitus Without Mention Of Complication;
Neuropathy

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Volume 15/Page 135

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JJRP 00384123

D821.137

R. 6301

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcomes	Reaction	67
						Seriousness		

Formul Strength-Unit dose (Therapy start date/end date)

PACKAGE INSERT. THIS PATIENT'S MOTHER DOESN'T WANT HER TO STOP USING RISPERIDONE BECAUSE

OF A HISTORY OF VIOLENCE WHEN SHE IS OFF ANTI-PSYCHOTICS.
ADDITIONAL INFORMATION RECEIVED ON 21-AUG-97: THE PATIENT STATES SHE IS STILL EXPERIENCING SYMPTOMS ALONG WITH DIFFICULTY BREATHING AND STATES THAT HER PHYSICIAN FEELS THESE EVENTS ARE PSYCHOSOMATIC SYMPTOMS. RISPERIDONE CONTINUES.

Company Remarks: THE INTERPRETATION OF SYMPTOMS AND DIAGNOSIS ARE TOO VAGUE FOR CAUSAL RELATION.

ADDITIONAL INFORMATION 28-AUG-97: THE PATIENT'S PHYSICIAN REPORTS THAT A MRI INFERRED MULTIPLE SCLEROSIS.

ADDITIONAL INFORMATION 09-SEP-97: THE TREATING PHYSICIAN REPORTS THAT AN MRI EVALUATION INDICATES A PATTERN OF ABNORMALITY STRONGLY SUGGESTIVE OF MULTIPLE SCLEROSIS. THE CONSULTING NEUROLOGIST FEELS THAT THE PATIENT'S COMPLAINTS CAN READILY BE TRACED TO THIS DISORDER, HOWEVER THERE IS NO EVIDENCE OF CORTICAL, MOTOR OR CNS ABNORMALITIES, VISUAL LOSS OR CHANGES IN HER GAIT. THE TREATING PHYSICIAN DOUBTS THAT HER PHYSICAL COMPLAINTS HAVE ANY PHYSICAL BASIS BUT ARE CONTRIVED IN AN EFFORT TO HAVE HER MEDICATIONS DISCONTINUED. SHE HAS HAD SIMILAR COMPLAINTS SINCE 1988. THE PATIENT'S MOST RECENT COMPLAINT IS PAIN NOT ASSOCIATED WITH MUSCLE SPASMS. ETIOLOGY UNKNOWN. HER DIAGNOSIS WAS CORRECTED TO SCHIZOAFFECTIVE DISORDER OF THE BIPOLAR TYPE. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

F O L L O W - U P 01-OCT-97:

INFORMATION RECEIVED FROM THE TREATING PHYSICIAN INDICATES THE FOLLOWING: THIS PATIENT'S "COLD AND BURNING SENSATIONS", NUMBNESS, COMPLAINTS OF SHALLOW BREATHING, INCONTINENCE AND "HEART PAINS" WERE FAMILIAR TO THE HOSPITAL STAFF FOR YEARS. SHE COMPLAINED EVERY DAY THAT HER CONDITION WORSENEO HOWEVER, THERE WAS NO CHANGE IN HER STATUS. ACCORDING TO HER PHYSICIAN: "SHE ALLEGES THAT SHE IS WEAK AND IS UNABLE TO WALK BUT WHEN ANGRY SHE NOT ONLY WALKS, SHE RUNS. THERE IS NO EVIDENCE OF MUSCLE WASTING AND THERE IS REMARKABLE MOTOR CONTROL, AS HER GAIT IS ELABORATED. AN EXAMPLE OF HER PHYSICAL ABILITY WAS WITNESSED BY THE STAFF WHEN SHE GETS INTO AND OUT OF THE WHEELCHAIR EFFORTLESSLY, WITH EXCELLENT CONTROL AND BALANCE". THE PHYSICIAN HAS NOT SEEN HER EXHIBIT ANY PHYSICAL DISCOMFORT OF ANY KIND. HER VISUAL FIELDS ARE REPORTEDLY ARE NORMAL AND SHE HAS NOT HAD ANY VISUAL CHANGES; INCLUDING VISUAL LOSS, OR DOUBLE VISION. THERE ARE NOT ANY TRUE MOTOR ABNORMALITIES EXCEPT FOR MINIMAL (BELOW THE KNEE) BILATERAL, PERIPHERAL NEUROPATHY-- POSSIBLY ATTRIBUTED TO DIABETES. THE DIABETES IS NOT BEING TREATED AT THIS POINT BECAUSE SHE HAS NOT HAD A RECURRENT OF THE ONE TIME ELEVATED BLOOD SUGAR OF OVER 1000 IN A FEW YEARS. THE PHYSICIAN REPORTS THAT SHE IS NOT CLUMSY AND DOES NOT HAVE ANY PROBLEMS WITH HER BALANCE. SHE DOES NOT EXHIBIT ANY CEREBELLAR SIGNS OR SYMPTOMS. THE MRI DEMONSTRATED "SMALL SUBCORTICAL LESIONS" AND "PERIAQUEDUCTAL LESIONS", YET AN MRI OF HER SPINE DID NOT SUGGEST MULTIPLE SCLEROSIS. THE NEUROLOGIST FOUND A POSITIVE BABINSKI REFLEX THAT WAS ABSENT A FEW WEEKS AGO. HER AFFECT IS NOT FLAT AS SHE HAS DEMONSTRATED RAGE VERY WELL. ANOTHER RADIOLOGIST IS BEING SOUGHT TO INTERPRET THE MRI AS SHE DOES NOT EXHIBIT ANY SYMPTOMS OF MULTIPLE SCLEROSIS; THE PERSISTENCE OF THESE SYMPTOMS IS EXPLAINED BY THE PATIENT'S DETERMINATION TO MANIPULATE HER WAY OFF MEDICATION. IT IS THE TREATING PSYCHIATRIST'S OPINION THAT SHE DOES NOT HAVE MULTIPLE SCLEROSIS OR ANY OTHER SERIOUS NEUROLOGICAL DISEASE.

F O L L O W - U P (31-OCT-97):

THE CONSUMER REPORTS THAT SHE DISCONTINUED THE USE OF RISPERIDONE AND THE FOLLOWING EVENTS ADDED: CHEST PAIN, STINGING PAIN AROUND THE HEART, NUMBNESS, AND DYSPNOEA. SHE ALSO REPORTS THAT SHE HAD SOME IMPROVEMENT IN HER ABILITY TO WALK WHEN SHE WAS NOT TAKING

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Volume 15/Page 136

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R. 6302

Ref.no.(Vers.no.) Ctry Prim. source Age Sex Latency Outcome Reaction 68
Seriousness
Formul Strength-Unit dose (Therapy start date/end date)
RISPERIDONE.

JANUSA27702(11) USA health 50yr F No Change/Not Yet Multiple Sclerosis Aggravated (Unknown)
professional Subsidized Constipation (??-OCT-1996)
Serious Gait Abnormal (??-OCT-1996)
Fascial Incontinence (??-OCT-1996)
Muscle Rigidity (??-OCT-1996)
Chest Pain (??-OCT-1996)
Paresthesia (??-OCT-1996)
Numbness Localized (Unknown)
Breathing Difficult (Unknown)
Pain (Unknown)
Neuropathy (Unknown)
Diabetes Mellitus (Unknown)

tablet -- Bag (15-JAN-1997 / Unknown)

Event Description: A CONSUMER REPORTS THAT SHE EXPERIENCED RIGIDITY DESCRIBED AS A "TIGHT VISE AROUND HER UPPER LEGS AND TRUNK". SHE IS UNABLE TO WALK WELL AND MUST STOP TO SIT BEFORE FALLING. THERE ARE TIMES WHEN SHE IS UNABLE TO WALK AT ALL. SHE HAS BEEN USING RISPERIDONE FOR ELEVEN MONTHS AND ALSO EXPERIENCES CONSTIPATION, WHICH IS RELIEVED BY MILK OF MAGNESIA, WHICH SOMETIMES CAUSES INCONTINENCE. ADDITIONAL INFORMATION WAS RECEIVED BY CONSUMER. SHE WAS ORIGINALLY ON RISPERIDONE FOR APPROXIMATELY 8 MONTHS WHEN THE EVENTS OCCURRED. RISPERIDONE WAS DISCONTINUED AND OLANZAPINE AND HALOPERIDOL WERE USED BUT SHE EXPERIENCED THE SAME EVENTS. RISPERIDONE WAS RESTARTED AND THE EVENTS RECURRED. THE PATIENT STATES THAT HER PHYSICIAN FEELS THAT HER SYMPTOMS ARE PSYCHOSOMATIC AND NOT DRUG RELATED.

FOLLOW UP:

ON 09-JUL-97 PATIENT REPORTS THAT HER SYMPTOMS PERSIST AND HER DOCTORS DO NOT BELIEVE SHE IS EXPERIENCING ANY PROBLEMS. ON 14-JUL-97 HER ADVOCATE REPORTED THAT THE PATIENT'S PHYSICIAN HAS NOT RECORDED THAT SHE HAS EXPERIENCED ANY ADVERSE EVENTS WITH RISPERIDONE USE. HE HAS TOLD THE ADVOCATE THAT THE EVENTS THE PATIENT DESCRIBES ARE NOT IN THE PACKAGE INSERT. THIS PATIENT'S MOTHER DOESN'T WANT HER TO STOP USING RISPERIDONE BECAUSE OF A HISTORY OF VIOLENCE WHEN SHE IS OFF ANTI-PSYCHOTICS.

ADDITIONAL INFORMATION RECEIVED ON 21-AUG-97: THE PATIENT STATES SHE IS STILL EXPERIENCING SYMPTOMS ALONG WITH DIFFICULTY BREATHING AND STATES THAT HER PHYSICIAN FEELS THESE EVENTS ARE PSYCHOSOMATIC SYMPTOMS. RISPERIDONE CONTINUES.

ADDITIONAL INFORMATION 28-AUG-97: THE PATIENT'S PHYSICIAN REPORTS THAT A MRI INFERRED MULTIPLE SCLEROSIS.

ADDITIONAL INFORMATION 09-SEP-97: THE TREATING PHYSICIAN REPORTS THAT AN MRI EVALUATION INDICATES A PATTERN OF ABNORMALITY STRONGLY SUGGESTIVE OF MULTIPLE SCLEROSIS. THE CONSULTING NEUROLOGIST FEELS THAT THE PATIENT'S COMPLAINTS CAN READILY BE TRACED TO THIS DISORDER, HOWEVER THERE IS NO EVIDENCE OF CORTICAL, MOTOR OR CVS ABNORMALITIES. VISUAL LOSS OR CHANGES IN HER GAIT. THE TREATING PHYSICIAN DOUBTS THAT HER PHYSICAL COMPLAINTS HAVE ANY PHYSICAL BASIS BUT ARE CONTRIVED IN AN EFFORT TO HAVE HER MEDICATIONS DISCONTINUED. SHE HAS HAD SIMILAR COMPLAINTS SINCE 1988. THE PATIENT'S MOST RECENT COMPLAINT IS PAIN NOT ASSOCIATED WITH MUSCLE SPASMS. ETIOLOGY UNKNOWN. HER DIAGNOSIS WAS CORRECTED TO SCHIZOAFFECTIVE DISORDER OF THE BIPOLAR TYPE. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

FOLLOW UP 01-OCT-97: INFORMATION RECEIVED FROM THE TREATING PHYSICIAN INDICATES THE FOLLOWING: THIS PATIENT'S "COLD AND BURNING SENSATIONS", NUMBNESS, COMPLAINTS OF SHALLOW BREATHING, INCONTINENCE AND "HEART PAINS" WERE FAMILIAR TO THE HOSPITAL STAFF FOR YEARS. SHE COMPLAINED EVERY

Causality Per Company: doubtful

Concomitant Diseases: Schizo-Affective Type Schizophrenia;
Diabetes Mellitus Without Mention Of Complication;
Neuropathy

Company Remarks: THE INTERPRETATION OF SYMPTOMS AND DIAGNOSIS ARE TOO VAGUE FOR CAUSAL RELATION.

1debaeck 16JUN00

Volume 15/Page 137

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JJRP 00384125
D821.139

R. 6303

Ref.no. (vers.no.) - City Prim. source Age Sex Latency Outcome Reaction 69
Seriousness

Formul Strength-Unit dose (Therapy start date/end date)

DAY THAT HER CONDITION WORSEMED HOWEVER, THERE WAS NO CHANGE IN HER STATUS. ACCORDING TO

HER PHYSICIAN: "SHE ALLEGES THAT SHE IS WEAK AND IS UNABLE TO WALK BUT WHEN ANGRY SHE NOT ONLY WALKS, SHE RUNS. THERE IS NO EVIDENCE OF MUSCLE WASTING AND THERE IS REMARKABLE MOTOR CONTROL, AS HER GAIT IS ELABORATED. AN EXAMPLE OF HER PHYSICAL ABILITY WAS WITNESSED BY THE STAFF WHEN SHE GETS INTO AND OUT OF THE WHEELCHAIR EFFORTLESSLY, WITH EXCELLENT CONTROL AND BALANCE". THE PHYSICIAN HAS NOT SEEN HER EXHIBIT ANY PHYSICAL DISCOMFORT OF ANY KIND. HER VISUAL FIELDS ARE REPORTSUDLY ARE NORMAL AND SHE HAS NOT HAD ANY VISUAL CHANGES; INCLUDING VISUAL LOSS, OR DOUBLE VISION. THERE ARE NOT ANY TRUE MOTOR ABNORMALITIES EXCEPT FOR MINIMAL (BELOW THE KNEE) BILATERAL, PERIPHERAL NEUROPATHY - POSSIBLY ATTRIBUTED TO DIABETES. THE DIABETES IS NOT BEING TREATED AT THIS POINT BECAUSE SHE HAS NOT HAD A RECURRENCE OF THE ONE TIME ELEVATED BLOOD SUGAR OF OVER 1000 IN A FEW YEARS. THE PHYSICIAN REPORTS THAT SHE IS NOT CLODY AND DOES NOT HAVE ANY PROBLEMS WITH HER BALANCE. SHE DOES NOT EXHIBIT ANY CEREBELLAR SIGNS OR SYMPTOMS. THE MRI DEMONSTRATED "SMALL SUBCORTICAL LESIONS" AND "PERIAQUEDUCTAL LESIONS", YET AN MRI OF HER SPINE DID NOT SUGGEST MULTIPLE SCLEROSIS. THE NEUROLOGIST FOUND A POSITIVE BABINSKI REFLEX THAT WAS ABSENT A FEW WEEKS AGO. HER AFFECT IS NOT FLAT AS SHE HAS DEMONSTRATED RAGE VERY WELL. ANOTHER RADIOLOGIST IS BEING SOUGHT TO INTERPRET THE MRI AS SHE DOES NOT EXHIBIT ANY SYMPTOMS OF MULTIPLE SCLEROSIS. THE PERSISTENCE OF THESE SYMPTOMS IS EXPLAINED BY THE PATIENT'S DETERMINATION TO MANIPULATE HER WAY OFF MEDICATION. IT IS THE TREATING PSYCHIATRIST'S OPINION THAT SHE DOES NOT HAVE MULTIPLE SCLEROSIS OR ANY OTHER SERIOUS NEUROLOGICAL DISEASE.

F O L L O W U P (31-OCT-87):

THE CONSUMER REPORTS THAT SHE DISCONTINUED THE USE OF RISPERIDONE AND THE FOLLOWING EVENTS ABATED: CHEST PAIN, STINGING PAIN AROUND THE HEART, NUMBNESS, AND DYSPNOEA. SHE ALSO REPORTS THAT SHE HAD SOME IMPROVEMENT IN HER ABILITY TO WALK WHEN SHE WAS NOT TAKING RISPERIDONE.

JAUSA28182(1) USA patient/consum M 0 day(s) at onset No Change/Not Yet Impotence (01-APR-1994)
er Subsidied Blood Sugar Increased (01-APR-1994)
Not Serious

tablet -- 3mg (01-APR-1994 / 01-APR-1995)

Causality Per Company: possible

tablet -- 3mg (01-JAN-1997 / Unknown)

Indications: Unspecified Schizophrenia

Concomitant Diseases: Diabetes Mellitus Without Mention of Complication

Event Description: A CONSUMER REPORTS THAT HE WAS ON RISPERIDONE FOR TWO YEARS AND EXPERIENCED IMPOTENCE. HE DISCONTINUED RISPERIDONE FOR APPROXIMATELY THREE MONTHS DUE TO A DESIRE TO HAVE A BABY. THE IMPOTENCE RESOLVED. HE RESTARTED RISPERIDONE AND THE IMPOTENCE RETURNED. HE ALSO REPORTED THAT HIS FASTING GLUCOSE IS IN THE 180'S WHILE ON RISPERIDONE.

JAUSA28420(1) USA health F 3 week(s) at onset Recovered Diabetes Mellitus (Unknown)
professional Serious Causality Per Company: doubtful

Volume 15/Page 138

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JJRP 00384126

D821.140

R. 6304

tablet - - -
Ref.no.(vers.no.) Ccy Prim. source Age Sex Latency Outcome Reaction 70
Seriousness
Formul Strength-Unit dose (Therapy start date/end date)
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Event Description: A PHYSICIAN REPORTS THAT A PATIENT DEVELOPED DIABETES MELLITUS THREE WEEKS AFTER BEGINNING RISPERIDONE. THE PATIENT EXHIBITED POLYURIA, POLYDIPSIA, AND ELEVATED BLOOD SUGAR. THE PATIENT WAS NOT DIABETIC PRIOR TO STARTING THE DRUG BUT DOES HAVE A FAMILY HISTORY OF DIABETES MELLITUS. RISPERIDONE WAS DISCONTINUED AND THE PATIENT'S BLOOD SUGAR CAME DOWN.

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JAUSA28741(1) USA health 15yr M No Change/Not Yet Diabetes Mellitus (Unknown)
professional Subsidized Urinary Incontinence (Unknown)
Serious

tablet - - - (16-MAR-1987 / Unknown) Causality Per Company: doubtful

Indications: Concentr. Impaired
Event Description: A PHYSICIAN REPORTS THAT HIS 16-YEAR-OLD MALE PATIENT EXPERIENCED POLYURIA, POLYDIPSIA, AND HYPERGLYCEMIA. HE ALSO EXPERIENCED URINARY INCONTINENCE. A DIAGNOSIS OF DIABETES MELLITUS WAS MADE AND INSULIN THERAPY WAS INITIATED. Concomitant Diseases: Obsessive-Compulsive Disorders; Unspecified Delay In Development

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JAUSA28880(1) USA health 28yr M 8 month(s) at onset No Change/Not Yet Diabetes Mellitus (01-JUL-1987)
professional Subsidized Weight Increase (Unknown)
Serious

tablet - - 6mg (28-OCT-1988 / Unknown) Causality Per Company: doubtful

Indications: Unspecified Psychosis
Event Description: A PHARM.D. REPORTS THAT A MALE CONSUMER HAS BEEN TREATED WITH RISPERIDONE SINCE 28-OCT-88. CONCOMITANT MEDICATION INCLUDES VALPROATE SODIUM. HE HAS A FAMILY HISTORY OF DIABETES MELLITUS. ROUTINE BLOOD SUGARS WERE WITHIN NORMAL LIMITS UNTIL 1-JUL-97. BLOOD SUGAR RESULT WAS 298 AND GLYCOZIDE WAS STARTED. HIS IDEAL BODY WEIGHT IS 183-188 LBS. HIS CURRENT WEIGHT IS 275LBS. REPORTER WAS UNABLE TO DETERMINE THE WEIGHT GAIN SINCE OCT-96.

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JAUSA29108(1) USA health 61yr F No Change/Not Yet Diabetes Mellitus Aggravated (Unknown)
professional Subsidized
Not Serious Causality Per Company: doubtful

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Volume 15/Page 139

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JJRP 00384127
D821.141

R. 6305

Ref.no. (vers.no.)	Ctry	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	71

Formul Strength Unit dose (Therapy start date/end date)

tablet -- 2mg (22-JUL-1997 / Unknown)

Indications: Unspecified Schizophrenia

Event Description: PHARMACIST REPORTS THAT A RESIDENT OF A PSYCHIATRIC HOSPITAL, WITH PREVIOUSLY CONTROLLED DIABETES, EXPERIENCED HYPERGLYCEMIA WHILE ON RISPERIDONE. THE PATIENT WAS PRESCRIBED RISPERIDONE TWO YEARS AGO AND HAD A SIMILAR REACTION. THE RISPERIDONE WAS DISCONTINUED FOR UNKNOWN REASONS AND THE SUGARS NORMALIZED. CURRENTLY, THE PATIENT HAS STARTED ON RISPERIDONE AND IS EXPERIENCING BLOOD SUGARS OVER 350 MG/DL. RISPERIDONE CONTINUES.

JANSA29273(1) USA health professional

27yr F 9 month(s) at onset

No Change/Not Yet Subsidized
Not Serious

Hyperglycaemia (04-AUG-1997)
Hyperprolactinaemia (Unknown)

tablet -- 2mg (01-NOV-1996 / Unknown)

Causality Per Company: doubtful

Event Description: A PHARMACIST REPORTS THAT A PATIENT HAS BEEN ON RISPERIDONE SINCE NOVEMBER 1996 FOR AUTISM AND OBSESSIVE - COMPULSIVE DISORDER AND HAS BEEN DOING EXTREMELY WELL. ON 04-AUG-97, THE PATIENT DEVELOPED ELEVATED GLUCOSE (350 - 400). SHE WAS TREATED WITH GLIPIZIDE, BUT THE GLUCOSE LEVEL REMAINED ELEVATED. SHE WAS STARTED ON INSULIN, AND THE GLUCOSE RETURNED TO NORMAL LEVELS. THE PATIENT HAS A FAMILY HISTORY OF DIABETES MELLITUS. SHE IS WITHIN HER NORMAL WEIGHT LIMIT. THE PATIENT'S FATHER REPORTED THAT IN ADDITION TO THE ELEVATED GLUCOSE LEVEL, THE PATIENT ALSO HAS AN ELEVATED PROLACTIN LEVEL (NOT SPECIFIED). RISPERIDONE CONTINUES.

Indications: Infantile Autism; Obsessive-Compulsive Disorders

JANSA29273(1) USA health professional

30yr F

No Change/Not Yet Subsidized
Not Serious

Glycosuria (Unknown)

Causality Per Company: doubtful

tablet -- 2mg (01-FEB-1997 / Unknown)

Indications: Stress

Event Description: A PHYSICIAN REPORTS THAT HER PATIENT WHO IS ON RISPERIDONE FOR POST TRAUMATIC STRESS, TESTED POSITIVE FOR URINE GLUCOSE. THE PATIENT'S SERUM GLUCOSE IS NEGATIVE. SHE HAS NO HISTORY OF DIABETES MELLITUS.

JANSA29371(1) USA health professional

25yr F

No Change/Not Yet Subsidized
Serious

Diabetes Mellitus (Unknown)

Causality Per Company: doubtful

Volume 15/Page 140

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 D821.142

JRF 00384128

R. 6306

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	72
Formul Strength-Unit dose (Therapy start date/end date)								
tablet . . . (15-JUL-1997 / Unknown)								
							Indications: Unspecified Disturbance Of Conduct	

Event Description: A PHYSICIAN REPORTS THAT A CONSUMER WAS TREATED WITH RISPERIDONE IN THE LAST MONTHS FOR TREATMENT OF BEHAVIORAL DISTURBANCES SECONDARY TO AUTISM. SINCE THE INITIATION OF THERAPY SHE HAS IMPROVED SIGNIFICANTLY BUT DEVELOPED INSULIN DEPENDENT DIABETES MELLITUS. HER FAMILY WANTS TO DISCONTINUE RISPERIDONE BUT THE TREATING PHYSICIAN IS RELUCTANT TO DO SO. AN UNCLE HAS DIABETES MELLITUS. ADDITIONAL INFORMATION IS NOT EXPECTED.

Concomitant Diseases: Infantile Autism

JANSA26054(1)	USA patient/consum	45yr M	Unknown	Not Serious	Hypoglycemia (Unknown) Anorexia (Unknown) Hearing Abnormally Acute (Unknown)
tablet 3 mg - 3mg (01-JUL-1994 / Unknown)					
Event Description: A CONSUMER REPORTS THAT HER BOYFRIEND HAS RECENTLY BEEN EXPERIENCING ANOREXIA, HYPOGLYCAEMIA AND PERCEIVES SOUNDS MORE ACUTELY. ADDITIONAL INFORMATION IS NOT EXPECTED.					Causality Per Company: doubtful Indications: Unspecified Psychosis

JANSA31021(3)	USA health professional	82yr M	Alive With Sequelae	Serious	Sepsis (Unknown) Respiratory Insufficiency (01-JUL-1997) Dehydration (01-JUL-1997) Lethargy (24-JUN-1997) Diabetes Mellitus (Unknown) Anaemia (Unknown) Joint Stiffness (Unknown)
tablet . . . 5mg (24-JUN-1997 / 01-JUL-1997)					
Event Description: A CONSUMER REPORTS THAT HER FATHER WAS TREATED WITH RISPERIDONE FROM 24-JUN-97 AT A DOSE OF 0.5 MG DAILY. CONCOMITANT MEDICATIONS INCLUDED HALOPERIDOL AND CLOZAPINE. ON 24-JUN-97 HE BECAME LETHARGIC AND WAS SUBSEQUENTLY HOSPITALIZED ON 01-JUL-97 FOR RESPIRATORY FAILURE. ALL OF HIS MEDICATIONS WERE DISCONTINUED. HE WAS TREATED WITH FLUMITRAZEPAM WHICH WAS DESCRIBED BY THE PATIENT'S DAUGHTER AS "AN ANTIDOTE FOR TREATMENT OF HIS CONSTRICTED LUNGS(NOS)". HE FULLY RECOVERED. A COUPLE OF WEEKS FOLLOWING THE DISCONTINUATION OF RISPERIDONE, HE DEVELOPED JOINT STIFFNESS, INSULIN DEPENDENT DIABETES, AND ANAEMIA WHICH REQUIRED TRANSFUSIONS. ADDITIONAL INFORMATION HAS BEEN REQUESTED.					Causality Per Company: doubtful Indications: Unspecified Disturbance Of Conduct
ADDITIONAL INFORMATION RECEIVED 07-JAN-98: THE PATIENT'S PRIMARY PHYSICIAN REPORTS THAT THE PATIENT EXPERIENCED LETHARGY AND WAS SUBSEQUENTLY HOSPITALIZED FOR WORSENING LETHARGY. THE ADMITTING DIAGNOSIS WAS DEHYDRATION WHICH RESOLVED FOLLOWING TREATMENT. HE RECEIVED AN ANTAGONIST MEDICATION (NOS) FOR TREATMENT OF THE LETHARGY, THOUGHT TO BE INDUCED BY THE POLYPHARMACY. HE DEVELOPED RESPIRATORY INSUFFICIENCY BUT DID NOT REQUIRE ANY RESPIRATORY ASSISTANCE. HE HAS A HISTORY OF PERIPHERAL VASCULAR DISEASE, CHF,					Concomitant Diseases: Unspecified Circulatory System Disorder; Parosia; Agitation

Idesback 16JUN00

Volume 15/Page 141

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JRP 00384129
D821.143

R. 6307

Ref.no.(vers.no.) Ctry Prim. source Age Sex Latency Outcome Reaction 73
 Seriousness

Formul Strength/Unit dose (Therapy start date/end date)

ASPIRATION AND ACITATION. DURING THE HOSPITAL COURSE HE DEVELOPED SEPSIS OF THE LOWER
 EXTREMITIES AND A LEFT-SIDED AMPUTATION WAS PERFORMED. HE ALSO EXPERIENCED ANAEMIA WHICH
 REQUIRED TRANSFUSIONS. HE HAS HAD MULTIPLE HAEMATOLOGICAL CONSULTS FOR POSITIVE QUAC
 STOOLS. HOWEVER THE FAMILY REFUSES DIAGNOSTIC STUDIES TO DETERMINE THE ETIOLOGY. THE
 PATIENT DID NOT EXPERIENCE ANY PULMONARY DISORDERS, IN FACT THE X-RAYS DID NOT REVEAL ANY
 INFILTRATES, PULMONARY OEDEMA OR PNEUMONIA.
 F O L L O W - U P (02-FEB-98):
 THE CONSUMER REPORTS THAT THE NAME OF THE ANTEDOTE USED TO TREAT HER FATHER'S CONGESTED
 LUNGS IS FLIMAZENTIL.

JAUSA31098(S) USA health 42yr F 10 month(s) at onset Recovered
 professional Serious
 tablet -- 6mg (31-DEC-1993 / 31-DEC-1998)
 tablet -- 3mg (01-JAN-1997 / Unknown)
 Event Description: A NURSE PRACTITIONER REPORTS THAT A CONSUMER WAS TREATED WITH
 RISPERIDONE FOR THE PAST FOUR YEARS. THE PATIENT'S SYMPTOMS IMPROVED, HOWEVER SHE WANTED
 TO BE WEANED OFF RISPERIDONE. IN THE LAST YEAR, RISPERIDONE DOSE WAS TITRATED DOWNWARD
 FROM 6 MG TO 3 MG DAILY. IN NOV-97 (MOS) WHEN SHE WAS ON A DOSE OF 3 MG DAILY SHE
 DEVELOPED CONSTIPATION AND SEVERE ABDOMINAL PAIN, AND WAS SUBSEQUENTLY HOSPITALIZED. SHE
 WAS DIAGNOSED WITH AN ILEUS WHICH RESULTED IN A SMALL BOWEL RESECTION. RISPERIDONE
 THERAPY CONTINUES. ADDITIONAL INFORMATION HAS BEEN REQUESTED.
 F O L L O W - U P (17-FEB-98):
 MEDICAL RECORDS RECEIVED INDICATE THAT THIS 42-YEAR-OLD FEMALE HAD A HISTORY OF
 SCHIZOPHRENIA, AN UMBILICAL HERNIOTHAPY AS A CHILD AND HYPOTENSION. SHE EXPERIENCED
 WORSENING ABDOMINAL PAIN ON THE EVENING OF 17-NOV-97, AND WENT TO A LOCAL MEDICAL CENTER,
 WHERE EVALUATION SHOWED HYPOTENSION, TACHYCARDIA, ACIDOSIS, AND ABDOMINAL DISTENTION.
 THE PATIENT WAS INTUBATED AND TRANSFERRED TO A UNIVERSITY HOSPITAL FOR PRESUMED SEPTIC
 SHOCK AND ISCHEMIC BOWEL. INITIAL EXAMINATION REVEALED AN INTUBATED FEMALE PATIENT WITH
 A NASOGASTRIC TUBE IN PLACE, TEMPERATURE 38.8F, BP 102/50, HEART RATE 98 - 120,
 RESPIRATORY RATE 23, SLIGHT RHONCHT, ABDOMINAL DISTENTION, BLOOD IN THE VAGINAL VAULT,
 AND BILATERAL LOWER EXTREMITY PETECHIAL. CENTRAL VENOUS PRESSURE WAS 9, AND PULMONARY
 WEDGE PRESSURE 10. INITIAL LABORATORY RESULTS WERE, REMARKABLY FOR WHITE BLOOD CELL 29.8
 WITH 62% POLYMORPHONUCLEAR LEUKOCYTES (PMNS) AND 26% STABS, PLATELETS 87,000, PROTHROMBIN
 TIME (PT) 15.3, PARTIAL THROMBOPLASTIN TIME >150, D-DIMER POSITIVE, SERUM CHLORIDE 120,
 SERUM BICARBONATE 14, GLUCOSE 831, CALCIUM 5.5, PHOSPHORUS 2.3, MAGNESIUM 1.1, LACTATE
 8.9, NORMAL THYROID STIMULATING HORMONE (TSH), AND THE PRESENCE OF GLUCOSE AND BLOOD IN
 THE URINE. INITIAL BLOOD GASES IN A VENOUS BLOOD SPECIMEN REVEALED A PH OF 7.14; AN
 ARTERIAL BLOOD GAS SOON AFTER SHOWED PH 7.24, PCO2 29, PO2 273, HCO3 13, AND O2
 SATURATION 99%. A DIAGNOSTIC PERITONEAL LAVAGE REVEALED GROSS BLOOD. THE PATIENT WAS
 AGGRESSIVELY RESUSCITATED. THE METABOLIC ACIDOSIS WAS REVERSED. TRANSFUSIONS OF FRESH
 FROZEN PLASMA AND PACKED RED CELLS WERE GIVEN. AN EXPLORATORY LAPAROTOMY REVEALED
 NECROTIC SMALL BOWEL. FOLLOWING SMALL BOWEL RESECTION, THE WOUND WAS LEFT OPEN, AND THE

Intestinal Ischemia (18-NOV-1997)
 Intestinal Necrosis (18-NOV-1997)
 Hypotension (18-NOV-1997)
 Condition Aggravated (18-NOV-1997)
 Tachycardia (18-NOV-1997)
 Respiratory Distress (18-NOV-1997)
 Tachypnoea (18-NOV-1997)
 Thrombosis (18-NOV-1997)
 Phlebitis (18-NOV-1997)
 Dic (18-NOV-1997)
 Lab Values Abnormal (18-NOV-1997)
 Acidosis Metabolic (18-NOV-1997)
 Diarrhoea (18-NOV-1997)
 Allergic Reaction (21-NOV-1997)
 Causality Per Company: possible
 Indications: Unspecified Psychosis
 Concomitant Diseases: Hypotension; Paraneur Type
 Schizophrenia

Lidbeck 18JUN00

Volume 15/ Page 142

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 D821.144

R. 6308

Ref.no.(vers.no.) Cty Prim. source Age Sex Latency Outcome Reaction 74
Seriousness

Formal Strength-Unit dose (Therapy start date/end date)

=====

PATIENT REMAINED INTUBATED DUE TO SIGNS (NOS) OF ADULT RESPIRATORY DISTRESS SYNDROME. THE SURGICAL PATHOLOGY REPORT REGARDING THE SMALL BOWEL SPECIMEN INDICATED DIAGNOSES OF (1) ISCHEMIC INFARCTION, HEMORRHAGIC; (2) MULTIFOCAL SUBTOTAL ISCHEMIC INJURY; AND, (3) ACUTE AND SUBACUTE PHLEBITIS. THE FOLLOWING COMMENT WAS MADE: THE BOWEL INFARCTION APPEARS TO BE THE RESULT OF VASCULAR COMPROMISE AS A RESULT OF A SEVERE ACUTE PHLEBITIS WITH ASSOCIATED THROMBOSIS. THE PREDOMINANCE OF EOSINOPHILS RAISES SEVERAL POSSIBILITIES, INCLUDING CHURG-STRAUSS VASCULITIS (LESS LIKELY IN VIEW OF THE ABSENCE OF GRANULOMATOUS INFLAMMATION), HYPERSENSITIVITY REACTION (INCLUDING DRUG-RELATED), OR IDIOPATHIC ORIGIN. SECOND-LOOK SURGERY 18-NOV-97 SHOWED A PATENT ANASTOMOSIS; A NASO-JEJUNAL TUBE WAS PLACED. TOTAL PARENTERAL NUTRITION AND JEJUNAL FEEDINGS WERE BEGIN, WITH GRADUAL WEANING AND CHANGE TO AN ORAL DIET. DIARRHEA DEVELOPED; A STOOL CULTURE REVEALED CLOSTRIDIUM DIFFICILE ON 24-NOV-97. ORAL METRONIDAZOLE WAS BEGIN, AND PARENTERAL ANTIBIOTICS WERE DISCONTINUED. ON 27-NOV-97, THERE WAS LESS DIARRHEA, AND AN ORAL DIET WAS BEING TOLERATED. DURING THE HOSPITALIZATION, LABORATORY RESULTS WERE NOTABLE FOR THE FOLLOWING: HEMOGLOBIN REACHED A NADIR OF 9.1, 19-NOV-97, UP TO 13.0 ON 26-NOV-97; COAGULATION PARAMETERS NORMALIZED BY 22-NOV-97; SERUM ELECTROLYTES AND GLUCOSE WERE NORMAL PRIOR TO DISCHARGE; CALCIUM WAS 7.9 AND ALBUMIN 2.3 ON 25-NOV-97. ALL BLOOD AND URINE CULTURES WERE NEGATIVE. A FINAL BLOOD COUNT WITH MANUAL DIFFERENTIAL 25-NOV-97 REVEALED WBC 15.4, WITH 62% PMNS, 8% STABS, AND 3% MYELOCYTES. LIVER FUNCTION TESTS WERE NOTABLE FOR ELEVATED LDH 300 ON 20-NOV-97; THE LDH ROSE TO 478 ON 23-NOV-97. THAT DAY, SGOT WAS 81, SGPT WAS 81, AND ALKALINE PHOSPHATASE (AP) WAS 142. ON 25-NOV-97, TESTS SHOWED LDH 426, SGOT 104, SGPT 175, AND AP 182. AN ALLERGIC NON-HEMOLYTIC TRANSFUSION REACTION WAS DIAGNOSED ON 21-NOV-97, CHARACTERIZED BY FEVER, HYPERTENSION, AND ERYTHEMATOUS PATCHES OVER THE UPPER TORSO. RISPERIDONE THERAPY CONTINUES.

F O L L O W U P (12-MAR-98):

CINC. DRUG INFORMATION COMPLETED, PATIENT PROFILE AND WEIGHT ADDED.

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JANSAS1168(1)	USA patient/consent 45yr F	1 day(s) at onset	Unknown Not Serious	Diabetes Mellitus Aggravated (03-JAN-1998)
				Causality Per Company: possible
tablet 1 mg - .5mg (02-JAN-1998 / 05-JAN-1998)				Indications: Unspecified Psychosis; Unspecified Parosoid State

Event Description: CALLER STATED THAT HER 45-YEAR-OLD DAUGHTER STARTED TAKING RISPERIDONE (0.5 MG TWICE DAILY) ON 02-JAN-98 FOR PSYCHOTIC, PARANOID BEHAVIOR EXHIBITED DURING OCCASIONAL "BESANDOWNS". DAUGHTER HAS INSULIN DEPENDENT DIABETES MELLITUS, AND BLOOD GLUCOSE LEVELS AS MEASURED WITH HOME GLUCOMETER ON 03-JAN-98, AND 04-JAN-98, WERE APPROXIMATELY 100 MG/DL ABOVE USUAL READINGS.

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JANSAS1711(1)	USA health professional	32yr F	8 month(s) at onset	No Change/Not Yet Subside	Diabetes Mellitus Aggravated (77-FEB-1998)

1debaeck 18JUN00

Volume 15/Page 143

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JJRP 00384131
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R. 6309

Ref.no.(vers.no.) Cty Prim. source Age Sex Latency Outcome Reaction 75
Seriousness
Formul Strength-Unit dose (Therapy start date/end date)
Not Serious Causality Per Company: possible
tablet - - 4mg (15-JUN-1997 / Unknown)
Indications: Unspecified Psychosis
Concomitant Diseases: Unspecified Schizophrenia
Event Description: PHYSICIAN REPORTS A 32-YEAR-OLD FEMALE WHOSE PREVIOUSLY CONTROLLED
HYPERGLYCEMIA WAS AGGRAVATED APPROXIMATELY SIX MONTHS AFTER RISPERIDONE INITIATION FOR
THE TREATMENT OF PSYCHOSIS ASSOCIATED WITH SCHIZOPHRENIA. PHYSICIAN RELATES THAT
PATIENT'S BLOOD GLUCOSE HAS BEEN AROUND 250 MG/DL FOR THE PAST FEW DAYS. THE PATIENT'S
DIABETES IS TREATED WITH METFORMIN. THE PATIENT CURRENTLY RECEIVES RISPERDAL 4 MG BID.
FURTHER INFORMATION IS NOT EXPECTED.

JAUSA31992(2) USA health 80yr M Recovered Diabetes Mellitus Aggravated (Unknown)
professional Not Serious Causality Per Company: possible
tablet 1 mg - .5mg (Unknown / 10-MAR-1998)

Event Description: A PHYSICIAN REPORTS THAT A PATIENT EXPERIENCED HYPERGLYCAEMIA (HGS)
DURING RISPERIDONE THERAPY. HE IS AN INSULIN DEPENDENT DIABETIC WHO WAS ON RISPERIDONE
0.5 MG DAILY LESS THAN A MONTH WHEN HIS PREVIOUSLY BLOOD SUGAR BECAME ELEVATED. THE
PHYSICIAN REFUSED TO PROVIDE ADDITIONAL INFORMATION.
F O L L O W - U P (18-JUN-99):
THE PHYSICIAN REPORTS THAT SINCE RISPERIDONE WAS DISCONTINUED THE PATIENT HAS HAD BETTER
GLUCOSE CONTROL.

JAUSA32202(1) USA patient/consu 90yr F 6 month(s) at onset No Change/Not Yet Hyperglycaemia (11-MAR-1998)
er Subsidized Causality Per Company: doubtful
Not Serious
solution 1 mg/mL - 1.5mg (15-AUG-1997 / Unknown)
Indications: Agitation
Company Remarks: Hyperglycaemia due to new onset of diabetes.

Event Description: CALLER REPORTS THAT HIS MOTHER-IN-LAW, A 90-YEAR-OLD WOMAN, HAS BEEN
TAKING RISPERIDONE ORAL SOLUTION, 1 MG IN THE MORNING, AND 0.6 MG AT HOUR OF SLEEP FOR
SIX TO EIGHT MONTHS FOR "AGITATION". APPROXIMATELY TWO WEEKS AGO, NURSING HOME STAFF
REPORTED HER TO BE INCREASINGLY LETHARGIC. BLOOD GLUCOSE (FINGERSTICK) TEST RESULTS
REVEALED BLOOD GLUCOSE LEVEL OF 530 MG/DL. THERE IS NO PREVIOUS OR FAMILY HISTORY OF
DIABETES. INSULIN THERAPY BY SUBCUTANEOUS INJECTION (TYPE AND AMOUNT UNKNOWN) HAS BEEN
INITIATED AND CONTINUES LAST REPORTED BLOOD GLUCOSE LEVEL 438 MG/DL. RISPERIDONE THERAPY

1dabaeck 18JUN00

Volume 15/Page 144

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JRP 00384132
D821.146

R. 6310

Ref.no.(vers.no.)	Cty	Prin. source	Age	Sex	Latency	Outcome Seriousness	Reaction	78
Formul Strength/Unit dose (Therapy start date/end date)								
CONTINUES.								
JANSA32508(1)								
USA patient/consu		31yr M	24 month(s)	at onset	No Change/Not Yet Subsided Not Serious	Hyperglycemia (11-APR-1998) Weight Increase (15-APR-1998)		
ar								
tablet 2 mg - 2mg (15-MAR-1999 / Unknown)		Causality Per Company: possible						
Event Description: A 31-YEAR-OLD MALE TAKING RISPERIDONE 2 MG DAILY SINCE MAR-98 FOR DEPRESSION REPORTS DEVELOPING HYPERGLYCAEMIA. ON 11-APR-98 A BLOOD TEST REVEALED ELEVATED BLOOD SUGAR OF 289 MG/DL. A FINGER STICK ON 13-APR-98 INDICATED A BLOOD GLUCOSE OF 271 MG/DL. HIS PHYSICIAN PRESCRIBED GLIPIZIDE ON 13-APR-98 AND HIS BLOOD GLUCOSE IS NOW WITHIN NORMAL LIMITS. ADDITIONALLY, THE PATIENT REPORTS THAT AFTER APPROXIMATELY ONE MONTH OF THERAPY, HE BEGAN GAINING WEIGHT. HIS WEIGHT IS PRESENTLY STABLE, BUT HE HAS GAINED A TOTAL OF THIRTY POUNDS.							Indications: Depressive Disorder, Not Elsewhere Classified	
JANSA32020(1)								
USA health professional		30yr M	22 week(s)	at onset	Unknown Not Serious	Lab Values Abnormal (18-SEP-1997) Hyperglycemia (15-APR-1998)		
tablet - - 3mg (14-APR-1997 / Unknown)		Causality Per Company: possible						
Event Description: A PHYSICIAN PRONED ABOUT A 36-YEAR-OLD INSTITUTIONALIZED MALE WHO HAS BEEN TREATED WITH RISPERIDONE FOR DISTURBED BEHAVIOR AND PSYCHOSIS. DURING ROUTINE LABS IT WAS FOUND THAT THE NEUTROPHILS, EOSINOPHILS AND GLUCOSE WERE ABNORMAL (SEE DIAGNOSTIC DATA). THE RISPERIDONE MEASUREMENT WAS <6 MCG/L WITH THE O-HYDROXY-RISPERIDONE RESULT 550 MCG/L.							Indications: Unspecified Psychosis; Unspecified Disturbance Of Conduct	
							Concomitant Diseases: Unspecified Delay In Development; Infantile Cerebral Palsy, Unspecified	
JANSA32941(1)								
USA health professional		38yr M			Unknown Serious	Myocardial Infarction (Unknown) Diabetes Mellitus (Unknown)		
tablet - - 3.5mg (Unknown / 15-MAY-1997)		Causality Per Company: doubtful						

10ebaeck 16JUN00

Volume 15/Page 145

Ref.no.(vers.no.)	Qty	Prim. source	Age	Sex	Laterality	Outcome Seriousness	Reaction	77
Formul Strength-Unit dose (Therapy start date/end date)								
Event Description: A PHYSICIAN REPORTS THAT A 38-YEAR-OLD MALE WITH A LONG HISTORY OF PARANOID AND SOMATIC COMPLAINTS/DELUSIONS WAS TREATED WITH RISPERIDONE WHEN HE DEVELOPED DIABETES MELLITUS. THE ELEVATED GLUCOSE (>400) WAS FOUND DURING ROUTINE LAB WORK. A HYPOLYCAEMIC MEDICATION (NOS) WAS STARTED AND RISPERIDONE THERAPY WAS DISCONTINUED. THE PATIENT INFORMED THIS PHYSICIAN THAT HE WAS TOLD THAT PERHAPS HE HAD EXPERIENCED A MYOCARDIAL INFARCTION IN THE PAST. THE REPORTER STRONGLY FEELS THAT WITH HIS HISTORY OF SOMATIC DELUSIONS THAT THIS INFORMATION IS HIGHLY SUSPECT. THE PATIENT IS LOST TO FOLLOW-UP AND ADDITIONAL INFORMATION FROM MEDICAL RECORDS ARE UNAVAILABLE. ADDITIONAL INFORMATION IS NOT EXPECTED.								
Indications: Unspecified Paranoid State								
Company Remarks: PATIENT HAS A HISTORY OF SOMATIC DELUSIONS. THE MYOCARDIAL INFARCTION HAS NOT BEEN CONFIRMED BY ANY OBJECTIVE RESULTS (LAB- ECG).								
=====								
JANSA33244(2)		USA health professional	50yr F			Death Serious	Death (Unknown) Hyperglycaemia (Unknown) Weight Increase (Unknown)	
tablet - - 4mg (15-OCT-1987 / 30-MAY-1988)								
Event Description: A PHYSICIAN REPORTS THE DEATH OF A PATIENT ON RISPERIDONE. THE PATIENT BEGAN RISPERIDONE IN OCT-87. HER BASELINE BLOOD SUGAR WAS 80. SHE DIED 30-MAY-88. CIRCUMSTANCES SURROUNDING HER DEATH ARE NOT KNOWN AT THIS TIME. AN AUTOPSY WAS DONE, BUT THE RESULTS ARE PENDING. HER BLOOD SUGAR AT AUTOPSY WAS OVER 600. IT IS BELIEVED SHE DIED OF DIABETIC KETOACIDOSIS. THE PATIENT HAD NEVER BEEN DIAGNOSED WITH DIABETES MELLITUS, BUT SHE HAD NOTICED, PRIOR TO HER DEATH, THAT SHE WAS GAINING WEIGHT. ADDITIONAL INFORMATION WAS REQUESTED.								
Causality Per Company: possible								
Indications: Unspecified Schizophrenia								
Concomitant Diseases: Arthritis								
Company Remarks: Since results of autopsy are not available yet, this case has been assessed as possible.								
=====								
JANSA33466(1)		USA health professional	30yr F			No Change/Not Yet Subsidized Not Serious	Hyperglycaemia (Unknown) Causality Per Company: possible	
tablet - - 2mg (25-MAY-1988 / Unknown)								
Event Description: A NURSE REPORTS THAT A 30-YEAR-OLD FEMALE DEVELOPED HYPERGLYCAEMIA DURING RISPERIDONE THERAPY. RISPERIDONE THERAPY CONTINUES.								
Indications: Unspecified Psychosis								
Concomitant Diseases: Paranoid Type Schizophrenia								
=====								
JANSA33466(2)		USA health professional	51yr F		3 month(s) at onset	Recovered Serious	Respiratory Distress (08-FEB-1988) Unconsciousness (08-FEB-1988) Hypotension (08-FEB-1988) Leukocytosis (08-FEB-1988) Injury (08-FEB-1988)	
tablet - - - (11-NOV-1987 / Unknown)								

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Ref.no.(vers.no.)	Ctry	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	78
Formul Strength-Unit dose (Therapy start date/end date)								
Event Description: A PHYSICIAN REPORTS THAT A 61-YEAR-OLD FEMALE HAS BEEN TREATED WITH RISPERIDONE SINCE 11-NOV-87 FOR IMPULSE CONTROL. SHE WAS FOUND UNRESPONSIVE WITH A LACERATION ON HER RIGHT PARIETAL AND TEMPORAL REGION OF HER SKULL. SHE WAS SEEN IN THE EMERGENCY ROOM. SHE HAD A GLAUCOMA SCORE OF 10, AND THE SODIUM WAS 114. ON THE SECOND DAY OF HER HOSPITALIZATION SHE DEVELOPED AN INCREASED TEMPERATURE (WGS) LEUKOCYTOSIS AND REQUIRED INTUBATION. SPECIFIC RESPIRATORY EVENT WAS UNSPECIFIED, A SOURCE OF INFECTION WAS NOT IDENTIFIED. EVENTUALLY SHE RECOVERED FOLLOWING DISCONTINUATION OF RISPERIDONE. SHE WAS TRANSFERRED TO A TRANSITION UNIT AND THEN TO REHABILITATION. THE SODIUM INCREASED TO 142.								
FOLLOW UP (05-OCT-88):								
PHYSICIAN IS NOT AWARE OF ANY PATIENT HISTORY OF PSYCHOGENIC POLYDIPSIA OR ANY EPISODES OF VOMITING AND DIARRHEA. WHEN PATIENT WAS LAST SEEN BY PHYSICIAN (DATE NOS), PATIENT WAS IN HER "USUAL STATE OF HEALTH (WGS)".								
////////////////////////////////////								
JANSA33838(1)	USA	health professional	35yr	M		Recovered Serious	Cholecystitis (Unknown) Diabetes Mellitus (15-JUL-1998)	
tablet 3 mg - 3mg								
Event Description: A PHYSICIAN REPORTS THAT A 35-YEAR-OLD MALE WAS HOSPITALIZED FOR CHOLECYSTITIS FOLLOWING COMPLAINTS OF RIGHT UPPER QUADRANT PAIN. HE BECAME ASYMPTOMATIC AND WAS DISCHARGED. HIS BLOOD SUGAR WAS ELEVATED TO 400. GLIPIZIDE WAS STARTED AND THE BLOOD SUGAR HAS STABILIZED.								
////////////////////////////////////								
JANSA33918(2)	USA	health professional	39yr	M	13 week(s) at onset	Unknown Serious	Arrhythmia (16-MAR-1998) Bradycardia (16-MAR-1998) Heart-Fluttering (77-APR-1998) Tachycardia (77-APR-1998) Diabetes Mellitus (30-JUL-1998) Hesitancy (30-JUL-1998) Cpk Increased (30-JUL-1998) Lab Values Abnormal (30-JUL-1998) Angioedema (04-APR-1998) Hypokalemia (30-JUL-1998) Condition Aggravated (30-JUL-1998)	
tablet 1 mg - 1mg (13-DEC-1997 / 08-JUL-1998)								
tablet 1 mg - 2mg (09-JUL-1998 / 06-AUG-1998)								
tablet 1 mg - 1mg (08-AUG-1998 / Unknown)								
Event Description: A NURSE REPORTS THAT A 39-YEAR-OLD BLACK MALE EXPERIENCED SINUS BRADYCARDIA WITH SINUS ARRHYTHMIA DURING RISPERIDONE THERAPY. HE HAS A HISTORY OF HYPERTENSION AND SMOKING AND IS BEING TREATED WITH AMPUTAMONE FOR SMOKING CESSATION. RISPERIDONE TREATMENT BEGAN ON 13-DEC-97 AT 1 MG TWICE DAILY. HIS HISTORY ALSO INCLUDES MODERATE MENTAL RETARDATION (INSTITUTIONALIZED SINCE 1976), MICROCEPHALY, ASTHMA, BRONCHITIS, A PERFORATED ULCER, ABNORMAL LIVER FUNCTION TESTS (WGS) AND A POSITIVE ANTIGEN SECONDARY TO HEPATITIS. IN APR-98, HE WAS DIAGNOSED WITH BILATERAL PARENCHYMAL PERMANENT KIDNEY DAMAGE WITH RENAL INSUFFICIENCY SECONDARY TO GLAUCULOPATHY. ON 16-MAR-98 AN ECG REVEALED MARKED SINUS BRADYCARDIA WITH SINUS ARRHYTHMIA. IN APR-98 HE COMPLAINED OF "HEART FLUTTERING". ON 04-APR-98 HE DEVELOPED ANGIOEDEMA SECONDARY TO THE								
Causality Per Company: possible								
Indications: Unspecified Psychosis								

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Volume 15/Page 147

Ref.no. (vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	79

Formul Strength-Unit dose (Therapy start date/end date)

=====

USE OF LISINAPRIL. LISINAPRIL WAS DISCONTINUED. HE WAS TREATED AND RECOVERED. ON 30-JUL-98 HIS EYES KEPT CLOSING AS IF HE WAS FATIGUED AND UPON CHECKING HIS VITAL SIGNS IT WAS FOUND THAT HE WAS BRADYCARDIC TO 48/MINUTE. HE WAS EXAMINED IN THE EMERGENCY ROOM AND ANOTHER ECG REVEALED A SIGNIFICANT CHANGE FROM THE MARCH ECG. VITAL SIGNS WERE BP 194/90, HEART RATE 100 BPM, TEMPERATURE 37.7. THIS ECG INDICATED A NON-SPECIFIC T-WAVE ABNORMALITY WITH SINUS BRADYCARDIA. IT WAS ALSO NOTED THAT HIS POTASSIUM WAS 2.8, GLUCOSE 282, AMYLASE 170, CPK 360, CREATININE 2.7, AND THE URINALYSIS REVEALED 1+ BLOOD AND PROTEIN. HE WAS TREATED (NUS) AND RELEASED. RISPERIDONE THERAPY CONTINUES. HYDROCHLOROTHIAZIDE WAS ADDED TO HIS TREATMENT REGIMEN FOLLOWING A REACTION TO LISINAPRIL. AFTER HE DEVELOPED BRADYCARDIA IT WAS DECIDED TO DISCONTINUE THE HYDROCHLOROTHIAZIDE BECAUSE IT WAS FELT THAT THE BRADYCARDIA WAS RELATED TO THE USE OF HYDROCHLOROTHIAZIDE. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

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CONCOMITANT DISEASES: Microcephalus; Paranoid Type Schizophrenia; Oligophrenia; Bronchitis, Not Specified As Acute Or Chronic; Renal Insuff.; Renal Impairment

FOLLOW UP (08-OCT-98):

THE REPORTER PROVIDED FOLLOW-UP LAB RESULTS AND (CPK RESULT CORRECTED TO 361). X-RAY RESULTS. THE HYPOKALEMIA AND HEMATURIA RESOLVED. NO WBC'S WERE IN THE URINE AND 24 HOUR CULTURE RESULTS WERE NEGATIVE. IT IS BELIEVED THAT THE ELEVATED CREATININE IS SECONDARY TO KIDNEY DAMAGE. HIS BLOOD SUGAR CONTINUES TO BE MILDLY ELEVATED AND ARE MONITORED TWICE DAILY. HE HAS NOT STARTED ON ANY THERAPY. RISPERIDONE WAS DECREASED TO 1 MG TWICE DAILY. THE BRADYCARDIA DID NOT RESOLVE FOLLOWING DISCONTINUATION OF HYDROCHLOROTHIAZIDE.

=====

JANSA33949(1) USA health 40yr M
professional
tablet 2 mg - 2mg (15-JUL-1997 / Unknown)

Unknown
Not Serious

Thrombocytopenia (Unknown)
Condition Aggravated (Unknown)
Diabetes Mellitus (Unknown)
Diarrhoea (77-JUN-1998)

Event Description: A PHYSICIAN REPORTS THAT A 40-YEAR-OLD MALE EXPERIENCED THROMBOCYTOPENIA AND DIABETES DURING RISPERIDONE THERAPY. HE HAS BEEN TREATED FOR APPROXIMATELY ONE YEAR WITH RISPERIDONE 2 MG DAILY. HE DEVELOPED WORSENING THROMBOCYTOPENIA DURING RISPERIDONE THERAPY AFTER METFORMIN WAS ADDED TO HIS TREATMENT REGIMEN FOR HIS DIABETES. HE ALSO EXPERIENCED SOME MILD DIARRHEA AS WELL. OUTCOME UNKNOWN.

Causality Per Reporter: very likely/certain

Causality Per Company: possible

Indications: Unspecified Psychosis

Concomitant Diseases: Unspecified Schizophrenia

=====

JANSA34228(1) USA health 44yr M 2 day(s) at onset
professional

No Change/Not Yet
Subsided
Serious

Hyperglycaemia (Unknown)
Causality Per Company: possible

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Volume 15/Page 148

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JURP 00384136
D821.150

R. 6314

Ref.no.(vers.no.)	Ctry	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	BO

Formul	Strength-Unit dose	(Therapy start date/end date)

tablet - - -

Indications: Unspecified Psychosis

Concomitant Diseases: Liver Dysfunction

Event Description: A PHARMACY INTERN REPORTS THAT A MALE PATIENT WITH A HISTORY OF ALCOHOL ABUSE AND ABNORMAL LIVER FUNCTION TESTS, DEVELOPED A BLOOD SUGAR OF 334 WITHIN A COUPLE OF DAYS OF RISPERIDONE INITIATION.

Company Remarks: No baseline data is available. Diabetes mellitus is diagnosed by fasting blood sugar level and OGTT.

JAUSA34248(2)

USA health
professional

M

Unknown
Not Serious

Taste Disorder (Unknown)
Diabetes Mellitus (Unknown)

tablet - - -

Causality Per Company: possible

Event Description: A PHYSICIAN REPORTS A PATIENT WHO DEVELOPED DIABETES MELLITUS AND TESTICULAR ENLARGEMENT WHILE ON RISPERIDONE. NO OTHER INFORMATION IS KNOWN AND IS NOT EXPECTED.

JAUSA34382(2)

USA health
professional

38yr F

No Change/Not Yet
Subsided
Not Serious

Pituitary Neoplasm Nos (Unknown)
Diabetes Mellitus (Unknown)
Prolactin Increased (Unknown)
Amenorrhoea (Unknown)
Headache (Unknown)

tablet - - 2mg (15-SEP-1997 / Unknown)

Causality Per Company: possible

Event Description: A PERSON TO PERSON SERVICE COORDINATOR REPORTS THAT A 38-YEAR-OLD FEMALE DEVELOPED A PITUITARY MICROADENOMA DURING RISPERIDONE THERAPY. THE PATIENT REPORTED AMENORRHOEA AND A PROLACTIN LEVEL 103 NG/ML. AS SHE ALSO REPORTED HEADACHES BUT BECAUSE SHE IS TAKING MULTIPLE MEDICATIONS FOR HIV IT HAS BEEN ATTRIBUTED TO THOSE. A MRI CONFIRMED A 1.5 CM MICROADENOMA. RISPERIDONE THERAPY CONTINUES AT THIS POINT, BUT THE PHYSICIAN IS CONSIDERING RISPERIDONE DISCONTINUATION. SHE ALSO DEVELOPED DIABETES DURING RISPERIDONE THERAPY.

Indications: Unspecified Disturbance Of Conduct

Concomitant Diseases: Unspecified Delay In Development

JAUSA34406(1)

USA health
professional

84yr M 4 day(s) at onset

Recovered
Not Serious

Hypoglycaemia (22-JUN-1998)
Muscle Rigidity (Unknown)

solution 1 mg/mL - .5mg (18-JUN-1998 / 22-JUN-1998)

Causality Per Company: possible

1dbaeck 18JUN00

Volume 15/Page 149

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JJRP 00384137
D821.151

R. 6315

Ref.no.(vers.no.) Cty Prim. source Age Sex Latency Outcome Reaction 81
 Seriousness
 Formol Strength-Unit dose (Therapy start date/end date)
 =====
 Event Description: A PHYSICIAN REPORTS THAT AN ELDERLY MALE DEVELOPED HYPOGLYCAEMIA DURING RISPERIDONE THERAPY. THE PATIENT WAS TRANSFERRED FROM ONE NURSING HOME TO ANOTHER WHEN HE DEVELOPED AGITATION AND AGGRESSION. HE WAS TREATED WITH LORAZEPAM. THE NEXT DAY, 17-JUN-88 HE EXPERIENCED URINARY RETENTION. ON 18-JUN-88 RISPERIDONE WAS ORDERED 0.5 MG TWICE DAILY. HE DEVELOPED "STIFFNESS" WHEN WALKING AND AFTER RECEIVING THE FIFTH DOSE HE WAS FOUND LETHARGIC, UNRESPONSIVE AND DIFFICULT TO AROUSE. HIS BLOOD SUGAR WAS CHECKED AND FOUND TO BE 32. HE WAS TREATED WITH 60% DEXTROSE. RISPERIDONE WAS DISCONTINUED AND HIS BLOOD SUGARS WERE MONITORED AND FOUND TO BE NORMAL. TO DATE HE HAS NOT HAD ANY FURTHER EPISODES OF HYPOGLYCAEMIA.
 Indications: Agitation; Explosive Personality Disorder
 Concomitant Diseases: Dementia; Retention Of Urine
 Company Remarks: Changes in blood sugar level have been reported in patients using donepin.

JAUSA24454(1) USA health 5yr M No Change/Not Yet Diabetes Mellitus (Unknown)
 professional Subsidied Appetite Decreased (Unknown)
 Serious
 - .5 mg - .5mg Causality Per Company: doubtful

Event Description: A PHARMACIST AND A PHYSICIAN REPORTED ON THE HOSPITALIZATION OF A CHILD FOR DIABETES MELLITUS WHILE ON RISPERIDONE. THE CHILD ALSO HAD A DECREASED APPETITE. HE WAS TREATED WITH IV INSULIN. ADDITIONAL INFORMATION HAS BEEN REQUESTED.
 Indications: Unspecified Psychosis

JAUSA35035(1) USA health 55yr F 7 week(s) at onset Unknown Diabetes Mellitus Aggravated (77-OCT-1998)
 professional Not Serious
 tablet 1 mg - .5mg (28-AUG-1998 / Unknown) Causality Per Company: possible
 Indications: Anxiety States

Event Description: PHYSICIAN REPORTS PATIENT WITH ADULT ONSET DIABETES MELLITUS HAS RECENTLY HAD BLOOD SUGARS THAT ARE RUNNING HIGH AT APPROXIMATELY 170 MG/DL. PATIENT NORMALLY RUNS BETWEEN 110-120 MG/DL. GLIBENCLAMIDE WAS INCREASED AS A RESULT. PHYSICIAN DOES NOT KNOW IF PATIENT RECOVERED AS A RESULT OF THE INCREASE.

JAUSA36042(2) USA health 25yr M Recovered Diabetes Mellitus Aggravated (Unknown)
 professional Not Serious
 tablet - - 8mg (15-AUG-1998 / Unknown) Causality Per Company: possible

1debacck 16JUN00

Volume 15/Page 150

Confidential/Produced in Litigation Pursuant to Protective Order

JJRP 00384138

D821.152

R. 6316

Ref.no.(vers.no.) Cty Prjs. scores Age Sex Latency Outcome Reaction 82
Seriousness
Formul Strength-Unit dose (Therapy start date/end date)
=====

tablet - - 12mg (20-OCT-1998 / Unknown)

Event Description: PHARMACIST REPORTS BLOOD SUGAR IN DIABETIC PATIENT IS ELEVATED AT
TIMES TO 600 MG/DL WHILE ON RISPERIDONE THERAPY. HIS GLUCOSE LEVELS USUALLY RAN BETWEEN
60-800 MG/DL PRIOR TO RISPERIDONE THERAPY. SPECIFIC DATES OF TESTS UNAVAILABLE.
REPORTER FURTHER NOTES THAT PATIENT IS EXTREMELY NON-COMPLIANT WITH DIABETES MANAGEMENT.

=====

JAUSA55234(1) USA health 35yr M No Change/Not Yet Condition Aggravated (02-NOV-1998)
professional Subsidied Diabetes Mellitus Aggravated (77-NOV-1998)
Serious Renal Function Abnormal (77-NOV-1998)

tablet - - 8mg

Causality Per Company: possible

Event Description: PHARMACIST REPORTS PATIENT WHO WAS BELIEVED TO BE NON-COMPLIANT WITH
HIS RISPERIDONE, WAS HOSPITALIZED ON 02-NOV-98 DUE TO AN EXACERBATION OF HIS PSYCHOSIS.
PATIENT WHO HAD BEEN A NON-INSULIN DEPENDENT DIABETIC FOR YEARS, HAD NORMAL BLOOD SUGAR
READINGS (IN THE LOW 100'S) INITIALLY UPON HOSPITALIZATION. HOWEVER, HIS BLOOD SUGARS
SUBSEQUENTLY BEGAN TO RUN HIGH BETWEEN 220 TO 280 DAILY. HE IS NOW RECEIVING REGULAR
HUMULIN INSULIN PEN PER A SLIDING SCALE. REPORTER ALSO NOTES THAT PATIENT HAS BEEN
EXPERIENCING SOME RENAL INSUFFICIENCY WITH A CREATININE LEVEL OVER ONE (NOS). ADDITIONAL
INFORMATION HAS BEEN REQUESTED.

Indications: Schizo-Affective Type Schizophrenia

Concomitant Diseases: Obesity; Diabetes Mellitus Without
Mention Of Complication

=====

JAUSA35484(1) USA health 20yr M No Change/Not Yet Ketoacidosis (10-DEC-1998)
professional Subsidied Diabetes Mellitus (10-DEC-1998)
Serious

tablet 3 mg - 8mg

Causality Per Company: possible

Event Description: PHYSICIAN REPORTS PATIENT WITH A FAMILY HISTORY OF DIABETES; WAS
HOSPITALIZED ON 10-DEC-98, AND DIAGNOSED WITH DIABETIC KETOACIDOSIS. URINE WAS POSITIVE
FOR KETONES AND BLOOD GLUCOSE LEVEL WAS ELEVATED (NOS). PATIENT WAS TREATED WITH BOTH
REGULAR AND NPH INSULIN (DOSE AND AMOUNT OF EACH GIVEN NOS). A TOTAL OF 150 UNITS WAS
ADMINISTERED. BLOOD GLUCOSE REMAINS HIGH (NOS). ADDITIONAL INFORMATION HAS BEEN
REQUESTED.

Company Remarks: It is more likely the diabetes was
inherited especially in view of the family history of
diabetes in this patient.

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JAUSA35494(1) USA health 40yr M 9 month(s) at onset No Change/Not Yet Diabetes Mellitus (12-JUN-1998)

1debaeck 18JUN00

Volume 15/Page 151

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DB21.153

R. 6317

Ref.no.(para.no.)	Cty	Pris. source	Age	Sex	Latency	Outcome Seriousness	Reaction
Formal Strength-Unit dose (Therapy start date/end date)							
professional						Subsided Serious	Polyuria (30-NOV-1998) Thirst Excessive (30-NOV-1998) Fatigue (30-NOV-1998)

tablet 1 mg - 1mg (15-AUG-1997 / 03-DEC-1998)

Event Description: MEDICAL STUDENT REPORTS PATIENT WITH A FAMILY HISTORY OF DIABETES WAS DIAGNOSED WITH DIABETES MELLITUS ON 12-JUN-98. HE WAS STARTED ON GLIPIZIDE AND MAINTAINED ON THIS UNTIL HE WAS HOSPITALIZED ON 30-NOV-98. PRESENTING SYMPTOMS IN THE EMERGENCY ROOM WERE FATIGUE, POLYURIA AND POLYDIPSIA. BLOOD GLUCOSE ON ADMISSION WAS 1,023 MG/DL. HE WAS TREATED WITH INSULIN (DOSAGE/ROUTE/TIME NOT SPECIFIED) AND ADMISSION TO THE INTENSIVE CARE UNIT OF THE HOSPITAL. AFTER ADMISSION AND THROUGH 10-DEC-98, HE RECEIVED 60 UNITS OF INSULIN INTERM. ACT AND 16 UNITS OF REGULAR INSULIN IN THE MORNING (WITH SLIDING SCALE COVERAGE) AND 50 UNITS OF INSULIN INTERM. ACT AND 10 UNITS OF REGULAR INSULIN (WITH SLIDING SCALE COVERAGE) IN THE AFTERNOON. ON 07-DEC-98, HIS BLOOD SUGAR READINGS WERE 490 MG/DL IN THE MORNING AND 530 MG/DL IN THE AFTERNOON (PRIOR READINGS NOT AVAILABLE). RISPERIDONE WAS DISCONTINUED ON 08-DEC-98 AND PATIENT WAS STARTED ON OLANAPINE. ON 09-DEC-98, PATIENT'S BLOOD SUGAR WAS 245 MG/DL IN THE MORNING AND 280 MG/DL IN THE AFTERNOON. ON 10-DEC-98, PATIENT'S BLOOD SUGAR READINGS WERE 190 MG/DL IN THE MORNING AND 80 MG/DL IN THE AFTERNOON. HIS INSULIN WAS REDUCED (NOS) AND HIS BLOOD SUGARS CONTINUED TO RUN AROUND 200 MG/DL.

Causality Per Company: possible
Indications: Unspecified Schizophrenia

JAGSA35023(1)	USA patient/consumer 6/yr F	0 day(s) at onset	No Change/Not Yet Subsided Not Serious	Diabetes Mellitus Aggravated (77-NOV-1998) Causality Per Company: possible

tablet 1 mg - 1mg (15-NOV-1998 / Unknown)

Concomitant Diseases: Anxiety States

Event Description: CONSUMER WITH DIABETES MELLITUS REPORTS SHE HAS EXPERIENCED ELEVATED BLOOD SUGARS WHILE ON RISPERIDONE THERAPY. RISPERIDONE THERAPY CONTINUES AND THE SYMPTOMS HAVE NOT ABATED.

JAGSA35888(1)	USA patient/consumer	# 29 month(s) at onset	No Change/Not Yet Subsided Not Serious	Diabetes Mellitus (77-DEC-1998) Vision Blurred (77-DEC-1998) Weight Increase (77-JAN-1998)

tablet 1 mg - 1mg (30-JUN-1998 / Unknown)

Causality Per Company: possible

Event Description: CONSUMER WITH DIABETES MELLITUS THAT WAS MANAGED WITH ORAL HYPERGLYCEMIC (NOS) HAS RECENTLY REQUIRED USE OF NPH INSULIN. PRESENTING SYMPTOMS TO

Indications: Bipolar Affective Disorder, Mixed

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Volume 15/Page 152

JRF 00384140

R. 6318

Ref.no.(verse.no.)	Ctry	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction

Formul Strength-Unit dose (Therapy start date/end date)
 PHYSICIAN WERE INCREASED THIRST, INCREASED URINATION AND OCCASIONAL BLURRED VISION.
 PATIENT ALSO NOTES A BRIGHT INCREASE OF 20 POUNDS IN THE PAST YEAR. RISPERIDONE THERAPY
 CONTINUES.

JAUSA36172(1)	USA	patient/consum	34yr F	5	week(s) at onset	No Change/Not Yet Subsided Serious	Diabetes Mellitus (07-FEB-1999) Thirst (08-FEB-1999) Appetite Increased (08-FEB-1999) Dehydration (08-FEB-1999) Tachycardia (08-FEB-1999)

tablet 4 mg - 4mg (02-JAN-1999 / 07-FEB-1999)

Event Description: CONSUMER REPORTS HIS WIFE EXPERIENCED INCREASED THIRST, INCREASED
 HUNGER, SEVERE DEHYDRATION AND TACHYCARDIA APPROXIMATELY 4 WEEKS AFTER INITIATION OF
 RISPERIDONE THERAPY. THE PATIENT WAS HOSPITALIZED ON 07-FEB-99 AND WAS DIAGNOSED WITH
 DIABETES MELLITUS. BLOOD SUGAR WAS 1000 MG/DL ON 07-FEB-99. RISPERIDONE WAS STOPPED ON
 07-FEB-99. THE EVENTS HAVE NOT YET ABATED.

Causality Per Company: possible
 Concomitant Diseases: Bipolar Disorder

JAUSA38549 (29)	USA	patient/consum	42yr M			No Change/Not Yet Subsided Not Serious	Depression (Unknown) Insomnia (??-FEB-1998) Tiredness (??-FEB-1998) Head Pain (??-FEB-1998) Rash (??-FEB-1998) Stomach Upset (01-MAR-1999) Diarrhoea (01-MAR-1999) Voice Alteration (11-MAR-1999) Feeling Of Numbness (??-APR-1998) Sobriety (Unknown) Somnolence (Unknown) Anger (Unknown) Walking Difficulty (Unknown) Irritability (15-MAY-1999) Anxiety (Unknown) Dizziness (Unknown) Photosensitivity Reaction (Unknown) Nightmares (Unknown) Extrapyramidal Disorder (Unknown) Shaking (Unknown) Burning Sensation (Unknown) Sweating Increased (31-AUG-1999) Hyperactivity (Unknown) Condition Aggravated (Unknown) Fall (Unknown)

tablet - - 5mg (??-JAN-1998 / Unknown)
 tablet - - 6mg

Event Description: CONSUMER REPORTS HE HAS EXPERIENCED INSOMNIA AND IS TIRED DURING THE
 DAY. HE ALSO REPORTS THAT HIS "HEAD HURTS", HE HAS INCREASED ANXIETY AND DEVELOPED A
 BODY RASH. RISPERIDONE THERAPY CONTINUES.
 ADDITIONAL INFORMATION RECEIVED ON 01-MAR-99: CONSUMER REPORTS ANXIETY CONTINUES. HE
 ALSO REPORTS HE EXPERIENCED INTERMITTENT DEPRESSION WHILE ON RISPERIDONE THERAPY.
 STARTING 01-MAR-99, PATIENT EXPERIENCED AN UPSET STOMACH AND DIARRHOEA. RISPERIDONE
 THERAPY CONTINUES. THE ADVERSE EVENTS HAVE NOT ABATED.
 ADDITIONAL INFORMATION (11-MAR-99): PATIENT REPORTS ALMOST DAILY THAT HE CONTINUES TO
 EXPERIENCE DEPRESSION (NIGHT-TIME), UPSET STOMACH AND A REDDENED RASH. PATIENT ALSO
 REPORTS SCREAMING AT THE TOP OF HIS LUNGS.
 ADDITIONAL INFORMATION (14-APR-99): CONSUMER REPORTS RASH CONTINUES. HE ALSO REPORTS HE
 HAS ITCHY, FLAKY SCALP AND HIS BODY IS HOT.
 Additional information 23-Apr-99:
 Person to person transfer:
 Consumer contacted Janssen multiple times and provided the following information:
 Depression continues and it feels like his skin "got hot" intermittently approximately
 six times within the last year. He also experienced somnolence which abated when
 risperidone was increased to 6 mg daily, the date of increase is unknown. Also unknown

1debacck 18JUN00

Volume 15/Page 153

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JJRP 00384141

D821.155

R. 6319

Ref.No.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcome	Reaction
						Seriousness	
Formul. Strength/Unit dose (Therapy start date/end date)							

is whether the somnolence was related to medication or depression. He reports anxiety again as he is going through unspecified medication changes. Anger, an anxiety attack with a stomach ache occurred, but disappeared within a few minutes. He is having "trouble walking," has an unspecified skin problem, is dizzy and experiences loss of balance. Dates for the previous events are not known. Lithium carbonate is discontinued on 10-May-99. Since 15-May-99 he's experienced anger, irritability and hyperactivity. On 17-May-99 he reports five anxiety attacks in five days, then fifteen minutes later phoned to report feeling tired. Consumer reports anxiety again. He attributes being sleepy to carbamazepine and then complains about the inability to sleep and calm down, and feeling hot. On 18-May-99 he describes feeling fearful, high anxiety and on 18-May-99 expressly states having "EPS" without elaborating any symptoms. Risperidone is being taken in 2 divided doses, 2mg in am and 4 mg in pm. Tiredness continues and he now reports being "shaky." On 27-May-99 it's reported that the dizziness abated after he ate breakfast, but three days later reports the dizziness returned.

Additional information 15-Jun-99:
 Person to Person transfer:
 According to Person to Person representative patient has a burning painful rash related to an extreme skin sensitivity to the sun. Patient reports getting sunburn just walking down the street and that it is incapacitating him. He does not describe this statement further and it is not medically confirmed. Further reported by the consumer is recurring nightmares, nervousness and shaking hands.
 Additional information received 23-Aug-99:
 Consumer reports his feet have started burning at night.
 Additional information received 01-Sep-99:
 Consumer reports he had an "anxiety attack" accompanied by increased sweating on 31-Aug-99.
 Additional information 09-Sep-99:
 Person to Person transfer:
 A person to person representative reports that the consumer complained again about depression and "sleeping alot."
 Additional information 17-Sep-99:
 Person to Person transfer:
 Consumer continues to report facial redness and flushing secondary to photosensitivity. Consumer also reports he experienced disturbance in his mood and hyperactivity.
 Person to Person transfer:
 Consumer reports he fell out of his chair during a group meeting and is feeling depressed. No other information is available.
 Additional information received 16-Oct-99:
 Consumer reported he experienced leg pain, mania, grandiose feelings and malaise while on risperidone therapy.
 Additional information received 21-Oct-99:
 Consumer reports his eyes are hurting while on risperidone therapy.
 Additional information received 25-Oct-99:
 Consumer reports he experienced the following additional adverse events while on risperidone therapy: muscle stiffness in left arm, an eye infection, elevated triglycerides, back pain, panic attacks, bleeding gums and an aggravation of his

Leg Pain (Unknown)
 Euphoria (Unknown)
 Mania (Unknown)
 Eye Pain (Unknown)
 Muscle Stiffness (Unknown)
 Eye Infection (Unknown)
 Back Pain (Unknown)
 Hypertiglyceridemia (Unknown)
 Gingival Bleeding (Unknown)
 Panic Reaction (Unknown)
 Infection Localised (77-NOV-1999)
 Appetite Increased (Unknown)
 Coughing (Unknown)
 Malaise (Unknown)
 Thirst (Unknown)
 Dental Disorder Nos (Unknown)
 Nervousness (77-DEC-1999)
 Eye Abnormality (Unknown)
 Pharyngitis (77-DEC-1999)
 Upper Resp Tract Infection (77-DEC-1999)
 Hypersensitivity (01-JAN-2000)
 Blood Sugar Increased (Unknown)

Causality Per Reporter: not assessed/not reported
 Causality Per Company: possible
 Indications: Schizo-Affective Type Schizophrenia
 Concomitant Diseases: Anxiety States

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Volume 15/ Page 154

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 JJRP 00384142
 D821.156

R. 6320

Ref.no.(vers.no.)	Ctry	Prim. source	Age	Sex	Latency	Outcome	Reaction	66

Formal Strength-Unit dose (Therapy start date/end date)
underlying schizophrenia. His eye infection has improved. It is unknown if he was prescribed prescription treatment.
Additional information received 09-Nov-99:
Consumer reports an oral infection further described as a toothache and inflamed gums. He reports it is being treated with antibiotic therapy. He also reports increased appetite, coughing and not feeling good
Additional information received 18-Nov-99:
Consumer reports increased thirst while on risperidone therapy.
Additional information received 29-Nov-99:
Consumer reports he had dental surgery while on risperidone therapy. He was prescribed ibuprofen and aspirin for pain associated with surgery.
Additional information received 02-Dec-99:
Consumer reports he experienced nervousness beginning 01-Dec-99 while on risperidone therapy.
Additional information received 10-Dec-99:
Consumer reports his eye doctor told him he has a benign growth on his eye and eye infection. He also reports a sore throat.
Additional information 29-Dec-1999:
Multiple contacts received from consumer from 29-Dec-1999 through Jan-10-2000.
Follow-up from consumer who now reports experiencing a "cold." His depression continues. He contacted Janssen later the same day to report that his cold is being treated with antibiotics. Additional events reported by consumer are as follows; sensitive to food (nos), high blood sugar (nos).

JAUSA36554(2)	USA health professional	30yr F	17 week(s) at onset	No Change/Not Yet Subeided Serious	Diabetes Mellitus (77-FEB-1999) Causality For Company: possible
tablet 2 mg - 2mg (16-OCT-1998 / Unknown)					Indications: Other Unknown And Unspecified Cause Of Morbidity Or Mortality

Event Description: PHYSICIAN REPORTS PATIENT ON RISPERIDONE EXPERIENCED ELEVATED BLOOD GLUCOSE AND WAS RECENTLY DIAGNOSED WITH DIABETES MELLITUS. SHE WAS NOT HOSPITALIZED AND IS BEING TREATED WITH ORAL HYPOLYCEMIC (NOS). RISPERIDONE THERAPY CONTINUES.

JAUSA36935(6)	USA patient/consum or	30yr F	29 month(s) at onset	No Change/Not Yet Subeided Not Serious	Tendinitis (08-FEB-1999) Bursitis (77-MAR-1999) Obsessive Reaction (77-MAR-1999) Compulsive Reaction (77-MAR-1999) Condition Aggravated (77-MAR-1999) Joint Pain (24-MAR-1999)
tablet 2 mg - 2mg (77-AUG-1999 / Unknown)					

1dehaeck 16JUN00

Volume 15/Page 155

Confidential/Produced in Litigation Pursuant to Protective Order
JJRP 00384143
D821.157

R. 6321

Ref.no.(vers.no.) Cry Prim. source Age Sex Latency Outcome Reaction 87
Seriousness
Formal Strength-Unit dose (Therapy start date/end date)
Event Description: CALLER TRANSFERRED FROM PERSON TO PERSON. CONSUMER ON RISPERIDONE
REPORTS THAT SHE WAS DIAGNOSED WITH TENDINITIS. RISPERIDONE THERAPY CONTINUES.
F O L L O W - U P (17-MAR-99):
CONSUMER REPORTS SHE EXPERIENCED WORSENING OF OBSESSIVE-COMPULSIVE SYMPTOMS STARTING
APPROXIMATELY ONE WEEK AGO. RISPERIDONE THERAPY CONTINUES.
ADDITIONAL INFORMATION RECEIVED 28-MAR-99:
CONSUMER REPORTS SHE WAS TREATED WITH AN INJECTION OF CORTISONE FOR TENDINITIS AND
MUSCULITIS ON 22-MAR-99. SHE REPORTS SHE DEVELOPED THESE EVENTS SEVERAL WEEKS AGO. ON 24-
MAR-99, PATIENT EXPERIENCED JOINT PAIN AND FATIGUE. THESE EVENTS HAVE IMPROVED BUT NOT
COMPLETELY RESOLVED. PATIENT ALSO REPORTS SHE EXPERIENCED AN ELEVATED PROLACTIN LEVEL
THE FIRST TWO YEARS SHE WAS ON RISPERIDONE THERAPY. PROLACTIN LEVEL HAS SINCE RETURNED
TO NORMAL. RISPERIDONE THERAPY CONTINUES. (CN 240604).
Additional information received 24-May-99:
Consumer reports increased blood glucose levels while on risperidone. Consumer indicates
glucose fasting blood level was 160 mg/dl. Baseline values unknown.

Fatigue (24-MAR-1999)
Hyperprolactinemia (77-AUG-1999)
Hyperglycemia (Unknown)

Causality Per Reporter: not assessed/not reported

Causality Per Company: doubtful

Indications: Bipolar Affective Disorder, Mixed;
Hallucinations

JANSA35831(1) USA health
professional

Unknown
Serious

Diabetes Mellitus (Unknown)

Causality Per Company: possible

Indications: Other Unknown And Unspecified Cause Of
Morbidity Or Mortality

Event Description: PHYSICIAN REPORTS PATIENT EXPERIENCED NEW ONSET DIABETES MELLITUS
WHILE ON RISPERIDONE THERAPY. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

JANSA37073(2) USA patient/consum 50yr F 32 month(s) at onset No Change/Not Yet
or Subsidied Serious

Diabetes Mellitus (77-MAR-1999)
Weight Increase (77-MAR-1997)
Hypercholesterolemia (77-MAR-1999)

tablet 1 mg - 1mg (90-JUN-1996 / Unknown)

Causality Per Company: possible

Event Description: CONSUMER REPORTS EXPERIENCING WEIGHT GAIN WHILE ON RISPERIDONE. OVER
THE PAST 2 YEARS, SHE HAS GAINED APPROXIMATELY 100 LBS AND WAS RECENTLY DIAGNOSED WITH
DIABETES TYPE II AND HYPERCHOLESTEROLEMIA.

Indications: Unspecified Psychosis

Concomitant Diseases: Delusions

JANSA37223(1) USA health 44yr F

No Change/Not Yet

Condition Aggravated (25-FEB-1999)

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Ref.no. (vers.no.)	Qty	Prim. source	Age	Sex	Latency	Outcome Seriousness	Reaction	88
Formul	Strength-Unit dose (Therapy start date/end date)							
professional						Subsided Serious	Diabetes Mellitus (77-MAR-1993)	

tablet - - -

Causality Per Company: possible

Indications: Unspecified Schizophrenia

Concomitant Diseases: Acute Pancreatitis

Event Description: PHARMACIST REPORTS PATIENT WAS HOSPITALIZED ON 25-FEB-93 FOR EXACERBATION OF HER UNDERLYING SCHIZOPHRENIA. SOMETIME DURING HER HOSPITALIZATION, SHE WAS DIAGNOSED WITH DIABETES MELLITUS. NO BLOOD SUGARS ARE AVAILABLE. SHE DOES HAVE A CONCOMITANT PANCREATITIS. REPORTER DOES NOT KNOW IF ANY TREATMENT HAS BEEN GIVEN. RISPERIDONE HAS BEEN DISCONTINUED. PATIENT HAS NOT YET RECOVERED. HE AND THE TREATING PHYSICIAN DOUBT A CAUSAL RELATIONSHIP TO THE RISPERIDONE. NO ADDITIONAL INFORMATION IS EXPECTED.

JRFEL1999000201(0) CAN literature 41yr M

Recovered
Serious

Hypoglycemia (Unknown)
Depression Aggravated (Unknown)
Suicidal Tendency (Unknown)
Confusion (Unknown)
Fatigue (Unknown)
Panic Reaction (Unknown)
Restlessness Marked (Unknown)
Hallucination (Unknown)

unspecified - - 6mg(dly)
unspecified - - 9mg(dly)

Causality Per Reporter: doubtful

Causality Per Company: doubtful

Indications: Schizo-Affective Type Schizophrenia

Concomitant Diseases: Pure Hypercholesterolemia; Hepatitis.
Unspecified

Event Description: 41-year-old male patient with MDDM and a 21-year-history of schizo-affective disorder, exhibited breakthrough psychotic and mood symptoms that necessitated increases of aripiprazole to 225 mg orally and risperidone to 9 mg/day. Within 5 weeks of taking higher than usual therapeutic doses patient described blackout with experiencing unreality about himself and his environment, confusion in thinking, a dreamlike state and distortion of time sense. This was followed by a period of extreme fatigue, fear, anxiety and panic. His family doctor was consulted soon after the event resolved and his blood glucose levels were found to be within normal range. Subsequently, the patient reported previous episodes of lesser intensity and duration. He reported that similar episodes had occurred during his heavy alcohol consumption several years previously. EKG after the event was normal. The episodes continued at a variable frequency, intensity and duration, along with increasing anxiety and restlessness for approximately two weeks following the initial blackout. During this period, the patient monitored his blood glucose levels by finger prick method at home. Levels varied from normal fasting range of 5 to 7 mmol/L to 2 to 7 mmol/L fasting. Some variation would be expected due to diet and exercise. However he reported that hypoglycemic levels occurred more frequently during this period. There was a simultaneous emergence of major depressive symptoms and suicidal thoughts leading to hospital admission within two weeks of the initial blackout report. Approximately seven days before the admission, reduction of aripiprazole and risperidone had been initiated. His fluoxetine and glibenclamide were continued without dose changes. On days 1 and 2 of admission, the patient was free of psychotropic drugs. On day 3 he was referred to an internist who documented hypoglycemic levels (2.9 mmol/L fasting). This resulted in discontinuing of the glibenclamide. On day 3 olanzapine was initiated due to

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Volume 15/Page 157

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JJRP 00384145

D821.159

R. 6323

Ref.no.(vers.no.)	Ctry	Prin. source	Age	Sex	Latency	Outcome Seriousness	Reaction	ES

Formul	Strength-Unit dose	(Therapy start date/end date)

Increasing intensity of hallucinations, depression and suicidal thoughts. Glibenclamide was restarted when no more fluctuations in blood glucose were seen. According to the authors concomitant use of glibenclamide and sertraline likely resulted in decrease of clearance of the sulfonylurea compound. Risperidone may have influenced the metabolism of sulphonylureas, but this is unlikely because risperidone primarily affected ZDR.

JRFUSA1899000568(2)	USA health professional	42yr M	2 year(s) at onset	Improved Serious	Diabetic Ketoacidosis (01-JUN-1998) Anemia (01-JUN-1998)

tablet 2 mg - 2mg (77-MAY-1997 / Unknown)

Event Description: Physician reports patient with no family history of diabetes nor any known risk factors developed diabetic ketoacidosis one year after initiation of risperidone therapy. Patient was hospitalized in the intensive care unit, was treated with insulin and has improved. Patient remains on insulin at this time. Risperidone therapy continues. Additional information has been requested.

Additional information 21-Jun-99:

Physician provided concomitant disease, age, history data, dosing and duration of risperidone and lab values. Patient presented to the hospital on 01-Jun-99 in diabetic ketoacidosis after two years of risperidone administration. Blood glucose was 665 mg/dl. Hemoglobin was reported as 11.4 g/dl. Blood gas values also provided. Patient is also reported as HIV positive. No further information was provided or is expected.

Causality Per Reporter: not assessed/not reported

Causality Per Company: possible

Indications: Depressive Psychosis

Concomitant Diseases: Human Immunodeficiency Virus Infection
With Specified Conditions

JRFUSA1999001217(3)	USA patient/consumer	51yr F	8 month(s) at onset	No Change/Not Yet Subsided Not Serious	Memory Loss (77-77-1997) Somnolence (77-77-1998) Drug Misadministration (77-SEP-1999) Unspecified (77-SEP-1999) Insomnia (Unknown) Pain (Unknown) Paranoid Reaction (77-OCT-1999) Diarrhea (77-OCT-1999) Stomach Upset (77-OCT-1999) Nausea (77-OCT-1999) Rash (77-JUL-1999) Abdominal Pain (77-OCT-1999) Peritonitis (28-OCT-1999) Intracranial Pressure Increased (77-OCT-1999) Asthma (Unknown) Numbness Localized (77-OCT-1999) Head Pain (77-OCT-1999) Therapeutic Effect Unexpected (77-OCT-1999) Condition Aggravated (Unknown)

tablet 0 mg - 3mg (77-MAY-1996 / Unknown)

Event Description: Consumer reports experiencing memory loss while taking risperidone. Risperidone continues.

Additional information 15-Jul-99:

Person to person transfer:

Consumer provided history, untreated diseases, and changes in dosing schedules of risperidone and concomitant medications. Consumer reports depression while taking risperidone, 6 mg daily. Risperidone continues.

Additional information 24-Aug-99:

Person to person transfer:

Consumer called to report feeling depressed today, claims a situation in her daily life may have been responsible, or it may be due to risperidone.

Additional information received 30-Aug-99:

Consumer reports difficulty getting up in the morning.

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Volume 15/Page 158

Confidential/Produced in Litigation Pursuant to Protective Order

JJRP 00384146

D821.160

R. 6324

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Outcomes Seriousness	Reaction
60							

Formul Strength-Unit dose (Therapy start date/end date)

Additional information received 18-Sep-99:
Consumer reports she "got mixed up" and took two doses too many of risperidone and experienced some unspecified adverse event. The outcome of the event is unknown.
Additional information received 21-Sep-99:
Consumer also reported insomnia.
Additional information received 04-Oct-99:
Consumer reports she experienced generalized aches, pains and "neck caving in" while on risperidone therapy. She attributes the pains to her underlying cancer. Risperidone therapy continues.
Additional information received 16-Oct-99:
Consumer reports she recently experienced paranoia, diarrhea, stomach upset, nausea, left lower quadrant pain and a rash while on risperidone therapy.
Additional information received 26-Oct-99:
Consumer reports the following additional adverse events while on risperidone therapy:
frightening dream, pressure in her right eye, weakness, numbness behind her right ear and a pain in her head running from ear to ear causing difficulty in turning her head (patient calling this a "stroke"). The pain did resolve. Consumer reports the rash on her right thigh is being treated with desoximetasone. Consumer also believes risperidone is curing her breast cancer.
Additional information received 02-Nov-99:
Consumer reports shaking and is hearing voices while on risperidone therapy.
Additional information received 12-Nov-99:
Consumer reports swelling and lumps under her arms, allergies, warts, infected teeth, white patch on elbow that itches and drooling while on risperidone therapy.
Additional information received 06-Dec-99:
Follow-up information provided from consumer. Consumer reports she experienced sleep apnea and tremors of right hand while on risperidone therapy.
Additional information 10-Dec-99:
Person to person transfer:
Consumer reports experiencing delusions and shortness of breath, with continued complaints of insomnia and stomach aches. No other details are provided.
Additional information received 17-Dec-99:
Delusions removed as an adverse event (is covered by condition aggravated). Depression removed as an adverse event (is already in JRFUSA1999001645)
Additional Information Received 22-December-1999 via Person to Person Transfer:
Consumer reports experiencing hair loss while on therapy with risperidone.
Additional information received 07-Jan-00:
Consumer reports an increased appetite, feels stressed, has heart palpitations, swollen feet and fatigue while on risperidone therapy.
Additional information received 17-Jan-00:
Consumer reports she experienced nasal congestion, muscle spasms in her back and dizziness while on risperidone therapy.
Additional information received 11-Feb-00:
Consumer reports she experienced acid indigestion, diabetes mellitus, the flu and general malaise while on risperidone therapy.

Shaking (Unknown)
Lymphadenopathy (??-NOV-1998)
Saliva Increased (08-NOV-1999)
Allergy (Unknown)
Common Wart (Unknown)
Tooth Disorder (Unknown)
Skin Discoloration (Unknown)
Itching (Unknown)
Sleep Apnoea (Unknown)
Tremor (Unknown)
Breath Shortness (01-JAN-1999)
Hair Loss (01-DEC-1999)
Appetite Increased (Unknown)
Mental Distress (Unknown)
Palpitation (Unknown)
Fatigue (Unknown)
Oedema Peripheral (Unknown)
Nasal Congestion (01-JAN-2000)
Spasms (01-JAN-2000)
Dizziness (17-JAN-2000)
Acid Indigestion (Unknown)
Malaise (??-FEB-2000)
Diabetes Mellitus Aggravated (Unknown)
Influenza-Like Symptoms (??-FEB-2000)

Causality Per Reporter: not assessed/not reported

Causality Per Company: possible

Indications: Schizo-Affective Type Schizophrenia

Concomitant Diseases: Diabetes Mellitus Without Mention Of
Complication; Neoplasm Of Unspecified Nature Of Breast;
Unspecified Arthropathy; Essential Hypertension; Orofacial
Dyskinesia; Urinary Frequency; Agoraphobia With Panic
Attacks; Osteoporosis

JRFUSA1999001399(9)	USA health professional	58yr F	8 day(s) at onset	Death Serious	Unspecified (13-JUL-1999) Stupor (11-JUL-1999)

Volume 15/Page 159

Confidential/Produced in Litigation Pursuant to Protective Order
JJP 00384147
D821.161

R. 6325

Fever (10-JUL-1999)

Ref.no.(vers.no.) Cty Prim. source Age Sex Latency

Outcome
Seriousness

Reaction

01

Formul Strength-Unit dose (Therapy start date/end date)

=====

tablet 1 mg - 1mg (08-JUL-1999 / 09-JUL-1999)

tablet 2 mg - 2mg (10-JUL-1999 / 13-JUL-1999)

Hyperglycemia (11-JUL-1999)
Sedation (11-JUL-1999)
Renal Function Abnormal (11-JUL-1999)
Spot Increased (11-JUL-1999)
Bilirubin Increased (11-JUL-1999)
Hypokalemia (11-JUL-1999)

Event Description: Initial report received from patient's son indicating that his mother had died suddenly while in a psychiatric facility for an aggravation of her underlying schizophrenia. Psychiatrist was able to provide additional information. Patient who had been in an assisted living facility was hospitalized on 08-Jul-99 for an aggravation of her underlying schizophrenia. She had not been compliant with taking her medication (olanzapine). Patient has a long history of psychiatric illness including multiple inpatient hospitalizations and treatment with fluphenazine decanate. Risperidone was initiated in the hospital on 08-Jul-99 at 1 mg twice daily. Lorazepam (Ativan) was initiated on 09-Jul-99 and sertraline hydrochloride (Zoloft) was initiated on 10-Jul-99. Risperidone dose was increased on 10-Jul-99 to 2 mg twice daily. Lorazepam was discontinued on 12-Jul-99, as patient seemed to be heavily sedated. On 13-Jul-99, patient was found in her wheelchair unresponsive and without a pulse. Cardiopulmonary resuscitation was performed but was unsuccessful. Vital signs prior to patient's death were normal other than an elevated temperature on 10-Jul-99 of 37.7 degrees Celsius. Labwork done on 11-Jul-99 revealed a BUN of 77, creatinine of 2 and glucose of 153. Albumin and protein levels were normal. These results did not reach the reporter until after the patient's death. Patient had no history of diabetes mellitus or no other significant medical history other than obesity (patient weighed approximately 102 kg). An EKG was not done on admission. Autopsy results are pending. Additional information has been requested.

Causality Per Reporter: not assessed/not reported

Causality Per Company: possible

Indications: Paranoid Type Schizophrenia; Depressive Disorder, Not Elsewhere Classified

Concomitant Diseases: Unknown

Additional information received 29-Dec-99:

Physician reports patient was found unresponsive on 13-Jul-99 and subsequently died. Labwork done 11-Jul-99 also revealed an elevated bilirubin and SGOT as well as a low potassium level. See diagnostic data for specific values. No autopsy results were provided. Additional information has been requested.

=====

JRFUSA1999001817(2) USA health professional

43yr M 365 day(s) at onset
No Change/Not Yet Subsidized Serious

Hyperglycemia (02-AUG-1999)
Hypertriglyceridemia (02-AUG-1999)

tablet 3 mg - 3mg (03-AUG-1999 / Unknown)

Causality Per Reporter: not assessed/not reported

Event Description: A pharmacist reports about a hospitalized patient who developed hyperglycemia during risperidone therapy. Patient has been hospitalized for at least a year at which time risperidone and valproate sodium was started. He has been receiving mirtazapine for several months (po). On 2-Aug-99, his blood sugar was 345. He has been treated with glyburide 5 mg daily and sliding scale insulin. The last blood sugar done over the last couple of days has been 180-170. Risperidone therapy continues. Additional information has been requested.

Causality Per Company: possible

Indications: Bipolar Affective Disorder, Mixed, Severe
Depressed, Specified As With Psychotic Behavior

Concomitant Diseases: Obesity

Additional information 17-Aug-99:

Pharmacist provided additional concomitant medication and lab studies including blood

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Volume 15/Page 160

Confidential/Produced in Litigation Pursuant to Protective Order

JJRP 00384148

D821.162

R. 6326

Ref.no.(vers.no.)	Cry	Pris.	source	Age	Sex	Latency	Outcome	Reaction	82

Formul Strength-Unit dose (Therapy start date/end date)

=====

sugar and triglyceride levels. No further information is expected.

=====

JRFUSA1898002213(4) USA patient/consum 36yr F
cr

No Change/Not Yet
Subsided
Not Serious

Tremor (Unknown)
Psychosis Aggravated (77-JUL-1999)
Stomach Upset (Unknown)
Dizziness (Unknown)
Hypoglycaemia (77-JUL-1999)
Fatigue (Unknown)
Muscle Stiffness (Unknown)

tablet 3 mg - 3ag (77-JAN-1999 / Unknown)
tablet 4 mg - 4ag (77-MAY-1999 / Unknown)

Event Description: Person to Person transfer:

Consumer reports that she has been taking risperidone since Jan-99. Recently she has been experiencing dizziness, a return of hallucinations and low blood sugar. Risperidone therapy continued.

Additional information received 08-Oct-99:

Consumer reports she "got stiff" after bupropion mesylate was discontinued after 5 years duration. She also reports lack of energy while on risperidone therapy.

Additional information 25-Oct-99:

Person to Person transfer:

Consumer reports a lack of energy/tiredness and dizziness. Reportedly these events abated 26-Oct-99, but on 28-Oct-99 she reports dizziness again. The hallucinations continue. Reportedly her physician has been made aware.

Additional information 18-Nov-99:

Person to person transfer:

Consumer called to ask if risperidone can cause the stomach aches or the jerking hand tremors she gets. She doesn't recall exactly when these symptoms began. Denies stomachache at present time. "It comes and goes", but the hand "jerks all the time".

Causality Per Reporter: not assessed/not reported

Causality Per Company: possible

Indications: Manic-Depressive Psychosis, Unspecified;
Unspecified Schizophrenia

=====

JRFUSA1898002303(0) USA health adul M
professional t

Unknown
Not Serious

Diabetes Mellitus Aggravated (Unknown)

tablet - - -

Causality Per Reporter: not assessed/not reported

Event Description: Physician reports patient experienced an aggravation of his underlying diabetes.

Causality Per Company: possible

Indications: Unknown

Concomitant Diseases: Diabetes Mellitus

=====

JRFUSA1898002436(3) USA health 8yr M 11 month(s) at onset
professional

No Change/Not Yet
Subsided

Diabetes Mellitus (77-SEP-1999)
Condition Aggravated (07-SEP-1999)

Volume 15/Page 161

Confidential/Produced in Litigation Pursuant to Protective Order

JJRP 00384149

D821.163

R. 6327

Ref.no.(vers.no.)	Cty	Pris. source	Age	Sex	Latency	Outcome Seriousness	Reaction	
						Serious		83

Formul Strength-Unit dose (Therapy start date/end date)

=====

tablet - - 1mg (77-OCT-1998 / 22-JUL-1999)
tablet - - 1.5mg (23-JUL-1999 / Unknown)

Causality Per Reporter: not assessed/not reported

Event Description: Psychiatrist reports patient was hospitalized for new onset diabetes mellitus (blood sugars not available) while on risperidone therapy. He reportedly has no family history of diabetes mellitus. Additional information has been requested.

Causality Per Company: doubtful

Additional information 24-Sep-99:

Physician provided additional information. Child has a long history of anxiety and behavioral problems including a hospitalization on 23-Oct-98. Over the summer he developed polyuria and polydipsia and was diagnosed with type I diabetes which requires several types of insulin. In addition, risperidone compliance has been poor. It is felt that the patient may not have been taking his medication 4-6 weeks prior to the current hospitalization, thus causing a relapse of his anxiety. Risperidone therapy has been discontinued.

Indications: Anxiety State, Unspecified

=====

JRFUSA1999003389(3) USA health
professional

80yr M

Recovered
Serious

Hypoglycemia (Unknown)

tablet .25 mg - .25mg

Causality Per Reporter: not assessed/not reported

Event Description: Physician reported to a sales representative that patient using risperidone was seen in the emergency room with a blood sugar of 18. No further information was provided. Additional information has been requested.

Causality Per Company: possible

Additional information received 12-Nov-99:

Physician provided additional information. Patient was hospitalized as a result of the event. He was treated (NOS) and recovered. Risperidone was discontinued.

Indications: Unspecified Psychosis

=====

JRFUSA1999003478(0) USA patient/consum unk
or

Unknown
Not Serious

Weight Increase (77-OCT-1999)
Blood Sugar Decreased (77-OCT-1999)

tablet - - (Unknown / 25-OCT-1999)

Causality Per Reporter: not assessed/not reported

Event Description: Person to person transfer: Consumer reports experiencing a weight gain while on therapy with risperidone. Consumer also reports experiencing a decreased blood sugar while on therapy with risperidone. Therapy discontinued, outcome is unknown.

Causality Per Company: possible

Indications: Unknown

=====

JRFUSA1999003548(1) USA patient/consum 37yr M
or

No Change/Not Yet
Subsided

Convulsions Grand Mal (77-77-1998)
Diabetes Mellitus (77-SEP-1999)

Volume 15/Page 162

Confidential/Produced in Litigation Pursuant to Protective Order

JJRP 00384150

D821.164

R. 6328

Ref.no.(vers.no.)	Cty	Prim. source	Age	Sex	Latency	Serious	Hepatocellular Damage (77-SEP-1999)
Formul	Strength-Unit dose	(Therapy start date/end date)				Outcome	Reaction
						Seriousness	94
tablet 4 mg - 2mg (77-77-1999 / Unknown) Event Description: Person to person transfer: Consumer reports he experienced grand mal seizures, blood sugar level of 380 mg/dl, liver damage, weight gain of 22.7 kg, joint pain and a "hard stomach" while on risperidone therapy. Risperidone therapy continues. The events have not abated.							
						Weight Increase (77-77-1999)	
						Joint Pain (77-SEP-1999)	
						Abdominal Distension (77-SEP-1999)	
						Causality Per Reporter: not assessed/not reported	
						Causality Per Company: possible	
						Indications: Explosive Personality Disorder	

JRFUSA1989004548(1)	USA health professional	30yr M	No Change/Not Yet Subsidized	Diabetes Mellitus (Unknown)
unspecified			No Serious	Causality Per Reporter: not assessed/not reported
				Causality Per Company: possible
Event Description: Neurologist reports patient with a pre-existing head injury and slight obesity was diagnosed with non-insulin dependent diabetes mellitus while on risperidone and bupropion HCL therapy. Blood sugar levels were not available. Patient's grandfather had diabetes. No further information was provided or is expected.				Indications: Depressive Disorder, Not Elsewhere Classified; Dementia Concomitant Diseases: Other And Unspecified Injury To Face And Neck

JRFUSA2000000200(4)	USA health professional	13yr F	15 day(s) at onset	No Change/Not Yet Subsidized	Leucopenia (31-DEC-1999)
				Serious	Neuroleptic Malignant Syndrome (31-DEC-1999)
					Drug Level Increased (31-DEC-1999)
					Dehydration (31-DEC-1999)
					Neutropenia (31-DEC-1999)
					Diabetes Mellitus (04-JAN-2000)
					Conjunctivitis (Unknown)
					Euphoria (31-DEC-1999)
tablet 1 mg - 1mg (17-DEC-1999 / 21-DEC-1999) tablet 1 mg - 3mg (22-DEC-1999 / 28-DEC-1999) tablet 1 mg - 4mg (28-DEC-1999 / 30-DEC-1999) tablet 1 mg - 4mg (01-JAN-2000 / 08-JAN-2000) tablet - - 2mg (09-JAN-2000 / 09-JAN-2000) tablet - - 2mg (11-JAN-2000 / 24-JAN-2000)					Causality Per Reporter: not assessed/not reported
Event Description: Psychiatrist reports patient in a psychiatric treatment facility					

Idabaack 18JUN00

Volume 15/Page 163

Ref.no. (vers.no.)	Cty	Prj	Source	Age	Sex	Latency	Outcome Seriousness	Reaction	95

Formul Strength/Unit dose (Therapy start date/end date)

developed neuroleptic malignant syndrome, dehydration, lithium toxicity, leucopenia and

conjunctivitis while on risperidone, loxapine, quetiapine fumarate and lithium therapies.

Patient was being tapered from quetiapine fumarate when risperidone was added on 17-Dec-89. Risperidone was then slowly titrated up to a total daily dose of 4 mg daily on 28-Dec-89. On 31-Dec-89, patient developed altered mental status, muscle rigidity, elevated temperature (37.7 Celsius), autonomic instability (blood pressure 170/80 with normal baseline of 120/80), and elevated creatine kinase (3,144 U/L). She was taken to the emergency room where she was treated with antibiotics for conjunctivitis and released (she was not hospitalized and no labwork was obtained). Her symptoms were initially not thought to be neuroleptic malignant syndrome. Labwork was obtained at the psychiatric treatment facility which revealed lithium toxicity (lithium level was 1.7 mmol/L), leucopenia (white cell count of 4,000 with baseline of 8,300) and dehydration. Her symptoms were later diagnosed by a consulting neurologist as neuroleptic malignant syndrome. Risperidone and lithium were stopped temporarily (nos) and quetiapine fumarate and loxapine were discontinued. Her creatine kinase levels have improved (see diagnostic data) and her lithium level and temperature returned to normal. She was rechallenged with risperidone and lithium and events did not recur. Her leucocyte count remains low. Additional information has been requested.

Additional information 24-Mar-00:

Follow-up information provided from physician's nurse. Nurse reports patient presented with lethargy, awkwardness, muscle rigidity and hand and tongue tremors. Vital signs were: temperature-100, blood pressure-140/85, respirations-18, pulse-112. Patient was also enuretic of large amount of urine through out the day. Additional lab values and data provided reveal new on set diabetes, neutropenia and elevated valproic acid level. Also additional creatine kinase levels and white blood cell counts provided. See diagnostic data. Risperidone, loxapine and quetiapine fumarate were held on 31-Dec-89 and lithium was held on 07-Jan-00. Risperidone was again held on 10-Jan-00. See therapy records for specific dosage information. Patient is being treated for diabetes with glyburide.

Causality Per Company: doubtful

Indications: Schizo-Affective Type Schizophrenia

Concomitant Diseases: Unspecified Acute Reaction To Stress;
Unspecified Disturbance Of Conduct; Secondary Parkinsonism;
Anemia, Unspecified

Idabaack 18JUN00

Volume 15/Page 164

JJRP 00384152

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D821.166

R. 6330

8.3 Epidemiology Study

JJRP 00384153
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D821.167

Janssen Research Foundation

NDA 20-272 and 20-588

Response to FDA Request for Information : Evaluation of the Effect of Risperdal® on Glucose Metabolism

Antipsychotics and Type II Diabetes

1

Antipsychotics and Type II Diabetes

Report submitted by

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to

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July 21, 2000

Volume 15/Page 165

**JJRP 00384154
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D821.168**

R. 6332

Background

Based on several reported cases, it is suspected that the atypical antipsychotics may induce or exacerbate type II diabetes (also known as non-insulin-dependent and adult onset diabetes)¹⁻¹⁴ Psychotic individuals became glucose intolerant after initiating therapy with clozapine or olanzapine. To our knowledge, no cases implicating risperidone have been reported. A review of earlier cases mostly involving clozapine found that the majority of afflicted individuals had risk factors for type II diabetes including obesity and Afro-American male.⁸ A later review of new diabetes cases treated with olanzapine found a weaker association with risk factors, with those identified including a family history of Type II diabetes and obesity.¹

Two mechanisms by which the atypicals may induce Type II diabetes have been suggested - their propensity to cause weight gain and their antagonism of 5-HT receptors.⁸ A strong relationship between the atypicals and weight gain has been observed in clinical trials and clinical experience.¹⁵⁻²² Obesity is a risk factor for Type II diabetes and was reported in many of the cited cases. Another mechanism may explain the association of the atypicals with Type II diabetes in cases where weight gain was not an issue. The atypicals are thought to exert their antipsychotic effect in part through antagonism of 5-HT receptors.²⁰ It is believed that this leads to a decrease in insulin and thereby to hyperglycemia. While these mechanisms apply to all of the atypicals, as noted, only clozapine and olanzapine have been implicated. In addition, there have been reports associating conventional antipsychotics with Type II diabetes.²¹⁻²³

Despite the several case reports and logical mechanisms linking atypical antipsychotics to Type II diabetes, the evidence is inconclusive. The reported cases were identified as new-onset cases, but this is only in the sense that none of the afflicted individuals had a prior medical history of glucose intolerance. It is possible that glucose intolerance prior to treatment was sub-clinical and that treatment with atypical antipsychotics exacerbated pre-existing conditions. More importantly, reported cases associating the atypical antipsychotics with type II diabetes are very few relative to the total number of psychosis patients treated with these drugs. Given the generally high frequency of type II diabetes, it would not be unusual to observe a few cases where the onset or worsening of this condition occurred following initiation of an antipsychotic therapy. What is needed is a study based on sufficiently large numbers of psychosis patients.

2 HECON Associates, Inc.

Volume 15/Page 166

JJRP 00384155

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D821.169

Antipsychotics and Type II Diabetes

3

This study further investigated the relationship between antipsychotic therapy and Type II diabetes using the claims records of several thousand psychosis patients drawn from two health plans. The large numbers enabled more conclusive determination of antipsychotic contributions to the onset or exacerbation of type II diabetes. However, because of other limitations affecting these data, we were less able to control for the pre-existence of type II diabetes than could be done in case studies or clinical trials. The extent to which we were able to review claims histories was limited and varied among individuals. The best that we could do was to establish that individuals did not require medical attention for type II diabetes for determined periods prior to initiation of specific antipsychotic therapies. Therefore, the need for diabetes medical attention after initiation of antipsychotic treatment could be interpreted as reflecting either the onset of diabetes or the exacerbation of a pre-existing condition.

We measured the onset or exacerbation of type II diabetes among individuals treated with the various antipsychotics. As a control, we also measured the onset or exacerbation of this condition among individuals with reported psychoses but without antipsychotic treatment (at least for the period encompassed by the data). To insure that we were measuring the onset or exacerbation of type II diabetes rather than continuation of already existing states of health, we included only psychosis patients who had complete data and no evidence of type II diabetes during a specified period prior to observation. The period was extended to assess the sensitivity of results to pre-existing type II diabetes.

Methods

The analysis was based on combined data for two large mixed indemnity and managed care health plans, one located in the northeast region of the U.S. and the other, in the southeast. The data available from each of these plans extended from January 1996 through December 1997. A total of 7,933 individuals within these two plans were identified as having some form of psychosis (ICD-9s 290.xx - 299.xx) and either not using any antipsychotics or using an antipsychotic therapy for at least 60 or more contiguous days. Those on antipsychotic therapy for less than 60 days were excluded because we felt that they qualified neither as treated individuals nor as controls. A total of 4,308 psychotic patients received at least 60 contiguous

3 HECON Associates, Inc.

Volume 15/Page 167

JJRP 00384156
Confidential/Produced in Litigation Pursuant to Protective Order
D821.170

Antipsychotics and Type II Diabetes

4

days of an antipsychotic therapy during the study period while 3,625 received no treatment. Five categories of antipsychotic therapy were defined:

- risperidone
- olanzapine
- clozapine
- high potency conventionals
- low potency conventionals

For treated psychotics, antipsychotic treatment episodes provided the basis for observation. For each of the above antipsychotic therapies, treatment episodes were generally measured from the date of the first prescription for an antipsychotic to the final date of treatment calculated from the date of the last prescription plus its days supply. Identification of a prescription 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. Therefore, no treatment episode began before April 1, 1996. For treatment episodes truncated by disenrollment or the end of the study period, the disenrollment date or 12/31/97 was used as the final date of treatment. Using this procedure, we determined 1591 treatment episodes with risperidone, 1178 with olanzapine, 1681 with high potency conventionals, 556 with low potency conventionals, and 81 with clozapine. Less than eighteen percent of treated psychotics had more than one treatment episode during the April 1996 through December 1997 period with either the same antipsychotic or a different one. Each episode is a separate observation. Also, treatment episodes with different antipsychotics overlap in part in about 25 percent of the observations. Temporary concurrent use of the prior antipsychotic is recommended when transitioning to a new antipsychotic therapy.

We felt that the boundaries of a treatment episode were not strictly appropriate for associating new or resurgent cases of type II diabetes. Specifically, we were concerned that some individuals may have discontinued an antipsychotic therapy before they initiated treatment for the type II diabetes that may have been induced or exacerbated by that therapy. To adjust for this potential problem, we lagged the observation period by 30 days. For example, if a treatment episode with a particular antipsychotic extended from June 15, 1996 through March 10, 1997, we made the observation period for identifying Type II diabetes from July 15, 1996 through April

4 HECON Associates, Inc.

Volume 15/Page 168

JJRP 00384157
Confidential/Produced in Litigation Pursuant to Protective Order
D821.171

Antipsychotics and Type II Diabetes

5

10, 1997. The 30-day lag is also consistent with the likelihood that any diabetic effects of antipsychotics will take some time to emerge after initiating therapy.

For untreated psychotics, observation periods for identifying new or resurgent cases of type II diabetes were constructed using three index dates as starting points: June 1, 1996; November 1, 1996 and April 1, 1997. Untreated individuals were randomly assigned these starting dates. Observation periods ranged from one or the other of the starting dates to the end of the study period (12/31/97) or to an individual's disenrollment date if it came first.

Individuals with type II diabetes were identified using ICD-9 codes specifically for this condition and its manifestations and NDCs for diabetes medications.

Type II diabetes ICD-9s: 250.x0 and 250.x2

Type II diabetes medications: first and second generation sulfonylureas, metformin, rezulin, and precose.

Among the 7,933 psychotics, a total of 647 individuals were identified using the above criteria. Many of these, however, had pre-existing type II diabetes (i.e. existing prior to the observation period) and were excluded depending on the length of the screening period.

Prior periods of different lengths were applied in screening for psychotics with pre-existing type II diabetes. We used 4-month, 6-month and 8-month periods. Observations reporting type II diabetes within the specified pre-screening period were excluded. Observations were also excluded if their claims records did not extend back to or beyond the beginning of the specified pre-screening period. Inability to observe type II diabetes due to truncation of data was not equivalent to not observing this condition within the specified period. Longer pre-screening periods reduced the number of observations. While this affected tests for statistical significance, we felt a need to assess the sensitivity of results to the pre-existence or prior proximity of type II diabetes.

Two kinds of analysis were performed, descriptive and multivariate. The descriptive analysis compares rates of type II diabetes among the five antipsychotic therapies and untreated psychotics. Patients are tracked forward 12 months from the beginning of their observation periods. The type II diabetes cases identified in each of 6 two-month intervals are noted relative

5 HECON Associates, Inc.

Volume 15/Page 169

JJRP 00384158

Confidential/Produced in Litigation Pursuant to Protective Order

D821.172

Antipsychotics and Type II Diabetes

6

to the remaining population in each interval. The remaining population in each interval excludes previously identified cases and individuals whose data terminated prior to the interval. This method of comparing rates of type II diabetes is necessary because observation periods vary considerably in length. For each antipsychotic therapy or all therapies combined, higher rates of type II diabetes relative to those of untreated psychotics suggest that antipsychotic treatment induces or exacerbates this condition. Higher rates of type II diabetes for one antipsychotic therapy vs. another suggest its stronger diabetic effects. Different sets of tables were generated based on 4 months, 6 months and 8 months pre-screening. Odds ratios with 95-percent confidence intervals comparing the antipsychotics to each other and to untreated psychotics were calculated from these data.

Because the data for this study are claims data and were not generated in a controlled trial, the odds ratios calculated from the tables may be somewhat misleading. The tables control only for differences in observation period length and for pre-existing type II diabetes. Other uncontrolled differences among the observations could cause rates of type II diabetes to vary aside from any effects of the antipsychotics. For example, type II diabetes is age related and age differences among the groups could make odds ratios calculated from the tables inaccurate. Logistic regression was used to estimate type II diabetes odds ratios for each of the antipsychotics vs. untreated psychotics. The logistic models control for age and other differences among the observations. Three logistic regressions were estimated excluding observations with pre-existing type II diabetes at 4, 6 and 8 months prior to observation.

The dependent variable in a logistic model is binary taking a value of one if the event (type II diabetes) occurs for a given observation and zero otherwise. Control variables specified in the model are as follows.

Age: a continuous variable. The likelihood of observing type II (a.k.a. adult onset) diabetes was assumed to increase with age.

Sex: a binary variable taking a value of one if male and zero if female. The case studies cited showed a much higher proportion of males than females acquiring type II diabetes after initiating antipsychotic treatment.

6 HECON Associates, Inc.

Volume 15/Page 170

JJRP 00384159

Confidential/Produced in Litigation Pursuant to Protective Order

D821.173

Antipsychotics and Type II Diabetes

7

Antipsychotic intensity: measured in standardized milligrams per day of treatment and equals zero for untreated psychotics. More severely psychotic patients may require higher antipsychotic doses and the likelihood of type II diabetes may be dose related. To enable comparisons among antipsychotics with different milligram scales, reported milligrams were converted to risperidone equivalents to account for the difference in dosing ranges for different drugs. Weights were calculated by dividing each antipsychotic's dose range in milligrams by risperidone's range and applied to the dose on each prescription record.

Observation period length: measured in months. The likelihood of observing type II diabetes increases with the period of observation. This control variable was necessary because antipsychotic treatment episodes and, therefore, observation periods for type II diabetes varied considerably in length. Observation periods for untreated psychotics also varied.

Use of other psychotropic drugs: antidepressants, anxiolytics, anticholinergics, hypnotics, and mood stabilizers measured in dollars per month. While to our knowledge it is not addressed in the literature, other psychotropic medications may also induce or exacerbate type II diabetes.

Type of health care coverage : a binary variable where managed care equals one and indemnity equals zero. Individuals in both plans had either an indemnity or managed care form of coverage. While type of health care coverage does not affect type II diabetes, it may affect the likelihood that the condition is diagnosed.

Concurrent use of antipsychotics: measured as the ratio of other antipsychotic days supply to treatment antipsychotic days supply; equals zero for the untreated psychotics. While we could not speculate as to how, we felt that the diabetic effects of the treatment antipsychotic might be altered by the concurrent use of another antipsychotic.

Type of psychosis: Type II diabetes may be psychosis related and, to the extent that groups differ with respect to type of psychosis, this could explain observed differences between untreated psychotics and psychotics treated with each of the antipsychotics. Psychotics were grouped into five categories: schizophrenia, bipolar and manic, major depressive, dementia, and other psychoses. These were represented by binary variables for the first

7 HECON Associates, Inc.

Volume 15/Page 171

JJRP 00384160

Confidential/Produced in Litigation Pursuant to Protective Order

D821.174

four with zeros for all four indicating the fifth category.

Antipsychotic exposure: Five variables measured exposure to each of the five antipsychotics as well as the absence of treatment. Each variable equaled the length of treatment in months if the observed patient used that therapy and zero otherwise. Zeros for all five of the antipsychotic therapies implied the sixth category - no treatment. It was realistically assumed that the likelihood of inducing or exacerbating type II diabetes was related to the length of treatment.

In addition to regression results, tables were constructed profiling the observations in each group with respect to each of the above characteristics. These tables are important because they convey significant differences among the treated and untreated groups that could cause the logistically estimated odds ratios to diverge from those directly calculated from the tables.

The odds ratio in a logistic model is as follows:

$$[P_1/(1-P_1)] / [P_0/(1-P_0)]$$

For each of the antipsychotic exposure variables specified, this is interpreted as follows:

P_1 is the probability of the event (Type II diabetes) occurring given one month of exposure to the antipsychotic.

$(1-P_1)$ is the probability of the event not occurring given one month of exposure to the antipsychotic.

P_0 is the probability of the event occurring given zero exposure to the antipsychotics.

$1-P_0$ is the probability of the event not occurring given zero exposure to the antipsychotic.

The odds ratio for each antipsychotic measures the degree by which some base probability of type II diabetes is greater due to one month of exposure to that antipsychotic. The base probability depends on other characteristics of the population to which the antipsychotic is applied. Odds ratios for months of antipsychotic exposure greater than one are obtained simply by raising the one-month odds ratio to a power equal to the desired months of exposure. For example, the odds ratio for 6 months of exposure to the antipsychotic is:

8 HECON Associates, Inc.

Volume 15/Page 172

JJRP 00384161

Confidential/Produced in Litigation Pursuant to Protective Order

D821.175

$$\{[P_1/(1-P_1)] / [P_0/(1-P_0)]\}^6$$

The logistic model as specified measures for each antipsychotic the odds of type II diabetes relative to no treatment. Odds ratios estimated as such can be easily manipulated to calculate the odds of type II diabetes of one antipsychotic relative to another. Consider, for example, antipsychotics (1) and (2):

$$\{[P_1/(1-P_1)] / [P_0/(1-P_0)]\} / \{[P_2/(1-P_2)] / [P_0/(1-P_0)]\} = [P_1/(1-P_1)]/[P_2/(1-P_2)]$$

Results

Table 1 compares treated and untreated psychotics excluding individuals who reported type II diabetes during the four months prior to observation or who did not have sufficient data to make this determination. Individuals in the treated group as a whole, in the untreated group and in each of the five antipsychotic categories are tracked forward for twelve months. Type II diabetes cases reported in each of 6 two-month intervals are divided by the remaining population in each interval to yield percentages. Percentages for treated psychotics as a whole are invariably much higher than the corresponding percentages for untreated psychotics, suggesting a diabetic effect of antipsychotics. Comparisons among the five antipsychotic categories suggest that this diabetic effect varies considerably depending on the specific antipsychotic therapy. Percentages for risperidone, while higher than those for untreated psychotics, are invariably much lower than those for olanzapine. Risperidone shows the same pattern in comparison to high potency and low potency conventionals. Comparison with clozapine is limited by the small number of psychotics treated with this medication. Regardless, the overall percentage of type II diabetes cases for clozapine is much higher than that for risperidone. The other antipsychotics have much higher percentages than risperidone in comparison to untreated psychotics.

Tables 2 repeats Table 1 excluding individuals who reported type II diabetes during the six months prior to observation or who did not have sufficient data to make this determination. While numbers of observations are reduced, the higher degree of screening may better reflect diabetic effects of the antipsychotics. The effect of six vs four months pre-screening is to reduce,

9 HECON Associates, Inc.

Volume 15/Page 173

JJRP 00384162

Confidential/Produced in Litigation Pursuant to Protective Order

D821.176

Antipsychotics and Type II Diabetes

10

for both treated and untreated psychotics, percentages reporting type II diabetes. However, percentages for treated psychotics as a whole remain much higher than those of untreated psychotics with differences being generally greater than at four months pre-screening. While percentages for all of the antipsychotics are generally lower than at four months pre-screening, they remain well above those of untreated psychotics. Again, risperidone's percentages are invariably lower than those of olanzapine, and they are generally lower than those of the other antipsychotics.

A yet higher degree of pre-screening is applied in Table 3 which excludes individuals who reported type II diabetes during the eight months prior to observation or who did not have sufficient data to make this determination. Percentages for treated psychotics as a whole are modestly reduced relative to six months pre-screening while those for the untreated psychotics are slightly increased. Risperidone's percentages remain much lower than those of the other antipsychotics. Interestingly, at eight months pre-screening risperidone's percentages are even generally lower than those of untreated psychotics.

In Table 4, odds ratios at two month intervals and cumulative odds ratios are calculated based on four months pre-screening (Tables 1). Comparisons are made between risperidone and the other antipsychotic categories and between the antipsychotic categories and untreated psychotics. Cumulative odds ratios are calculated at 4, 6, 8, 10 and 12 months into the observation periods. The denominators in calculating cumulative odds ratios reflect weighted observations. Weighting is necessary because observation periods vary in length. Each observation is weighted by the number of two-month intervals in which it appears. An observation that appears in one two-month interval is counted once; one that appears in two-month intervals is counted twice, and so forth. The cumulative odds ratios for olanzapine vs. risperidone are close to 2.0 as are those for low potency conventionals vs. risperidone. The cumulative odds ratios for high potency conventionals vs. risperidone are slightly lower. Odds ratios for clozapine range much higher but these are limited by the few observations for this antipsychotic. Cumulative odds ratios for risperidone vs. untreated psychotics range from 1.28 to 1.40 while those for the other antipsychotics vs. untreated psychotics range from slightly under 2.0 to above 6.0.

10 HECON Associates, Inc.

Volume 15/Page 174

JJRP 00384163
Confidential/Produced in Litigation Pursuant to Protective Order
D821.177

Cumulative odds ratios calculated at 12 months (as demonstrated in Table 4) and based on 4 months, 6 months, and 8 months pre-screening are reported in Tables 5-7. Comparisons are made between risperidone and the other antipsychotic categories and between the antipsychotic categories and untreated psychotics. A 95-percent confidence interval is presented for each odds ratio. Referring to Table 5 which is based on 4 months pre-screening, we see that the odds ratios for each of the other antipsychotics vs. risperidone are well in excess of 1.0 with most being around 2.0. While all of the odds ratios for each of the antipsychotics vs. untreated are above 1.0, that for risperidone is much lower and close to 1.0. None of the confidence intervals encompass "1" suggesting that differences in diabetic effect between the groups compared are all statistically different from zero.

With the exception of that for clozapine, odds ratios for each of the other antipsychotics vs. risperidone remain about the same when we exclude individuals based on 6 months pre-screening (Table 6). Odds ratios for each of the antipsychotics vs. untreated psychotics generally increase, suggesting a stronger diabetic effect than reflected with 4 months pre-screening. However, this is reversed particularly for risperidone when odds ratios are calculated on the basis of a population pre-screened at 8 months (Table 7). The odds ratio for risperidone vs. untreated is close to "1" while those for the other antipsychotics remain far above this level. Correspondingly, odds ratios for each of the other antipsychotics vs. risperidone increase considerably. Based on the 95-percent confidence intervals, all of the odds ratios in both tables are significantly different from "1".

The data and odds ratios in Tables 1-7 do not reflect observation beyond 12 months. A number of observation periods were longer than 12 months with some extending to 20 months. To avoid making the tables and calculations more cumbersome, we ignored type II diabetes cases occurring beyond 12 months. We felt that differences between treated and untreated psychotics and among the five antipsychotic categories would be adequately conveyed with up to 12 months of observation.

Odds ratios calculated directly from the tables can be misleading especially if the groups being compared are dissimilar in other ways that can affect the onset or exacerbation of type II diabetes. The preceding tables control only for pre-existing type II diabetes and for observation

11 HECON Associates, Inc.

Volume 15/Page 175

JJRP 00384164

Confidential/Produced in Litigation Pursuant to Protective Order

D821.178

Antipsychotics and Type II Diabetes

12

period length, both of which affect the likelihood of observing this condition in any given group.

Age is an important variable which was not taken into account. The likelihood of acquiring Type II diabetes, a.k.a. adult onset diabetes, is certainly age related. Other psychotropic medications such as antidepressants, anxiolytics and mood stabilizers may also affect type II diabetes, and use of these was not controlled for either. Lastly, if antipsychotics are in fact a problem, then the onset or exacerbation of type II diabetes must be affected by the amount of time treated with an antipsychotic. Because treatment and observation periods are unequal for many treated individuals, odds ratios calculated from the tables do not reflect adequate control for differences in antipsychotic exposure. The 30-day lag between observation period and treatment period caused observation periods to be shorter by 30 days for those whose periods were truncated by the general end-date for data (12/31/97) or by disenrollment prior to this date. These and other potentially important differences among individuals were discussed in the Methods section.

The various groups are profiled in Tables 8 and 9 with respect to characteristics that we thought might affect the onset, exacerbation or reporting of type II diabetes. Both of these tables are based on the largest population used in the analysis, i.e. that screened for pre-existing type II diabetes at four months prior to observation. Table 8 provides a general outline of the psychotic populations being compared. Treated psychotics are significantly older than untreated psychotics and have a higher proportion of females. Treated psychotics also have a much higher proportion of individuals with indemnity coverage vs. managed care. While this characteristic does not affect the onset or exacerbation of type II diabetes, it may affect the likelihood of seeking professional care (reporting). Observation periods among untreated psychotics are more than double those of treated psychotics increasing the likelihood of observing type II diabetes in that group. Treated and untreated psychotics also differ considerably with respect to type of psychosis. Schizophrenia is virtually absent among untreated psychotics. Individuals with bipolar, major depressive and manic forms of psychosis are the principal users of antipsychotics.

A more detailed profile is provided in Table 9 where treated psychotics are separated by type of antipsychotic. Users of risperidone and olanzapine are similar in age while users of high and low potency conventionals are considerably older. Users of clozapine are younger. All of the antipsychotic categories have a higher proportion of females. Indemnity is the principal form

12 HECON Associates, Inc.

Volume 15/Page 176

JJRP 00384165

Confidential/Produced in Litigation Pursuant to Protective Order

D821.179

Antipsychotics and Type II Diabetes

13

of coverage across all categories. Observation periods are longest for clozapine and shortest for olanzapine. Treatment periods, which on average are longer than observation periods, are also longest for clozapine and shortest for Olanzapine. The breakdown of patients by type of psychosis shows significant differences among the antipsychotics. Clozapine has the largest proportion with schizophrenia while low potency conventionals have the smallest. All antipsychotic categories except clozapine have major depressive psychosis as the dominant type. Antipsychotic intensity (standardized mgs per day of treatment) differs substantially among the antipsychotics with olanzapine having the highest intensity and low potency conventionals the lowest. It seems logical that antipsychotic intensity would be associated with diabetic effects. Among treated psychotics, olanzapine users have the highest per capita use of other psychotropic medications while those treated with high potency conventionals have the lowest. Untreated psychotics have lower per capita use of other psychotropic medications than any of the antipsychotic categories. These medications may also affect type II diabetes. Lastly, concurrent use of different antipsychotics is most frequent among individuals treated with clozapine and least frequent among those treated with high potency conventionals.

Table 10 shows how type II diabetics were actually identified among treated and untreated psychotics. Individuals were identified by the first medical claim for type II diabetes (NIDDM) or if it appeared first, by the first prescription claim for an antidiabetic medication. Among those identified from diabetes medical claims, the overwhelming majority had NIDDM without complication. There are no appreciable differences between psychotics treated with antipsychotics and those who were untreated. Among those recognized from prescription claims for antidiabetic medications, the largest proportion reported second generation sulfonylureas. Psychotics not treated with antipsychotics have a much higher proportion who reported metformin. These findings provide no evidence that identification of type II diabetes may have differed between treated and untreated psychotics.

Logistic Regression Results

Logistic regression models were estimated to control for differences among the groups of psychotics that were not controlled or adequately controlled in the tables. The logistic regression

13 HECON Associates, Inc.

Volume 15/Page 177

JJRP 00384166

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D821.180

Antipsychotics and Type II Diabetes

14

model described in the Methods section was estimated three times: excluding psychotics reporting type II diabetes at four months, at six months, and at eight months prior to observation.

Results for the model based on four months pre-screening are reported in Table 11. The model was estimated on the basis of 7,395 observations, 206 of whom reported type II diabetes while 7,189 did not. Of particular interest are the estimated odds ratios for each of the explanatory variables (the parameter estimates are simply the logs of these ratios). Since the goal was to estimate diabetic effects of the antipsychotics, the focus is on the five variables for each of the five antipsychotic categories. These variables measure for each observation, exposure in months to each of the antipsychotics. The excluded group or base for comparison is untreated psychotics. These are represented by zero values for all five antipsychotic indicators, thereby indicating no exposure or treatment. As discussed in the Methods section, the odds ratio for each antipsychotic reflects the odds of type II diabetes for one month of exposure to that antipsychotic vs. zero exposure.

As the odds ratios indicate, risperidone has the smallest diabetic effect which is not at all statistically significant. The diabetic effects of olanzapine, high potency conventionals and low potency conventionals are all statistically significant at $p < .01$ or better. Clozapine's diabetic effect is significant only at $p < .10$, but this is likely due to its relatively small sample. Olanzapine and clozapine have the highest odds ratios (largest diabetic effects) which is consistent with the case literature. For this population, pre-screened at four months prior to observation, the average treatment duration across all antipsychotics is 6.8 months. Each of the estimated odds ratios are re-expressed to reflect 6.8 months rather than one month of treatment. These ratios are more in line with those calculated from the descriptive tables. The odds of each of the other antipsychotics relative to risperidone are also calculated from the estimated ratios and re-expressed assuming 6.8 months of treatment (see Methods section). Ratios are generally lower than those directly calculated from the data (refer to Table 5). This may be explained by the better control for inter-group differences achieved with a logistic model.

Among the control variables, age is highly significant ($p < .01$) as would be expected for type II diabetes. Since "Age" is a continuous variable expressed in years, its odds ratio indicates the percent increment in the likelihood of Type II diabetes as an individual ages by one year.

14 HECON Associates, Inc.

Volume 15/Page 178

JJRP 00384167

Confidential/Produced in Litigation Pursuant to Protective Order

D821.181

Antipsychotics and Type II Diabetes

15

Logically, the length of the observation period also affects the likelihood of observing type II diabetes ($p < .01$). Interestingly, the use of non-antipsychotic psychotropic medications is highly correlated with the likelihood of type II diabetes. Since mechanisms through which antipsychotics and other medications may affect Type II diabetes have not been fully investigated, it is certainly reasonable to conjecture at this stage that antidepressants, anxiolytics, mood stabilizers, etc. may also induce or exacerbate this condition. None of the other control variables are statistically significant. The type of psychosis indicators do not even approach statistical significance and, as Tables 8 and 9 indicate, there is considerable variation among the groups in this regard. Because the forms of psychosis differ considerably, the lack of statistical significance for any of these indicators is at odds with the view that a higher incidence of type II diabetes is psychosis related. The insignificance of antipsychotic intensity, however, is puzzling. It would seem logical that if an antipsychotic in fact has a diabetic effect, then higher doses of that medication should have more of an effect. The association between antipsychotic dose and reporting of type II diabetes is investigated in more detail later.

Tables 12 and 13 report logistic regression results based on pre-screening for type II diabetes at 6 months and 8 months prior to observation. The remaining population with a six month pre-screening numbers 5,500 with 128 reporting type II diabetes (Table 12). Pre-screening at eight months further reduces the population to 4,979 with 101 reporting type II diabetes. Results for these cleaner populations are generally the same as those for the population pre-screened at four months. It is noteworthy that risperidone's odds ratio (diabetic effect), which continues to be statistically insignificant, becomes lower falling to below "1". The odds ratios of the other antipsychotics remain statistically significant with those for low potency conventionals, clozapine, and high potency conventionals increasing. Olanzapine's odds ratio remains about the same. Again, odds ratios are re-expressed assuming the average treatment duration for each treated population. Odds ratios for each of the other antipsychotics vs. risperidone are also calculated. The same control variables are statistically significant with the populations pre-screened at six and eight months as with the population pre-screened at four months. Antipsychotic intensity remains statistically non-significant but improves considerably. In contrast, the psychosis types become progressively less significant.

15 HECON Associates, Inc.

Volume 15/Page 179

JJRP 00384168

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D821.182

Antipsychotic Intensity

The relationship between antipsychotic intensity and Type II diabetes is further investigated in Tables 13 and 14. Observations for treated psychotics are divided into high, medium and low intensity groups (top, middle and bottom thirds in terms of mgs per day of treatment). Table 13 compares high and medium intensity to low intensity. For all treated psychotics, the odds of type II diabetes are only slightly greater for the high intensity vs. the low intensity group. Strangely, the odds are greater for the medium vs. low intensity group. This overall finding casts doubt on the possibility that antipsychotic intensity is in any way related to the onset or exacerbation of type II diabetes. Comparisons for risperidone show an inverse relationship between antipsychotic intensity and type II diabetes, but this is not inconsistent with the absence of a significant diabetic effect for this medication. Results for high and low potency conventionals and clozapine also do not support a positive relationship with antipsychotic intensity. Only the odds ratios for olanzapine suggest that diabetic effect increases with antipsychotic intensity. In Table 14, treated psychotics within each of the three levels of antipsychotic intensity are compared to untreated psychotics. Again, there is no consistent relationship between antipsychotic intensity and type II diabetes. Without a sufficient understanding of how each antipsychotic given its pharmacology might cause or exacerbate type II diabetes, it is difficult to assign any meaning to these findings.

Discussion

A possible relationship between the atypical antipsychotics, olanzapine and clozapine, and type II diabetes has been suggested in several case reports. A few earlier reports indicated a possible association with conventional antipsychotics. To our knowledge, risperidone has not been implicated. Because of the small numbers involved and the relatively high frequency of type II diabetes, case findings are inconclusive. To overcome this limitation and to provide an alternative source of evidence, we used administrative data from two large health plans to investigate the medical histories of several thousand psychotics both treated and untreated with antipsychotics. We performed descriptive analyses and logistic regression, both controlling for pre-existing type II diabetes, to assess the effects of different antipsychotics in causing or

16 HECON Associates, Inc.

Volume 15/Page 180

JJRP 00384169

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D821.183

Antipsychotics and Type II Diabetes

17

exacerbating this condition.

Consistent with the case findings, both the descriptive and logistic regression results show risperidone to have little or no diabetic effect. In contrast, the other antipsychotics including olanzapine, clozapine and high and low potency conventionals had statistically significant effects which were relatively large. Psychotics untreated with antipsychotics were used as a control. Odds ratios (diabetic effects) calculated directly from the data were generally substantially larger than those estimated with logistic regression. However, directly calculated ratios did not control or adequately control for important factors such as age, the use of non-antipsychotic psychotropic medications, and length of exposure to each antipsychotic, all of which were highly significant. Based on the logistic analysis, type of psychosis was not at all statistically significant which casts doubt on the view that diabetic effects are psychosis rather than antipsychotic related. Antipsychotic intensity (mgs per day of treatment) was also statistically non-significant. A direct detailed comparison of treated psychotics with different levels of antipsychotic intensity also failed to show any consistent association with type II diabetes. The meaning of this lack of association can be found only after the mechanisms through which antipsychotics might cause or exacerbate type II diabetes are fully understood.

Given the large numbers used in this study and the efforts made to identify individuals with pre-existing type II diabetes and to otherwise control for confounding influences, we believe that our findings in relation to risperidone and the other antipsychotics are reliable. In contrast to the other antipsychotics, it seems that risperidone has little or no diabetic effect and is safer in this regard.

17 HECON Associates, Inc.

Volume 15/Page 181

JJRP 00384170

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D821.184

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18 HECON Associates, Inc.

Volume 15/Page 182

JJRP 00384171

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19 HECON Associates, Inc.

Volume 15/Page 183

JJRP 00384172

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D821.186

Table 1 Frequency of Type II Diabetes Cases as Forward Observation Period Increases
Excludes Pre-existing Diabetes at Four Months Prior to Observation

<u>Treated psychosis population</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	47	1.15%	26	####	18	####	10	####	9	####	8	1.16%
Remaining population	4097		3171		2122		1470		1032		687	
subtracted - no data	na		879		1902		2536		2964		3300	
subtracted - already identified	na		47		73		91		101		110	
<u>Untreated psychosis population</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	17	0.56%	11	####	14	####	8	####	11	####	7	0.35%
Remaining population	3042		2969		2889		2794		2389		2007	
subtracted - no data	na		56		125		206		603		974	
subtracted - already identified	na		17		28		42		50		61	
<u>Risperidone</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	10	0.77%	5	####	3	####	1	####	2	####	2	0.88%
Remaining population	1294		1007		677		461		322		228	
subtracted - no data	na		277		602		815		953		1045	
subtracted - already identified	na		10		15		18		19		21	

Table 1 (cont.)

<u>Olanzapine</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	12	1.23%	8	####	5	#####	3	####	2	####	2	1.82%
Remaining population	979		740		483		321		207		110	
subtracted - no data	na		227		476		633		744		839	
subtracted - already identified	na		12		20		25		28		30	
<u>High potency</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	17	1.30%	7	####	8	#####	5	####	3	####	2	0.84%
Remaining population	1303		1017		691		491		352		239	
subtracted - no data	na		269		588		780		914		1024	
subtracted - already identified	na		17		24		32		37		40	
<u>Low potency</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	4	0.87%	6	####	2	#####	1	####	2	####	2	2.17%
Remaining population	459		355		232		167		126		92	
subtracted - no data	na		100		217		280		320		352	
subtracted - already identified	na		4		10		12		13		16	

Table 1 (cont.)

<u>Clozapine</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	4	6.35%	0	####	0	#####	0	####	0	####	0	0.00%
Remaining population	63		52		39		30		25		18	
subtracted - no data	na		7		20		29		34		41	
subtracted - already identified	na		4		4		4		4		4	

Table 2 Frequency of Type II Diabetes Cases as Forward Observation Period Increases
 Excludes Pre-existing Diabetes at Six Months Prior to Observation

<u>Treated psychosis population</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	36		20		15		7		8		5	
		1.04%		0.76%		0.88%		0.61%		1.03%		1.05%
Remaining population	3471		2842		1713		1149		777		474	
subtracted - no data	na		793		1702		2251		2616		2911	
subtracted - already identified	na		36		56		71		78		86	
<u>Untreated psychosis population</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	7		5		6		4		4		3	
		0.39%		0.28%		0.35%		0.24%		0.31%		0.32%
Remaining population	1801		1755		1700		1642		1284		941	
subtracted - no data	na		39		89		141		495		834	
subtracted - already identified	na		7		12		18		22		26	
<u>Risperidone</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	8		4		3		0		2		1	
		0.73%		0.48%		0.55%		0.00%		0.84%		0.63%
Remaining population	1095		837		544		354		237		159	
subtracted - no data	na		250		539		726		843		919	
subtracted - already identified	na		8		12		15		15		17	

Table 2 (cont.)

<u>Olanzapine</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	11		7		5		3		2		2	
		1.16%		0.98%		1.07%		0.96%		1.00%		1.87%
Remaining population	949		715		487		311		201		107	
subtracted - no data	na		223		464		615		722		814	
subtracted - already identifi	na		11		18		23		26		28	
<u>High potency</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	11		5		5		3		3		0	
		1.08%		0.64%		0.99%		0.87%		1.28%		0.00%
Remaining population	1018		779		505		348		234		138	
subtracted - no data	na		228		497		651		780		853	
subtracted - already identifi	na		11		18		21		24		27	
<u>Low potency</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	2		4		2		1		1		2	
		0.58%		1.47%		1.18%		0.85%		1.15%		3.39%
Remaining population	360		272		170		118		87		59	
subtracted - no data	na		86		184		234		264		291	
subtracted - already identifi	na		2		6		8		9		10	

Table 2 (cont.)

<u>Clozapine</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	4		0		0		0		0		0	
		8.00%		0.00%		0.00%		0.00%		0.00%		0.00%
Remaining population	50		39		27		20		18		12	
subtracted - no data	na		7		19		26		28		34	
subtracted - already Identifi	na		4		4		4		4		4	

Table 3 Frequency of Type II Diabetes Cases as Forward Observation Period Increases
Excludes Pre-existing Diabetes at Eight Months Prior to Observation

<u>Treated psychosis population</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	25		13		14		5		4		4	
		0.82%		0.57%		0.95%		0.51%		0.63%		1.11%
Remaining population	3036		2294		1474		973		635		361	
subtracted - no data	na		717		1524		2011		2344		2614	
subtracted - already identified	na		25		38		52		57		61	
<u>Untreated psychosis population</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	7		5		5		4		4		3	
		0.41%		0.30%		0.31%		0.25%		0.32%		0.32%
Remaining population	1728		1684		1633		1582		1255		939	
subtracted - no data	na		37		83		129		452		764	
subtracted - already identified	na		7		12		17		21		25	
<u>Risperidone</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	3		2		3		0		0		1	
		0.32%		0.28%		0.65%		0.00%		0.00%		0.80%
Remaining population	929		706		459		296		193		125	
subtracted - no data	na		220		465		625		728		796	
subtracted - already identified	na		3		5		8		8		8	

Table 3 (cont.)

<u>Olanzapine</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	9		4		5		3		2		2	
		0.98%		0.58%		1.10%		0.99%		1.03%		1.94%
Remaining population	921		695		456		304		195		103	
subtracted - no data	na		217		452		599		705		795	
subtracted - already identified	na		9		13		18		21		23	
<u>High potency</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	8		4		5		1		2		0	
		0.93%		0.62%		1.22%		0.37%		1.14%		0.00%
Remaining population	859		648		410		272		175		93	
subtracted - no data	na		203		437		570		666		746	
subtracted - already identified	na		8		12		17		18		20	
<u>Low potency</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	2		3		1		1		0		1	
		0.68%		1.38%		0.76%		1.14%		0.00%		2.78%
Remaining population	292		218		132		88		61		36	
subtracted - no data	na		72		155		198		224		249	
subtracted - already identified	na		2		5		6		7		7	
	290		215		131		87		61		35	

Table 3 (cont.)

<u>Clozapine</u>	<u>2 months</u>	<u>pct</u>	<u>4 months</u>	<u>pct</u>	<u>6 months</u>	<u>pct</u>	<u>8 months</u>	<u>pct</u>	<u>10 months</u>	<u>pct</u>	<u>12 months</u>	<u>pct</u>
Additional cases	3		0		0		0		0		0	3
		7.69%		0.00%		0.00%		0.00%		0.00%		0.00%
Remaining population	39		30		20		16		14		8	
subtracted - no data	na		6		16		20		22		28	
subtracted - already identify	na		3		3		3		3		3	
	36		30		20		16		14		8	124

Table 4
Odds Ratios at Two Month Intervals and Cumulative Odds Ratios of Diabetes By Treatment Group:
Excludes Pre-Existing Diabetes at Four Months Prior to Observation Period

	2 months		4 months		6 months		8 months		10 months		12 months	
	Diabetes		Diabetes		Diabetes		Diabetes		Diabetes		Diabetes	
<u>Risperidone</u>	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Olanzapine vs. Risperidone	12	968	8	732	6	478	3	318	2	205	2	108
Olanzapine	10	1,284	5	1,002	3	674	1	460	2	320	2	226
Risperidone	1.59		2.19		2.35		4.34		1.56		2.09	
Odds Ratio												
<u>Cumulative Olanzapine vs. Risperidone</u>												
Olanzapine			20	1,700	25	2,178	28	2,498	30	2,701	32	2,809
Risperidone	Not Applicable		15	2,286	18	2,960	19	3,420	21	3,740	23	3,966
Odds Ratio			1.79		1.89		2.02		1.98		1.98	
<u>High Potency vs. Risperidone</u>												
High Potency	17	1,288	7	1,010	8	683	5	486	3	349	2	237
Risperidone	10	1,284	5	1,002	3	674	1	460	2	320	2	226
Odds Ratio	1.70		1.39		2.63		4.73		1.38		0.95	
<u>Cumulative High Potency vs. Risperidone</u>												
High Potency			24	2,298	32	2,979	37	3,465	40	3,814	42	4,051
Risperidone	Not Applicable		15	2,286	18	2,960	19	3,420	21	3,740	23	3,966
Odds Ratio			1.59		1.77		1.92		1.87		1.79	
<u>Low Potency vs. Risperidone</u>												
Low Potency	4	455	6	349	2	230	1	168	2	124	2	90
Risperidone	10	1,284	5	1,002	3	674	1	460	2	320	2	226
Odds Ratio	1.13		3.45		1.85		2.77		2.58		2.51	
<u>Cumulative Low Potency vs. Risperidone</u>												
Low Potency			10	804	12	1,034	13	1,200	15	1,324	17	1,414
Risperidone	Not Applicable		15	2,286	18	2,960	19	3,420	21	3,740	23	3,966
Odds Ratio			1.90		1.91		1.95		2.02		2.07	
<u>Clozapine vs. Risperidone</u>												
Clozapine	4	59	0	82	0	39	0	30	0	25	0	18
Risperidone	10	1,284	5	1,002	3	674	1	460	2	320	2	226
Odds Ratio	8.71		0.00		0.00		0.00		0.00		0.00	
<u>Cumulative Clozapine vs. Risperidone</u>												
Clozapine			4	111	4	150	4	180	4	205	4	223
Risperidone	Not Applicable		15	2,286	18	2,960	19	3,420	21	3,740	23	3,966
Odds Ratio			5.49		4.39		4.00		3.48		3.09	

Table 4
Odds Ratios at Two Month Intervals and Cumulative Odds Ratios of Diabetes By Treatment Group:
Excludes Pre-Existing Diabetes at Four Months Prior to Observation Period

	2 months		4 months		6 months		8 months		10 months		12 months	
	Diabetes		Diabetes		Diabetes		Diabetes		Diabetes		Diabetes	
<u>Risperidone vs. Untreated</u>	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Risperidone	10	1,284	5	1,002	3	874	1	460	2	320	2	228
Untreated	17	3,025	11	2,858	14	2,875	8	2,786	11	2,378	7	2,000
Odds Ratio	1.39		1.34		0.91		0.76		1.35		2.53	
<u>Cumulative Risperidone vs. Untreated</u>												
Risperidone			16	2,286	18	2,980	19	3,420	21	3,740	23	3,866
U	Not Applicable		28	5,983	42	8,858	50	11,644	61	14,022	68	18,022
Odds Ratio			1.40		1.28		1.29		1.29		1.37	
<u>Olanzapine vs. Untreated</u>	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Olanzapine	12	968	8	732	5	478	3	318	2	206	2	108
Untreated	17	3,025	11	2,858	14	2,875	8	2,786	11	2,378	7	2,000
Odds Ratio	2.21		2.94		2.15		3.29		2.11		5.29	
<u>Cumulative Olanzapine vs. Untreated</u>												
Olanzapine			20	1,700	25	2,178	28	2,488	30	2,701	32	2,809
Untreated	Not Applicable		28	5,983	42	8,858	50	11,644	61	14,022	68	18,022
Odds Ratio			2.51		2.42		2.61		2.55		2.68	
<u>HIGH potency vs. Untreated</u>	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
High Potency	17	1,288	7	1,010	8	683	5	486	3	349	2	237
Untreated	17	3,025	11	2,858	14	2,875	8	2,786	11	2,378	7	2,000
Odds Ratio	2.35		1.86		2.41		3.68		1.86		2.41	
<u>Cumulative High Potency vs. Untreated</u>												
High Potency			24	2,296	32	2,879	37	3,465	40	3,814	42	4,051
Untreated	Not Applicable		28	5,983	42	8,858	50	11,644	61	14,022	68	18,022
Odds Ratio			2.23		2.27		2.49		2.41		2.44	
<u>Low Potency vs. Untreated</u>	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Low Potency	4	455	6	349	2	230	1	166	2	124	2	90
Untreated	17	3,025	11	2,858	14	2,875	8	2,786	11	2,378	7	2,000
Odds Ratio	1.68		4.82		1.79		2.10		3.49		6.35	
<u>Cumulative Low Potency vs. Untreated</u>												
Low Potency			10	804	12	1,034	13	1,200	15	1,324	17	1,414
Untreated	Not Applicable		28	5,983	42	8,858	50	11,644	61	14,022	68	18,022
Odds Ratio			2.68		2.45		2.62		2.60		2.83	

Table 4
Odds Ratios at Two Month Intervals and Cumulative Odds Ratios of Diabetes By Treatment Group:
Excludes Pre-Existing Diabetes at Four Months Prior to Observation Period

<u>Clozapine vs. Untreated</u>	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
clozapine	4	59	0	52	0	39	0	30	0	35	0	18
untreated	17	3,025	11	2,958	14	2,875	8	2,786	11	2,378	7	2,000
Odds Ratio	12.08		na		na		na		na		na	
<u>Cumulative Clozapine vs. Untreated</u>												
Clozapine			4	111	4	150	4	180	4	205	4	223
untreated	Not Applicable		28	5,983	42	8,658	50	11,644	61	14,022	68	16,022
Odds Ratio			7.70		5.62		5.18		4.49		4.23	

Table 5
Odds Ratios Based on 12 Months Cumulative Observation
with 95-Percent Confidence Intervals and Excluding
Pre-existing Diabetes at Four Months Prior to Observation

	<u>Yes</u>	<u>No</u>	<u>Odds Ratio</u>	<u>95% confidence interval</u>	
				<u>lower</u>	<u>upper</u>
Olanzapine	32	2809			
Risperidone	23	3966	1.964	1.918	2.012
High potency	42	4051			
Risperidone	23	3966	1.788	1.749	1.827
Low potency	17	1414			
Risperidone	23	3966	2.073	2.019	2.129
Clozapine	4	223			
Risperidone	23	3966	3.093	3.001	3.188
All other treated	95	8497			
Risperidone	23	3966	1.928	1.895	1.962
Risperidone	23	3966			
Untreated	68	16022	1.366	1.348	1.385
Olanzapine	32	2809			
Untreated	68	16022	2.684	2.646	2.723
High potency	42	4051			
Untreated	68	16022	2.443	2.409	2.477
Low potency	17	1414			
Untreated	68	16022	2.833	2.791	2.875
Clozapine	4	223			
Untreated	68	16022	4.226	4.162	4.292
Treated	118	12463			
Untreated	68	16022	2.231	2.205	2.257

Table 6
Odds Ratios Based on 12 Months Cumulative Observation
with 95-Percent Confidence Intervals and Excluding
Pre-existing Diabetes at Six Months Prior to Observation

	<u>Yes</u>	<u>No</u>	<u>Odds Ratio</u>	<u>95% confidence interval</u>	
				<u>lower</u>	<u>upper</u>
Olanzapine	30	2720			
Risperidone	18	3208	1.966	1.916	2.016
High potency	27	2993			
Risperidone	18	3208	1.608	1.568	1.648
Low potency	12	1054			
Risperidone	18	3208	2.029	1.969	2.091
Clozapine	4	162			
Risperidone	18	3208	4.401	4.255	4.551
All other treated	73	6927			
Risperidone	18	3208	1.878	1.842	1.915
Risperidone	18	3208			
Untreated	29	9094	1.760	1.729	1.791
Olanzapine	30	2720			
Untreated	29	9094	3.459	3.397	3.521
High potency	27	2993			
Untreated	29	9094	2.829	2.779	2.88
Low potency	12	1054			
Untreated	29	9094	3.570	3.502	3.64
Clozapine	4	162			
Untreated	29	9094	7.743	7.587	7.902
Treated	91	10135			
Untreated	29	9094	2.816	2.776	2.856

Table 7
Odds Ratios Based on 12 Months Cumulative Observation
with 95-Percent Confidence Intervals and Excluding
Pre-existing Diabetes at Eight Months Prior to Observation

	<u>Yes</u>	<u>No</u>	<u>Odds Ratio</u>	<u>95% confidence interval</u>	
				<u>lower</u>	<u>upper</u>
Olanzapine	25	2649			
Risperidone	9	2699	2.830	2.756	2.907
High potency	20	2437			
Risperidone	9	2699	2.461	2.395	2.529
Low potency	8	819			
Risperidone	9	2699	2.929	2.834	3.027
Clozapine	3	124			
Risperidone	9	2699	7.255	6.993	7.527
All other treated	56	6009			
Risperidone	9	2699	2.795	2.737	2.854
Risperidone	9	2699			
Untreated	28	8793	1.047	1.028	1.066
Olanzapine	25	2649			
Untreated	28	8793	2.964	2.853	3.078
High potency	20	2437			
Untreated	28	8793	2.577	2.477	2.681
Low potency	8	819			
Untreated	28	8793	3.068	2.865	3.284
Clozapine	3	124			
Untreated	28	8793	7.598	6.385	9.041
Treated	65	8708			
Untreated	28	8793	2.344	2.296	2.394

Table 8 Description of Psychosis Population with no Type II Diabetes at Four Months Prior to Observation

	<u>All Psychotics</u>	<u>Pct</u>	<u>All Psychotics on Antipsychotics</u>	<u>Pct</u>	<u>All Psychotics not on Antipsychotics</u>	<u>Pct</u>
<u>Age</u>						
Mean (SD)	43.9	na	45.3 (19.3)	na	41.9	na
Median	44	na	44	na	43	na
<u>Gender</u>						
Male	2824	38.2%	1588	36.6%	1236	40.4%
Female	4571	61.8%	2746	63.4%	1825	59.6%
<u>Type of Health Care Coverage</u>						
Managed Care	2453	33.2%	1205	28.4%	1248	40.8%
Indemnity	4852	65.6%	3039	71.6%	1813	59.2%
<u>Observation Period</u>						
Mean (SD) length in months	9.4 (5.9)	na	6.4 (4.6)	na	13.8 (4.8)	na
Median length in months	9.2	na	4.9	na	14.2	na
<u>Basis of Psychosis Diagnosis</u>						
Schizophrenia (ICD-9 295.xx)	776	10.5%	744	17.2%	32	1.0%
Bipolar and Manic (ICD-9 296.0, 296.1, 296.4-296.9)	2527	34.2%	932	21.5%	1595	52.1%
Major Depressive (ICD-9 296.2, 296.3)	2730	36.9%	1681	38.8%	1049	34.3%
Dementia (ICD-9 290.xx)	484	6.5%	276	6.4%	208	6.8%
Other Psychoses (ICD-9 291.xx-294.xx, 297.xx, 298.xx, 299.xx)	878	11.8%	701	16.2%	177	5.8%

Table 9 Detailed Description of Psychosis Population with no Type II Diabetes at Four Months Prior to Observation

	All Psychotics or <u>Antipsychotics</u>	All Psychotics on <u>Risperidone</u>	All Psychotics on <u>Olanzapine</u>	All Psychotics on <u>High potency Conv.</u>	All Psychotics on <u>Low potency conv.</u>	All Psychotics on <u>Clozapine</u>	All Psychotics not <u>on antipsychotics</u>
Age							
Mean (SD)	45.3 (18.3)	43.0 (20.7)	43.1 (16.9)	48.4 (18.7)	48.3 (20.5)	39.4 (14.1)	41.9 (14.8)
Median	44	42.5	43	47	46	40	43
Gender							
Male	1588	550	396	465	161	26	1236
Female	2748	818	651	911	329	37	1825
Type of Health Care Coverage							
Managed Care	1205	428	308	417	115	29	1248
Indemnity	3039	942	739	959	365	34	1813
Observation Period							
Mean (SD) length in months	6.4 (4.6)	6.4 (4.7)	5.6 (3.5)	6.7 (4.9)	6.8 (5)	8.8 (5.4)	13.8 (4.8)
Median length in months	4.9	4.7	4.6	5	4.9	7.2	14.2
Treatment Period							
Mean (SD) length in months	6.8 (4.7)	6.9 (4.8)	6.1 (3.6)	7 (5.1)	7.1 (5.2)	9.4 (5.5)	0
Median length in months	6.2	4.8	5	6.3	6	7.7	0
Base of Psychosis Diagnosis							
Schizophrenia (ICD-8 295.xx)	744	181	235	228	54	36	32
Bipolar and Manic (ICD-9 296.0, 296.1, 296.4-296.9)	932	270	260	277	113	12	1695
Major Depressive (ICD-9 296.2, 296.3)	1681	579	398	508	189	9	1049
Dementia (ICD-9 290.xx)	276	242	22	119	49	0	208
Other Psychoses (ICD-9 291.xx-294.xx, 297.xx, 298.xx, 299.xx)	701	191	134	244	75	6	177
Intensity of Antipsychotic Therapy							
Mean (SD) mgs /day of treatment	2.7 (2.6)	2.5 (2.3)	4 (2.4)	2 (2.4)	2.1 (3)	3.2 (2.8)	na
Median mgs/day of treatment	1.9	1.8	3.5	1.2	1.2	2.6	na
Use of Other Psychotropic Drugs							
Mean (SD) expenditure/month	66.42 (90.51)	69.76 (84.08)	77.26 (107.34)	56.61 (79.97)	60.11 (76.19)	78.18 (175.52)	48.29 (72.91)
Median expenditure/month	41.38	50.4	50.71	32.85	31.23	24.35	20.21
Concurrent use of other Antipsychotics							
Yes	900	288	258	246	108	22	na
No	3434	1100	789	1130	374	41	na

Volume 15/Page 200

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Table 10 **Basis of Diabetes Diagnosis Within Psychotic Patients**
Excludes Psychotics with Pre-existing Type II Diabetes at Four Months Prior to Observation

<u>Basis of Diabetes Diagnosis</u>	<u>All psychotics with a diagnosis of diabetes</u>	<u>All psychotics with a diagnosis of diabetes who were on antipsychotics</u>	<u>All psychotics with a diagnosis of diabetes who were Not on antipsychotics</u>
<u>ICD-9 codes</u>			
250.00, 250.02	132	89	43
NIDDM w/o complication			
250.10, 250.12	3	2	1
NIDDM w/ ketoacidosis			
250.20, 250.22	1	1	0
NIDDM w/ hypersmolarity			
250.30, 250.32	0	0	0
NIDDM w/ other coma			
250.40, 250.42	0	0	0
NIDDM w/ renal manifestations			
250.50, 250.52	3	2	1
NIDDM w/ ophthalmic manifest			
250.60, 250.62	1	0	1
NIDDM w/ neurological manifest			
250.70, 250.72	2	1	1
NIDDM w/ periph circ dsord			
250.80, 250.82	2	2	0
NIDDM w/ oth spec manifest			
250.90, 250.92	5	4	1
NIDDM w/ unspec complications			
<u>Type II Diabetes Medications</u>			
First generation sulfonylureas	1	1	0
Second generation sulfonylureas	27	17	10
Metformin	11	2	9
Rezulin	2	2	0
Precose	0	0	0

Table 11 **Logit Regression Results - Type II Diabetes Among Psychotics**
Excludes Pre-existing Type II Diabetes at Four Months Prior to Observation

Number reporting type II diabetes (1)	208
Number not reporting type II diabetes (0)	7189
Total	7395

Analysis of Maximum Likelihood Estimates

Variable	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Odds Ratio	Odds Ratio (1)	Odds Ratio (2)	Odds Ratio (3)
Intercept	-6.3336	0.4189	227.555					
Age	0.0274	0.00491	31.0088	0.0001	1.028			
Sex (male = 1)	0.0745	0.162	0.2402	0.6241	1.077			
Observation period (months)	0.0601	0.0139	33.2884	0.0001	1.083			
Antipsychotic intensity (standardized mgs per day)	0.0186	0.0448	0.1732	0.6773	1.019			
Other psychotropic drugs (\$ per month)	0.00207	0.000583	12.5779	0.0004	1.002			
Concurrent antipsych (ratio of days supply)	-0.00008	0.3547	0	0.9998	1			
Coverage (managed care=1; indemnity=0)	0.0822	0.1628	0.2548	0.6137	1.088			
Schizophrenia (yes=1; no=0)	0.4093	0.3116	1.7253	0.189	1.508			
Bipolar/manic (yes=1; no=0)	0.1479	0.2707	0.2975	0.5855	1.159			
Major depressive (yes=1; no=0)	0.1781	0.2606	0.4671	0.4943	1.195			
Dementia (yes=1; no=0)	0.2229	0.3283	0.4548	0.4984	1.25			
Risperidone (yes = treat. dur. in mos.; no = 0)	0.019	0.0102	0.9713	0.3244	1.019	1.137	1	1
Olanzapine (yes = treat. dur. in mos.; no = 0)	0.0738	0.028	8.0851	0.0045	1.077	1.656	1.057	1.457
High potency (yes = treat. dur. in mos.; no = 0)	0.0444	0.0158	7.9312	0.0049	1.045	1.349	1.026	1.187
Low potency (yes = treat. dur. in mos.; no = 0)	0.0555	0.0218	6.4961	0.0108	1.057	1.458	1.037	1.283
Clozapine (yes = treat. dur. in mos.; no = 0)	0.0737	0.0427	2.9848	0.084	1.077	1.656	1.057	1.457

Patients with "other psychoses" are represented by zeros for each of the four specified psychosis categories.

Patients untreated with antipsychotics are represented by zeros for each of the five specified antipsychotic categories.

(1) Odds relative to untreated at 6.8 months of treatment

(2) Odds relative to risperidone

(3) Odds relative to risperidone at 6.8 months of treatment

Table 12 **Logit Regression Results - Type II Diabetes Among Psychotics**
Excludes Pre-existing Type II Diabetes at Six Months Prior to Observation

Number reporting type II diabetes (1)	128
Number not reporting type II diabetes (0)	5372
Total	5500

Analysis of Maximum Likelihood Estimates

Variable	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Odds Ratio	Odds Ratio (1)	Odds Ratio (2)	Odds Ratio (3)
Intercept	-6.4807	0.5329	147.8599	0.0001				
Age	0.0244	0.00622	15.302	0.0001	1.025			
Sex (male = 1)	0.0163	0.1952	0.007	0.9335	1.016			
Observation period (months)	0.1059	0.0242	19.4431	0.0001	1.113			
Antipsychotic intensity (standardized mgs per day)	0.0388	0.0505	0.5889	0.4429	1.04			
Other psychotropic drugs (\$ per month)	0.00205	0.000683	9.0022	0.0027	1.002			
Concurrent antipsych (ratio of days supply)	0.269	0.3728	0.5207	0.4705	1.309			
Coverage (managed care=1; indemnity=0)	-0.0892	0.2152	0.0897	0.7622	0.934			
Schizophrenia (yes=1; no=0)	0.2462	0.3758	0.4258	0.5121	1.278			
Bipolar/manic (yes=1; no=0)	0.0405	0.3395	0.0143	0.905	1.041			
Major depressive (yes=1; no=0)	0.2502	0.3152	0.4238	0.5152	1.228			
Dementia (yes=1; no=0)	0.236	0.4041	0.341	0.5592	1.266			
Risperidone (yes = treat. dur. in mos.; no = 0)	0.0176	0.027	0.4278	0.5131	1.018	1.119	1	1
Olanzapine (yes = treat. dur. in mos.; no = 0)	0.0778	0.0295	6.9426	0.0084	1.091	1.633	1.0619	1.460
High potency (yes = treat. dur. in mos.; no = 0)	0.0418	0.0249	2.7968	0.0945	1.042	1.296	1.0236	1.158
Low potency (yes = treat. dur. in mos.; no = 0)	0.0795	0.028	8.0342	0.0046	1.083	1.653	1.0639	1.477
Clozapine (yes = treat. dur. in mos.; no = 0)	0.1159	0.0485	5.7209	0.0168	1.123	2.077	1.1031	1.858

Patients with "other psychoses" are represented by zeros for each of the four specified psychosis categories.

Patients untreated with antipsychotics are represented by zeros for each of the five specified antipsychotic categories.

(1) Odds relative to untreated at 6.3 months of treatment

(2) Odds relative to risperidone

(3) Odds relative to risperidone at 6.3 months of treatment

Table 13 Logit Regression Results - Type II Diabetes Among Psychotics
Excludes Pre-existing Type II Diabetes at EightMonths Prior to Observation

Number reporting type II diabetes (1)	101
Number not reporting type II diabetes (0)	4878
Total	4979

Analysis of Maximum Likelihood Estimates

Variable	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Odds Ratio	Odds Ratio (1)	Odds Ratio (2)	Odds Ratio (3)
Intercept	-6.8573	0.6229	121.1922	0.0001				
Age	0.0258	0.00706	13.393	0.0003	1.026			
Sex (male = 1)	-0.2037	0.2251	0.8193	0.3654	0.816			
Observation period (months)	0.1298	0.0276	22.097	0.0001	1.139			
Antipsychotic Intensity (standardized mgs per day)	0.0723	0.0548	1.754	0.1854	1.075			
Other psychotropic drugs (\$ per month)	0.00197	0.000781	6.3572	0.0117	1.002			
Concurrent antipsych (ratio of days supply)	0.1306	0.4676	0.0781	0.78	1.14			
Coverage (managed care=1; indemnity=0)	-0.0124	0.24	0.0027	0.9588	0.988			
Schizophrenia (yes=1; no=0)	-0.0784	0.4744	0.0273	0.8688	0.925			
Bipolar/manic (yes=1; no=0)	0.1596	0.3816	0.175	0.6757	1.173			
Major depressive (yes=1; no=0)	0.1599	0.3656	0.1913	0.6619	1.173			
Dementia (yes=1; no=0)	0.3957	0.4438	0.795	0.3726	1.485			
Risperidone (yes = treat. dur. in mos.; no = 0)	-0.0195	0.037	0.2765	0.5988	0.981	0.890	1	1
Olanzapine (yes = treat. dur. in mos.; no = 0))	0.0748	0.0315	5.817	0.0178	1.077	1.572	1.098	1.787
High potency (yes = treat. dur. in mos.; no = 0))	0.0572	0.0284	4.0541	0.0441	1.059	1.419	1.080	1.595
Low potency (yes = treat. dur. in mos.; no = 0))	0.0973	0.0348	7.7572	0.0053	1.102	1.808	1.123	2.033
Clozapine (yes = treat. dur. in mos.; no = 0))	0.1585	0.0659	5.786	0.0162	1.172	2.633	1.195	2.960

Patients with "other psychoses" are represented by zeros for each of the four specified psychosis categories.

Patients untreated with antipsychotics are represented by zeros for each of the five specified antipsychotic categories.

(1) Odds relative to untreated at 6.3 months of treatment

(2) Odds relative to risperidone

(3) Odds relative to risperidone at 6.3 months of treatment

Table 14
Dose Response of Antipsychotic Drug Treatment and Type II Diabetes
Excludes Psychotics with Pre-existing Type II Diabetes at Four Months Prior to Observation

<u>Antipsychotic Use and Level of Intensity</u>	<u>All psychotics with a diagnosis of diabetes</u>	<u>All psychotics without a diagnosis of diabetes</u>	<u>Relative Risk with 95% Confidence Intervals</u>		
			<u>Relative to subjects in the lower intensity category</u>	<u>lower</u>	<u>upper</u>
<u>All Antipsychotics</u>					
High Intensity	41	1433	1.047	1.01	1.088
Medium Intensity	44	1387	1.161	1.119	1.205
Low Intensity	38	1391			
<u>Risperidone</u>					
High intensity	4	402	0.348	0.327	0.371
Medium Intensity	6	416	0.505	0.474	0.538
Low Intensity	15	525			
<u>Olanzapine</u>					
High intensity	25	637	2.204	2.072	2.345
Medium intensity	1	41	1.370	1.24	1.514
Low Intensity	6	337			
<u>High potency conventionals</u>					
High intensity	8	275	1.108	1.028	1.195
Medium intensity	26	676	1.465	1.381	1.555
Low Intensity	10	381			
<u>Low potency conventionals</u>					
High intensity	3	91	0.877	0.771	0.997
Medium Intensity	10	238	1.118	1.012	1.235
Low Intensity	5	133			
<u>Clozapine</u>					
High Intensity	1	28	0.268	0.201	0.358
Medium intensity	1	16	0.489	0.335	0.656
Low intensity	2	15			

**Table 15 Dose Response of Antipsychotic Drug Treatment and Type II Diabetes
Comparison with Untreated Psychotics**
Excludes Psychotics with Pre-existing Type II Diabetes at Four Months Prior to Observation

<u>Antipsychotic Use and Level of Intensity</u>	<u>Psychotics w/ diabetes</u>	<u>Psychotics w/o diabetes</u>	<u>Relative Risk with 95% Confidence Intervals</u>		
			<u>Relative to Untreated</u>	<u>lower</u>	<u>upper</u>
<u>All Antipsychotics</u>					
High intensity	42	1449	1.040	1.01	1.071
Medium intensity	46	1402	1.177	1.143	1.212
Low intensity	39	1407	0.998	0.969	1.028
<u>Untreated Psychotics</u>	83	2978			
<u>Risperidone</u>					
High intensity	4	402	0.357	0.345	0.369
Medium intensity	6	416	0.517	0.501	0.535
Low intensity	15	525	1.294	1.252	1.337
<u>Untreated Psychotics</u>	83	2978			
<u>Olanzapine</u>					
High intensity	25	637	1.408	1.364	1.454
Medium intensity	1	41	0.875	0.845	0.906
Low intensity	6	337	5.251	5.077	5.43
<u>Untreated Psychotics</u>	83	2978			
<u>High potency conventionals</u>					
High intensity	8	275	1.044	1.009	1.08
Medium intensity	26	676	1.380	1.337	1.425
Low intensity	10	381	0.531	0.513	0.549
<u>Untreated Psychotics</u>	83	2978			
<u>Low potency conventionals</u>					
High intensity	3	91	1.183	1.142	1.225
Medium intensity	10	238	1.508	1.457	1.56
Low intensity	5	133	0.754	0.728	0.78
<u>Untreated Psychotics</u>	83	2978			
<u>Clozapine</u>					
High intensity	1	28	1.281	1.237	1.327
Medium intensity	1	16	2.242	2.165	2.323
Low intensity	2	15	4.485	4.329	4.646
<u>Untreated Psychotics</u>	83	2978			

Volume 15/Page 206

JJRP 00384195

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B.4 Literature Review

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ATYPICAL ANTIPSYCHOTICS AND DIABETES: A REVIEW

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CONTENTS:

- 1. Introduction**
- 2. Evidence for a relationship between atypical antipsychotics and diabetes**
 - case reports
 - longitudinal and controlled studies
- 3. Evidence for a relationship between atypical antipsychotics and impairment of glucose homeostasis**
- 4. Limitations of existing studies**
- 5. Diabetes and other psychotropic medications**
- 6. Diabetes and schizophrenia.**
- 7. Does the evidence favor a diabetogenic effect of atypical antipsychotics in patients with schizophrenia?**
- 8. What about mechanisms?**
- 9. Executive Summary**

Volume 15/Page 207

JJRP 00384197
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ATYPICAL ANTIPSYCHOTICS AND DIABETES

1. INTRODUCTION.

Since 1994, a number of case reports have appeared in the literature documenting the onset of diabetes mellitus in patients with schizophrenia who were being treated with clozapine and olanzapine. These reports have raised considerable concern about the diabetogenic potential of these agents. However, given that most of the reports are of anecdotal nature without controls, they also raise the question of where there is a true cause-effect relationship between the atypical antipsychotics and the onset of diabetes. (However, even though the class of atypical antipsychotics includes four medications (clozapine, risperidone, olanzapine and quetiapine), at the time of this review the world literature is limited to reports concerning clozapine and olanzapine.) After all, diabetes is a common disease, and its appearance may be simply a coincidental development in these patients. This discussion will attempt to address whether the published data that exists up to this time provide sufficient evidence to link the use of these agents with the development of diabetes.

2. EVIDENCE FOR A RELATIONSHIP BETWEEN ATYPICAL ANTIPSYCHOTICS AND DIABETES.

There are two types of reports that have appeared in the literature describing this connection. Most are case reports, usually describing single cases. A few describe small numbers of cases and yet fewer represent attempts to study larger groups of patients on atypical antipsychotics and/or also provide information that includes non-treated controls for comparison.

Case reports. About 20 cases of new onset diabetes have been described in the literature since 1994. They paint a picture of subjects that were not previously known to have diabetes, who developed the disease weeks to months after beginning therapy with one of the atypical antipsychotics. There are some unifying characteristics in many of the patients described. These characteristics include the following:

- A. Presence of Risk Factors for development of diabetes. Many, but not all subjects has one or more of the following risk factors that predispose them to the development of diabetes:
 1. Ethnicity with increased risk for diabetes (many African American).
 2. Family history that also increases risk for diabetes.
 3. Prior overweight or obesity status, that also increases risk for diabetes.
- B. Similar responses to these medications in subjects who develop diabetes.
 1. Increase in weight in some, but importantly not all subjects who develop diabetes.
 2. Onset of diabetes within weeks or several months after the initiation of treatment.
 3. Development of severe metabolic decompensation in many of the patients described, with frequent mention of diabetic ketoacidosis.
 4. Continuing need for concomitant diabetic medications as long as the antipsychotics continue to be used.

Volume 15/Page 208

JJRP 00384198

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D821.212

C. Patients have similar responses to stopping treatment after diabetes is diagnosed.

1. Many patients have an improvement in glucose homeostasis after medications are stopped (87% of patients in whom this could be evaluated).
2. Some patients have complete reversal of their diabetes (67% of patients).
3. In a few subjects, reintroduction of atypical antipsychotics has resulted in a recrudescence of diabetes (n=3).

Longitudinal and Controlled Studies:

One longitudinal follow-up study was performed in Boston (Henderson, 2000). In this study, 82 patients who received clozapine were followed for a mean of 5 years. In this group of predominantly male (73%) patients, risk factors that had been observed in the case reports were noticeably absent. Patients were Caucasian (92%), only two of the 82 patients had a family history of diabetes and their mean BMI indicated only borderline obesity, at 27Kg/m² at the start of treatment. Despite the apparent dearth of risk factors, this study found that 37% of the patients were newly diagnosed with diabetes during the follow-up period. This was reflected as a linear increase in the incidence of diabetes, at a rate of about 7% per year. Weight gain also occurred, but reached a plateau after about the 4 years of treatment, and was not found to be a statistical risk factor for diabetes. There was no control group for this study.

Another study of diabetes included control patients (Hagg, '98). The control subjects were treated with classical antipsychotics and formed a comparison group for the possible diabetogenic effects of the atypical agents. This study has a cross-sectional design and was performed in northern Sweden (Hagg, '98). In this study, 63 schizophrenic patients on clozapine were compared with 67 patients who were receiving classical depot neuroleptics. The prevalence of diabetes in the patients receiving clozapine was approximately 12%; in contrast the other patients had about a 6% prevalence rate. This difference was not statistically significant. For comparison purposes, the authors point out that the prevalence of diabetes was estimated to be about 2% in the general Northern Sweden population in this area, if matched for weight and gender with the clozapine group. Nevertheless, the only controlled study of this subject is suggestive, but appears to be underpowered to provide an answer to this important question.

Within the clozapine group, no risk factors for diabetes were identified; all patients were Caucasians, body weight was not higher in those with diabetes compared with those without, and family history was not different. This may explain why a more dramatic difference between the groups was not seen.

3. EVIDENCE FOR A RELATIONSHIP BETWEEN ATYPICAL ANTIPSYCHOTICS AND IMPAIRED GLUCOSE HOMEOSTASIS.

The Henderson longitudinal study suggests that the incidence of new diabetes in schizophrenic patients treated with the atypical antipsychotic clozapine is cumulative over time, unlike the case reports, which seem to describe a relationship to initiation of treatment, with diabetes occurring in the first weeks or months. If indeed the Henderson study is correct, it might take a long period of follow-up to detect significant differences between a treated group and controls. For this reason, some cross-sectional studies also looked at surrogates for a diabetes outcome, namely

impaired glucose tolerance (IGT) which is diagnosed using an OGTT (oral glucose tolerance test); or other metabolic measurements.

Thus, the Henderson study also looked at fasting plasma glucose (FPG) concentrations in their cohort of 82 patients, of whom 37% developed diabetes diagnosed and treated by primary care physicians. A single FPG measurement (two are necessary according to the American Diabetes Association guidelines) was elevated in an extraordinary 67% of patients!

The Hagg study performed an OGTT after screening using a random blood glucose measurement of ≥ 6.7 mmol/L. Thus they were able to diagnose IGT. In the clozapine-treated group, 10% had IGT versus only 3% in the control group.

Another Swedish study looked at a small group of patients on clozapine (n=13), none of whom had diabetes (Melkersson, '99). This study looked at the relationship between glucose, insulin and drug levels. They demonstrated a correlation between plasma insulin and clozapine concentrations, but no abnormalities in glucose tolerance or diabetes were found. This cross-sectional study was small and limited in its contribution to the question posed here.

4. LIMITATIONS OF EXISTING STUDIES.

Case reports: Individual case reports by their very nature are anecdotal. Although case reports may reflect a real pathogenetic connection, a cause-effect relationship between a drug and the onset of a common disease such as diabetes cannot be proven. Isolated case reports, no matter how frequent, also cannot be used to determine the true incidence of a real drug effect, because there is effectively no denominator. The presence of other medications taken by patients also clouds the picture. In the case of reports linking clozapine or olanzapine with diabetes, the predominance of severe metabolic decompensation in the patients described is in stark contrast to the group reports, where, in cross-sectional or follow-up studies much milder diabetes is generally reported. This suggests that the relationship between diabetes and the drugs is much less likely to be considered as a side effect of the medication because of the relatively high frequency of type 2 diabetes in most populations. However, when a patient with type 2 diabetes develops severe decompensation, whether it is actually ketoacidosis or not, it is more likely that the drug may be identified as a probable cause. (Many of the case reports, though described as ketoacidosis, in fact do not provide sufficient information to be certain that this is the correct diagnosis – in some it clearly is not!). This is because physicians automatically look for a precipitating factor in patients with ketoacidosis – it is a part of the clinical evaluation of this severe complication of diabetes; unlike routine clinical diabetes, where it is unusual to search for an overt precipitating factor.

Thus, possible explanations for a spurious connection between the onset of diabetes during treatment with certain atypical antipsychotics are the following:

1. Diabetes is a common disease. The observations in case reports may simply describe the coincidence of drug usage and diabetes. The fact that some patients continued to have diabetes even after the medications were stopped suggests that the diabetes in those cases may be unrelated to drug exposure.

2. Diabetes is more common in schizophrenia than in non-psychotic subjects. If this is true, it is this increased prevalence that is being noticed, not necessarily the effect of the medications per se.
3. The severity of onset of diabetes in some subjects. As explained above, this increases the likelihood of a connection being made between the medication and diabetes, because the physician is more likely to consider a cause-effect relationship.

The likelihood that these explanations can explain the case reports will be discussed in more detail below.

Longitudinal and Controlled Studies: These also have limitations. The sole longitudinal study (Henderson, 2000) appears to provide the most important evidence to suggest that there is a connection between diabetes and the atypical antipsychotics. They found an extremely high rate of new onset diabetes (at least 37%) over five years. The major problem with this study is the fact that it is uncontrolled. If there is something inherently different about their population that predisposes it to diabetes, it may spuriously raise the incidence of diabetes, independent of the drug used. Furthermore, the diabetes part of the overall study of clozapine appears to be a retrospective in nature. The approaches to screening and diagnosis of diabetes that were chosen were less than ideal. A prospective study designed to evaluate diabetes would most likely not have used these. However, this would not change their overall conclusions. Indeed, it is possible that an even higher rate of diabetes would have been found had the trial been appropriately designed.

5. DIABETES AND OTHER PSYCHOTROPIC MEDICATIONS.

There are some data to suggest that chlorpromazine might also influence glucose metabolism. The clinical significance of those findings is not clear at this time. It appears that the best data come from the reports discussed above on clozapine and olanzapine.

6. DIABETES AND SCHIZOPHRENIA.

A number of studies have suggested that schizophrenia might be associated with an increased prevalence of diabetes. The original observations appear in the older literature, and the quality of the publications varies, so that while the data overall seem to be fairly consistent, it is difficult to draw conclusions from these non-population based studies. However, while schizophrenia may represent another risk factor for diabetes, it appears unlikely to be the cause of the metabolic syndromes described here.

7. DOES THE EVIDENCE FAVOR A DIABETOGENIC EFFECT OF THE DRUGS IN PATIENTS WITH SCHIZOPHRENIA?

The most compelling data are to be found in the Henderson study, although it is important to remember that it is an uncontrolled study. Nevertheless, that report suggests an extremely high incidence of new onset diabetes in schizophrenic patients. If these data can be extrapolated to

Volume 15/Page 211

JJRP 00384201

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other populations (especially high risk groups), one would expect to have had a virtual epidemic of diabetes among patients with schizophrenia who are using atypical antipsychotics (within 5 years of starting treatment, more than a third of all patients should be affected). One might also expect that psychiatrists using these agents would have noticed diabetes if it were occurring with this degree of frequency. However, it is known that almost 50% of people with type 2 diabetes in the U.S. are undiagnosed (NHANES data). It is therefore possible that schizophrenic patients who do not have other medical problems and have mild, asymptomatic diabetes may also go undiagnosed if checks for diabetes are not part of routine follow-up. This could explain the fact that a connection with diabetes may not have been noticed in the psychiatry community. However, this study needs to be confirmed before the incidence figures can be accepted as proven.

The case reports are interesting in two respects; their severity and the response to stopping therapy. As mentioned above, case reports cannot be used to determine cause-effect relationships because they are uncontrolled reports. The most incriminating aspect of the case reports is therefore not the development of diabetes in response to clozapine or olanzapine, because this could be coincidental - as pointed out above. However, the severity of the diabetes is suggestive of a drug-induced state, because ketoacidosis is uncommon in type 2 diabetes, and thus could theoretically be attributed to an effect of a drug. But, as pointed out above, we need to keep in mind that these severe cases may represent a reporting bias.

The second important aspect of the case reports may be more relevant in support of an effect of the drugs to cause diabetes. The consequences of stopping the medications are of great interest. Some patients continue with diabetes despite discontinuation of drug, leading to the conclusion that the drug may have contributed to the initiation of the disease, but that it may have developed anyway. But, most patients do not have continued diabetes - it appears to resolve in many cases (67% of cases, see above). This would be highly unlikely if diabetes were simply a coincident occurrence.

8. WHAT ABOUT MECHANISMS?

The transient nature of the diabetes in response to the drugs is also interesting because in addition to providing further evidence for causality, it may also be helpful in an attempt to understand the mechanisms involved in a putative drug effect. If diabetes is a result of the medications, it could be a direct drug-mediated effect or an indirect effect mediated by the propensity for treated patients to weight gain. It is well-known that weight gain and obesity predispose to diabetes by decreasing insulin sensitivity. It appears less likely that weight gain is the mechanism involved because diabetes often occurred in patients who did not gain weight and weight gain was not a risk factor in the Henderson study. In addition, the response to stopping treatment in many of the case reports is instructive. In many cases, improvement in diabetes control occurred within 2 weeks, too fast for this to be an effect due to weight loss. This response to discontinuation therefore suggests that a drug effect is a direct action of these agents, and not secondary to the weight gain. Furthermore, the rapid response to stopping medications reflects a possible effect of the drug to inhibit insulin secretion, which is more likely to cause ketosis and also to explain a more rapid recovery than is an effect upon insulin resistance. This must be seen as speculative however. Little work has been done to look at mechanisms, though two case reports actually try to do so (n=1 patient each).

Volume 15/Page 212

JJRP 00384202

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D821.216

An explanation for the variety of effects seen (mild versus severe diabetes), as well as a difference in the incidence of new diabetes in the two group studies published (Henderson versus Hagg) may reside in the fact that these agents may not have a uniform effect, either qualitatively or quantitatively, in all subjects. This may relate to drug characteristics, such as concentrations achieved, or more likely, inherent differences in the individuals and/or populations being treated. Interaction of drug with genetically programmed dysfunction of glucose homeostasis in target tissues, such as, the liver, muscle or endocrine pancreas could explain a variety of responses. These need to be tested.

9. EXECUTIVE SUMMARY.

The discussion presented above has summarized most of the pertinent existing data that relates the atypical antipsychotics to the development of diabetes. I have also provided an analysis of these data, which tend to suggest that diabetes is indeed a possible consequence of the use of some of these agents (clozapine and olanzapine) and not just a result of the effects of schizophrenia. The data are obviously not complete. There are serious limitations to most of the reports in the literature so far. However, the data are difficult to dismiss, even though imperfect. The most compelling data derive from the Henderson study, which is weakly supported by another relatively small and underpowered, controlled, group study (Hagg). Also, the case reports are contributory: the combination of marked severity of diabetes soon after starting medication together with its apparent reversibility in many of the case reports is quite supportive of the concept that clozapine and olanzapine are diabetogenic.

To determine whether there is a clear danger to subjects taking clozapine and olanzapine for the development of diabetes, a prospective, carefully designed study of these agents in a large population of users, together with appropriate controls is necessary to determine the incidence and frequency of this problem in schizophrenic patients. In addition, careful metabolic studies in non-schizophrenic subjects with different degrees of glucose tolerance – normal, impaired and frankly diabetic subjects exposed to atypical antipsychotics might provide mechanistic information to supplement epidemiological data.

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Volume 15/Page 213

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Volume 15/Page 214

JJRP 00384204

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Volume 15/Page 215

JJRP 00384205
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