

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 XV

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VII. CERTIFICATE OF COUNSEL

Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.3 : Descriptive Statistics of Body Weight Increase >7% in Subjects >18 Years

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17FEB2004 12:56
Sys-um Used: Arrow3.1/aSAF.WEIGHT.2

RIS-POOLED WEIGHT ANALYSE

aSAF.WEIGHT.3 : Descriptive statistics of Body Weight Increase >7% in Subjects >18 Years (continued)

ANALYSIS SET: ALL SUBJECTS

TRIAL TYPE: SHORT TERM

AGE CATEGORY: >65

	N	Mean	SE	SD	Med	Min	Max	Base Mean	Change from Overall Baseline						
									N	Mean	SE	SD	Med	Min	Max
Weight, kg															
PLACEO															
OVERALL															
BASELINE	28	51.9	1.90	10.07	51.9	35	59								
END POINT	28	56.0	2.00	10.57	56.3	40	76	51.9	28	6.1	0.47	2.53	5.4	3	14
RISPERIDONE															
OVERALL															
BASELINE	95	52.5	1.21	11.84	50.9	35	91								
END POINT	95	59.3	1.35	13.12	55.0	38	98	52.5	95	5.8	0.23	2.27	5.0	3	15
HA OPRFTRCT															
OVERALL															
BASELINE	4	55.4	5.21	10.42	55.6	43	58								
END POINT	4	61.4	5.51	11.02	61.3	48	75	55.4	4	6.0	0.37	0.73	5.7	5	7
OLANZAPINE															
OVERALL															
BASELINE	10	64.0	5.44	17.20	65.0	37	95								
END POINT	10	72.6	5.61	17.73	73.3	46	137	64.0	10	8.6	1.20	3.73	7.6	5	18

See footnotes on the first page of the table.

R. 6884

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D919.428

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Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.3 : Descriptive Statistics of Body Weight Increase >7% in Subjects >18 Years

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17FEB2004 12:56
Sys_em Used: Arrow3.1/aSAF.WEIGHT.2

RIS-POOLED WEIGHT ANALYSE

aSAF.WEIGHT.3 : Descriptive statistics of Body Weight Increase >7% in Subjects >18 Years (continued)

ANALYSIS SET: ALL SUBJECTS
TRIAL TYPE: LONG TERM
AGE CATEGORY: 18-65

	N	Mean	SE	SD	Med	Min	Max	Base Mean	Change from Overall Baseline						
									N	Mean	SE	SD	Med	Min	Max
Weight, kg															
RISPERIDONE															
OVERALL	943	74.1	0.55	16.79	71.5	37	155								
BASLINE	943	85.1	0.62	18.98	83.0	42	177	74.1	943	11.1	0.20	6.15	9.1	3	97
END POINT															
HALOPERIDOL															
OVERALL	136	71.9	1.49	17.41	69.8	34	154								
BASLINE	136	84.9	1.73	20.21	83.5	38	176	71.9	136	13.1	0.59	8.01	10.4	4	50
END POINT															
OLANZAPINE															
OVERALL	105	74.1	1.46	14.23	73.0	40	112								
BASLINE	105	81.9	1.57	16.25	85.0	56	125	74.1	105	10.8	0.49	5.06	9.0	5	29
END POINT															

See footnotes on the first page of the table.

Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.3 : Descriptive Statistics of Body Weight Increase >7% in Subjects >18 Years

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17FEB2004 12:56
System Used: Arrow3.1/aSAF.WEIGHT.2

RIS-POOLED WEIGHT ANALYSE

aSAF.WEIGHT.3 : Descriptive statistics of Body Weight Increase >7% in Subjects >18 Years (continued)

ANALYSIS SET: ALL SUBJECTS

TRIAL TYPE: LONG TERM

AGE CATEGORY: >65

	N	Mean	SE	SD	Med	Min	Max	Change from Overall Baseline							
								Base Mean	N	Mean	SE	SD	Med	Min	Max
Weight, kg															
RISPERIDONE															
OVERALL															
BASELINE	108	57.9	1.31	13.64	55.2	35	106								
END POINT	108	65.0	1.40	14.51	62.6	39	116	57.9	108	7.1	0.24	2.52	6.8	3	17
OLANZAPINE															
OVERALL															
BASELINE	1	102.0			102.0	102	102								
END POINT	1	110.0			110.0	110	110	102.0	1	8.0			8.0	8	8

See footnotes on the first page of the table.

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7.2. Annexes

Annex 1: Narratives

Risperidone: Effects on Glucose Metabolism

Cross-Reference Table of Narratives for Patients who Died, had Serious Adverse Events or Discontinued Due to Glucose-Related Adverse Events (Feb 2002)

Cross-reference table of narratives for 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)					
INT-61 (Double-blind short-term)					
A30445*	RIS oral	Hyperglycemia		X	
A30755	RIS oral	Diabetes mellitus		X	
USA-79 (Double-blind long-term)					
0054	RIS	Diabetes mellitus		X	
0601*	RIS	Diabetes mellitus		X	
0084*	HAL	Diabetes mellitus Hypoglycemia		X	
0302	HAL	Diabetes mellitus		X	
0349*	HAL	Hyperglycemia	X	X	
INT-45 (Double-blind short-term)					
A30142*	RIS	Hyperglycemia Hypoglycemia		X	
USA-102 (Double-blind short-term)					
A30030	PLA	Uncontrolled diabetes		X	
USA-6 (Open-label long-term)					
0254	RIS	Hypoglycemia		X ^b	
INT-85 (Open-label short-term)					
A30272*	RIS	Hyperglycemia		X	
ELDERLY (>65 years)					
AUS-5 (Double-blind short-term)					
160	PLA	Hypoglycemia		X	
USA-63 (Double-blind short-term)					
0911*	PLA	Hyperglycemia		X	
4113*, ^d	PLA	Hyperglycemia	X	X	(X ^d)
0115*	RIS	Hypoglycemia		X	
1204 ^{a,c}	RIS	Diabetic coma	X	X	X
2613*	RIS	Hyperglycemia	X		
4013	RIS	Hyperglycemia		X	
4014*	RIS	Diabetes mellitus		X	
INT-23 (Open-label long-term)					
A00118*	RIS	Diabetes mellitus		X	
A00367	RIS	Hypoglycemia		X	(X ^d)
USA-70 (Open-label long-term)					
2916*	RIS	Diabetes mellitus		X	
4118	RIS	Hyperglycemia	X	X	
4206	RIS	Hyperglycemia		X	
TOTAL			5^e	22	1^e

Risperidone: Effects on Glucose Metabolism

Cross-Reference Table of Narratives for Patients who Died, had Serious Adverse Events or Discontinued Due to Glucose-Related Adverse Events (Feb 2002)

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

A patient narrative is provided in Annex 1 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 an endocrine disorder other than a glucose-related one.

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

c: Patient 0076 from trial USA-79 (HAL) was listed in the August 2000 report as having discontinued due to a glucose-related event, but is not included in this table as the discontinuation was due to other reasons. A narrative is provided.

d: This patient died but the cause of death was not due to a glucose-related adverse event. A narrative is provided in Annex 1 for completeness.

e: One patient is indicated because this 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.

Narratives from trials RIS-INT-61, RIS-AUS-5, and RIS-INT-85 are located at the end of Annex 1.

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-USA-79

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

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.

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-USA-79

<u>ECG data:</u>						
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

<u>Concomitant medication:</u>	<u>Dosage*</u>	<u>Start</u>	<u>End</u>
<u>Psychotropic medication:</u>			
Haloperidol	10mg QD	15DEC92	24JUN96
<u>Other concurrent medication:</u>			
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.

<u>Other adverse events (verbatim):</u>	<u>Severity</u>	<u>Relation to study med</u>	<u>Start</u>	<u>End</u>
Headache (intermittent)	mild	none	06SEP96	14OC196
Tooth extraction	mild	none	04MAR97	04MAR97
Scapular cyst	mild	none	24JUN97	still present
Haloneus melanocytic nevus	mild	none	24JUN97	still present

<u>Clinical laboratory tests:</u>							
Abnormal laboratory values:		(Day 0)					
<u>Laboratory test:</u>	<u>Reference range</u>	<u>Baseline</u>	<u>Day 29</u>	<u>Day 190</u>	<u>Day 302</u>	<u>Day 365</u>	<u>Day 533</u>
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: Effects on Glucose Metabolism
AE Narratives RIS-USA-79

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 Uncontrolled diabetes mellitus	Relation to study med none	Start 26DEC97
	End 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 anteroapical 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 anteroapical 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

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.

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-USA-79

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:	Dosage*	Start	End
Psychotropic medication:			
Chlorpromazine HCl	25mg TID	12NOV96	25AUG97
Other concurrent medication:			
Insulin	not recorded	prior	ongoing
Nifedipine	not recorded	prior	ongoing
Ursodiolocholic 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):	Severity	Relation to study med	Start	End
Gastritis	mild	none	27DEC97	31DEC97

Clinical laboratory tests:

Abnormal laboratory values:		(Day 0)					
Laboratory test:	Reference range	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: Effects on Glucose Metabolism
AE Narratives RIS-USA-79

Risperidone—RIS-USA-79
Premature Discontinuation Summary

Subject:	A30076 REC	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			
Adverse event (verbatim):	Severity	Relation to study med	Start	End
Elevated glucose	mild	possible	17JUL97	Subseq
Elevated uric acid	mild	possible	28AUG97	not specified
Elevated alkaline phosphatase	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

Clinical narrative:

The patient, a 45-year-old man, began study medication treatment on July 18, 1996. On July 17, 1997, after approximately one year on study medication, the patient was referred to an internist secondary to abnormal laboratory results; his AST, ALT, alkaline phosphatase, GGT, glucose, and MCV were all mildly elevated (note: the patient was discontinued based on laboratory values other than those reported from standard blood draws for the study; the exact laboratory values were not available). These results were confirmed with a retest on August 1, 1997. On August 21, 1997, the patient saw an internist, who recommended he withdraw from the study. The patient contacted the site and was discontinued immediately; he completed final visit assessments on August 28.

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-USA-79

1997. Physical examination results indicated tremor in both hands. The PANSS score was 47 (63 at baseline) and the CGI was "moderate" and unchanged relative to baseline. There were a couple of notable changes in the Extrapyramidal Symptom Rating Scale (ESRS). Expressive automatic movements (of the parkinsonism subscale) worsened from "very mild decrease in facial expressiveness" at baseline to "rare spontaneous smile, decreased blinking, voice slightly monotonous" at final visit, and tremors in both arms increased from "absent" to "moderate amplitude." The CGI subscale of the ESRS for dyskinesia remained "absent" throughout the study, and the parkinsonism CGI increased from "absent" to "mild" at study end. There is no further information concerning resolution of the abnormal laboratory values. The investigator considered all elevations in laboratory values to be possibly related to study medication.

Screening and Final Visit ECG results were reported by the site as within normal limits. Week 28 ECG results indicated non-specific T abnormality and borderline QTc. Week 52 ECG results reported borderline QT interval and Week 100 ECG results showed borderline QTc. All ECG abnormalities were judged by the site to be not clinically significant. This patient was discontinued from the study after 400 days at the recommendation of an internist because of liver function test abnormalities. Liver function abnormalities are expected with haloperidol. However, the underlying cause of the mild hepatic inflammation late in the course of the study (Day 365) is not clear from the provided information. The patient had liver function tests at 2 earlier assessments that were within normal limits while on the same dose of study medication (15 mg/day). Concomitant medications or conditions associated with liver dysfunction were not reported. Possible causes for mild hepatic inflammation include alcohol ingestion or use of over-the-counter medications such as NSAIDs or acetaminophen; the possibility of alcoholism is suggested by the increase in MCV. Arguing that haloperidol may have contributed is the improvement in laboratory values at Day 427. There was mild and intermittent monocytosis of unclear etiology. Monocytosis is not expected with haloperidol; common causes of monocytosis include infections and hematologic malignancies. Mild hyperglycemia was evident from Day 365 onward. Hyperglycemia is expected with haloperidol and it is possible that the study medication caused hyperglycemia in this patient, or the patient was in a non-fasting condition. There was borderline or mild prolongation of the QT on Days 196, 365, and 700. Many anti-psychotic medications lead to repolarization abnormalities as do a large number of other medications and metabolic abnormalities; such conditions and medications were not reported. Haloperidol may have contributed to the lengthened QT since it had increased after Screening; on the other hand, the QT remained prolonged at Week 100, long after study discontinuation, arguing that another factor may be contributing.

ECG data:

Date	Timepoint	Heart rate (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTc (ms)
11JUL96	SCREEN	85	154	72	344	409
31JAN97	WEEK 28	80	160	90	370	430
17JUL97	WEEK 52	73	140	70	420	460
28AUG97	WEEK 100	83	160	60	380	450

Concomitant medication:	Dosage*	Start	End
Psychotropic medication:			
Haloperidol	10 mg q day	22AUG97	not specified
Other concurrent medication:			
None			

Other adverse events (verbatim):	Severity	Relation to study med	Start	End
Hematuria	mild	possible	31JAN97	not specified
Intermittent L side tremor hand, arm & foot	mild	possible	01OCT96	19JUN97
Intermittent bilateral tremors of hand	moderate	possible	20JUN97	not specified
Intermittent rt side tremor in hand, arm	mild	possible	19NOV96	19JUN97

Clinical laboratory tests:

Abnormal laboratory values:

Laboratory test:	Reference range	Baseline	Day28	Day198	Day365	Day380	Day400+(-7)*	Day427+(-34)*
Monocytes	0 - 10%	11.3		11		13		
MCV	76 - 100 cu microns	94			104	103		106
Serum gluc	60 - 115 mg/dL	94			163	134	147	129
Uric acid	2 - 9 mg/dL	8.2	9.3			9.6		9.1
SGPT (ALT)	0 - 55 U/L	41				60	63	
SGOT (AST)	0 - 50 U/L	33				68	71	
GGT	0 - 65 U/L	45			69	69		

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

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-USA-79

Risperidone—RIS-USA-79
Serious Adverse Event/Treatment 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			
Serious adverse event (verbatim):	Severity	Relation to study med	Start	End
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

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-USA-79

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 ESKS 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	Heart 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

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-USA-79

<u>Other concurrent medication:</u>	<u>Dosage*</u>	<u>Start</u>	<u>End</u>
NPPI 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>		(Day 0)				
<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: Effects on Glucose Metabolism
AE Narratives RIS-USA-79

Risperidone—RIS-USA-79
Serious Adverse Event Summary

Subject:	A30302RED	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 SCPT is of dubious significance without other reported abnormalities in liver function tests.

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

Risperidone: Effects on Glucose Metabolism
 AE Narratives RIS-USA-79

<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
Runny nose	mild	possible	20JAN98	25FEB98
<u>Clinical laboratory tests:</u>				
Abnormal laboratory values:		(Day 0)		
<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

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-USA-79

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.

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-USA-79

<u>ECG data:</u>						
<u>Date</u>	<u>Timepoint</u>	<u>Heart rate (bpm)</u>	<u>PR (ms)</u>	<u>QRS (ms)</u>	<u>QT (ms)</u>	<u>QTc (ms)</u>
15JUL97	SCREEN	101	150	100	352	457

<u>Concomitant medication:</u>	<u>Dosage*</u>	<u>Start</u>	<u>End</u>
<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.

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

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

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-45

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

Subject: RED #A30142	Investigator: RIIHIKANGAS 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)

ECG DATA

Date	Time	HR (bpm)	QRS (ms)	QT (ms)	QTc (ms)	QTic (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	Start	End
insulin		
sc human 10-12+8 iu	before trial	13AUG1998
insulin isophane, human biosynthetic		
sc human 30 iu	before trial	22AUG1998
lisinopril		
pc 20 mg	before trial	ongoing at end of trial
temazepam		
pc 20 mg	before trial	ongoing at end of trial
perphenazine		
pc 8 mg	12AUG1998	12AUG1998
redol comp.		
po 10 ml x 3	13AUG1998	16AUG1998

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-45

A30142 (cont.)

CONCOMITANT MEDICATION

Medication Doseage	Start	End
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
clotutinol hydrochloride pc 10 ml x 2-3	19AUG1998	20AUG1998
propranolol pc 20 mg	19AUG1998	ongoing at end of trial
paracetamol pc 500 mg	21AUG1998	21AUG1998
cefuroxime sodium iv 4.5 g	22AUG1998	31AUG1998
insulin sc human 10-6+8 iu	22AUG1998	22AUG1998
pentoxifylline citrate pc 15 ml	22AUG1998	23AUG1998
insulin sc human 10-12 iu	23AUG1998	23AUG1998
insulin isophane, human biosynthetic sc human 10 10 iu	23AUG1998	23AUG1998
lactulose pc 20 ml	23AUG1998	25AUG1998
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 pc 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
micronazole nitrate 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
cefaalexin monohydrate pc 500 mg x 3	31SEP1998	06SEP1998

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-45

CONCOMITANT MEDICATION (A30142 cont.)

Medication	Start	End
insulin		
sc human 8+6+6 iu	31SEP1998	01SEP1998
insulin isophane, human biosynthetic		
sc human 4+10 iu	31SEP1998	09SEP1998
insulin		
sc human 10-8+6 iu	32SEP1998	11SEP1998
insulin isophane, human biosynthetic		
sc human 4+8 iu	10SEP1998	13SEP1998
clobutinol hydrochloride		
pc 10 ml	12SEP1998	12SEP1998
insulin		
sc human 10-12+6 iu	12SEP1998	12SEP1998
insulin		
sc human 10-8+6 iu	13SEP1998	21SEP1998
clobutinol hydrochloride		
pc 10 ml	14SEP1998	14SEP1998
insulin isophane, human biosynthetic		
sc human 6+8 iu	14SEP1998	ongoing at end of trial
sodium picosulfate		
pc 23 gtt	15SEP1998	15SEP1998
insulin		
sc human 10-6+6 iu	22SEP1998	ongoing at end of trial
clobutinol hydrochloride		
pc 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 14300 at week 4 11500 at week 8

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

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-USA-102

JRR--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: 11 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: clemidine (0.1mg); docusate sodium (500mg); enalapril maleate (40mg); furosemide (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)	QTc(ms)	QTcF(ms)
18DEC1998	DB	BASLINE	59	154	90	442	438 BL	430 BL
05JAN1999	POST	Month 1	70	148	134	452	438 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, SGM 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).

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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).

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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.

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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).

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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.

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.

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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

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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/casanthanol (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.

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

COUNTRY:	USA
INVESTIGATOR:	I. 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.

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.

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RISPERIDONE-RIS-USA-63
PREMATURE DISCONTINUATION SUMMARY

COUNTRY:	USA
INVESTIGATOR:	K. Sakanye, 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.

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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.

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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).

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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.

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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.

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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 Elantran 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.

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

■ 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, fibrosis 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 25/02/93 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 23, 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 RPS:
 - 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 PO from 20JUN96 to 19JUL96),
 - sulfadiazine silver (bid PO 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 PO from 02OCT96 to 18OCT96),
 - tetracycline (bid PO from 16SEP96 to 01OCT96).

Other adverse events:
 - dizziness (moderate; drug-related; adverse event resolved) from 16JUN96 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.

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-23

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

RISPERIDONE-RIS-USA-70
SERIOUS ADVERSE EVENT/PREATURE 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.

RISPERIDONE-RIS-USA-70
SERIOUS ADVERSE EVENT/PREATURE 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, teargen and famotidine (May 21, 1997-ongoing), furosemide and fluconazole (November 3, 1997-ongoing), insulin (October 21, 1997-ongoing), glyburide (October 30, 1997-ongoing), triamcinolone 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), Rocheffin (October 20, 1997-unknown), influenza vaccine (October 6, 1997), 5% dextrose/1/4 normal saline

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.

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).

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-AUS-5

JRP--TRIAL RIS-AUS-005
SMR CLS ADV-RSK HVKN' SUMMARY

Subject: RED #160	Investigator: AMES, D., MD
Age: 90 years	Trial medication: PLACEBO
Race: Caucasian	Treatment duration: 83 days
Sex: male	Treatment start: July 14, 1999
Country: AUSTRALIA	Treatment stop: October 4, 1999

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
*hypoglycaemia (hypoglycemia)	severe	doubtful	05SEP99	06SEP99	treatment	54
*haematemesis (haematemesis)	severe	possibly	06SEP99	06SEP99	treatment	55

** days after start treatment

BASELINE SUBJECT DATA

- Vascular Dementia: uncomplicated
- Baseline Total AGGRESSION: 35.0
- Baseline MMSE Total: 11
- TIME FROM THE PREV. PSYCHIATRIC INSTIT.: 1
- Medical and surgical history: not significant
- Concomitant disorders: genito-urinary: urinary/faecal incontinence, prostatectomy 1984;
other: occasional falls
- Physical examination: neurological: brisk reflexes, abnormal gait.
- Previous medications: temazepam (10 mg p/o nocte prn)

TREATMENT DATA:

Trt. Phase	Treatment	Start	Stop	Daily Dose (mg)	Duration
WASH OUT	PLACEBO	07JUL1999	13JUL1999	0	7
TREATMENT	PLACEBO	14JUL1999	17AUG1999	0	35
TREATMENT	PLACEBO	18AUG1999	18AUG1999	0	1
TREATMENT	PLACEBO	19AUG1999	05SEP1999	0	18
TREATMENT	PLACEBO	06SEP1999	06SEP1999	0	1
TREATMENT	PLACEBO	07SEP1999	09SEP1999	0	3
TREATMENT	PLACEBO	09SEP1999	10SEP1999	0	1
TREATMENT	PLACEBO	11SEP1999	03OCT1999	0	23
TREATMENT	PLACEBO	04OCT1999	04OCT1999	0	1

CLINICAL NARRATIVE

RED had uncomplicated vascular dementia. On September 5, 1999, 54 days after the start of double-blind treatment with placebo, he had hypoglycemia (1.6 mmol/L). On the following day, he experienced hematemesis and was hospitalized. Both of these serious adverse events were judged severe and possibly related to treatment with the study drug. They resolved on September 6, 1999. The subject returned to the nursing home on September 10, 1999.

The subject had no significant medical or surgical history. Concomitant medical conditions at baseline, abnormalities at baseline physical examination, previous medications, vital signs data, concomitant medications, other adverse events, and clinical laboratory test abnormalities are provided in the corresponding sections of this patient profile.

VITAL SIGNS DATA

Date	Phase Time	Weight (kg)	Pulse (b/min)	SBP (mmHg)	DBP (mmHg)	BMI
06JUL99	TREATMSCREENING		76	150	70	
04OCT99	TREATMEEK 12		60			

Risperidone: Effects on Glucose Metabolism
 AE Narratives RIS-AUS-5

CONCOMITANT MEDICATION

Medication Dosage	Start	End
amlodipine besilate 5 mg p/o mane	before trial	ongoing at end of trial
chloramphenicol instill tds	before trial	16JUL1999
fosinopril sodium 10 mg p/o mane	before trial	ongoing at end of trial
gliclazide 160 mg p/o bd	before trial	06SEP1999
lacri-lube apply topical bd	before trial	ongoing at end of trial
lactulose 20 mls p/o mane	before trial	ongoing at end of trial
paracetamol 500mg-1g p/o nocte	before trial	04AUG1999
quinine sulfate 300 mg p/o nocte	before trial	ongoing at end of trial
sorbolene cream with 10% glycerine top dry limbs bd prn	before trial	ongoing at end of trial
temazepam 10 mg p/o nocte prn	before trial	ongoing at end of trial
paracetamol 500mg-1g p/o nocte prn	04AUG1999	ongoing at end of trial
oxazepam 15 mg p/o bd	21AUG1999	27AUG1999
oxazepam 30 mg p/o bd	27AUG1999	ongoing at end of trial
lomotil 2 tablets tds p/oprn	03SEP1999	04SEP1999
dextrose and sodium chloride injection 1000mL ivi 8hourly	06SEP1999	06SEP1999
furosemide 80 mg ivi stat	06SEP1999	06SEP1999
gliclazide 80 mg p/o daily	06SEP1999	07SEP1999
glucagon hydrochloride 1mg ini statum	06SEP1999	06SEP1999
glucose 15 grammes p/o stat	06SEP1999	06SEP1999
insulin 4 u/s s/c stat	06SEP1999	06SEP1999
ranitidine 150 mg p/o bd	06SEP1999	ongoing at end of trial
sodium chloride 1000mL ivi 12 hourly a.p.c.	06SEP1999	06SEP1999
glucose 150 mg p/o daily	07SEP1999	11SEP1999
glucose 1000mL ivi 12 hourly	07SEP1999	07SEP1999
coloxyl with senna 2 tablets p/o bd	08SEP1999	ongoing at end of trial
gliclazide 80 mg p/o bd	08SEP1999	08SEP1999
isosorbide mononitrate 30 mg p/o daily	08SEP1999	11SEP1999
travad enema 130 mL p/r stat	08SEP1999	08SEP1999
gliclazide 40 mg p/o daily	09SEP1999	ongoing at end of trial
isosorbide mononitrate 60 or 80 mg p/o daily	11SEP1999	ongoing at end of trial
trimethoprim 300 mg p/o daily	11SEP1999	17SEP1999

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-AUS-5

CONCOMITANT MEDICATION

Medication	Dosage	Start	End
oxazepam	30 mg p/o daily	12SEP1999	12SEP1999
oxazepam	15 mg p/o daily	13SEP1999	13SEP1999

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
sleep disorder (interrupted sleep pattern)	moderate	possibly	2 JUL99		treatment	8
aggressive reaction (increasing aggression)	mild	not	21AUG99	27AUG99	treatment	39
aggressive reaction (increasing aggression)	mild	not	27AUG99		treatment	45
constipation (faecal impaction)	moderate	possibly	02SEP99	06SEP99	treatment	51
diarrhoea (diarrhoea)	moderate	doubtful	02SEP99	04SEP99	treatment	51
fall (fall)	mild	possibly	03SEP99	03SEP99	treatment	52
bronchitis (moist chest)	mild	doubtful	06SEP99	06SEP99	treatment	55
bronchospasm (wheezy chest)	mild	doubtful	06SEP99	06SEP99	treatment	55
extrasystoles (irregular pulse)	moderate	possibly	06SEP99	06SEP99	treatment	55
pallor (pale colour)	moderate	possibly	06SEP99	06SEP99	treatment	55
pulmonary congestion (mild pulmonary venous congestion)	mild	not	06SEP99	06SEP99	treatment	55
urinary retention (urinary retention)	moderate	doubtful	06SEP99	06SEP99	treatment	55
urinary tract infection (urinary tract infection)	mild	not	07SEP99	17SEP99	treatment	56
somnolence (drowsiness)	mild	possibly	1 SEP99	13SEP99	treatment	60
fall (fall)	mild	possibly	29SEP99	29SEP99	treatment	78
fall (fall)	mild	possibly	30SEP99	30SEP99	treatment	79
injury (black eyes)	moderate	not	30SEP99		treatment	79
somnolence (drowsiness)	moderate	possibly	03OCT99		treatment	82

** days after start treatment

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)
calcium (2.1-2.6 mmol/l)
2.08 at screening
vitamin b12 (0-200 pg/ml)
327 at screening

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-AUS-5

JRF--TRIAL RIS-INT-61
SERIOUS ADVERSE EVENT SUMMARY

PATIENT #A30445

Subject: ■ #A30445	Investigator: Thumulla u., MD
Age: 50 years	Trial medication: RIS 6 MG ORAL
Race: Caucasian	Run-in duration: 56 days
Sex: female	Depot duration: 72 days
Country: Germany	Treatment start: April 3, 2000
Diagnosis: 13 years	Treatment stop: June 26, 2000
Trial term: June 26, 2000	Term type: Completed

Trial termination reason:
treatment1=depot/oral(1), treatment2=depot/oral(2)
oral(1)=risperidone
oral(2)=risperidone for oral treatment group, placebo for depot treatment group

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
*hyperglycaemia (hyperglycaemia)	severe	not	14APR00	14APR00	treatment1	12
*hypertension aggravated (hypertension crisis)	severe	not	14APR00	14APR00	treatment1	12

** days after start treatment

BASELINE SUBJECT DATA

- Diagnosis: schizophrenia(paranoid)
- Medical and surgical history: genito-urinary: uterus myomatosis
- Concomitant disorders: cardiovascular: hypertension under control by medication;
endocrine: diabetes mell. under control by medication; genito-urinary: urinary infection
; other: hyperuricaemia, liver increase (ggt)
- Physical examination: no abnormalities
- Previous medications: haloperidol decanoate (3 ml qmo)

TREATMENT DATA:

Trt. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
RUN-IN	RIS ORAL		07FEB2000	20FEB2000	6	14
RUN-IN	RIS ORAL		21FEB2000	06MAR2000	6	15
RUN-IN	RIS ORAL		07MAR2000	02APR2000	6	27
TREATMENT1	PLA DEFOT/RIS ORAL 1		03APR2000	16APR2000	3/6	14
TREATMENT1	PLA DEFOT/RIS ORAL 2		17APR2000	23APR2000	3/6	7
TREATMENT2	PLA DEFOT/RIS ORAL		24APR2000	01MAY2000	3/6	8
TREATMENT2	PLA DEFOT/RIS ORAL 3		02MAY2000	14MAY2000	3/6	13
TREATMENT2	PLA DEFOT/RIS ORAL 4		15MAY2000	28MAY2000	3/6	14
TREATMENT2	PLA DEFOT/RIS ORAL 5		29MAY2000	12JUN2000	3/6	15
TREATMENT2	PLA DEFOT/RIS ORAL 6		13JUN2000	26JUN2000	3/6	14

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-AUS-5

CLINICAL NARRATIVE

■ (CRF ID A30445) was a white female with a 13-year history of paranoid schizophrenia. She was 50-years old at the time of trial entry. She entered the run-in period of clinical trial RIS-INT-61 on 7 February 2000 and completed run-in 2 April 2000. During run-in, she received risperidone 6 mg/day for 56 days. On 3 April, she was randomized to receive double blind treatment. She received oral risperidone 6 mg/day and placebo depot injection biweekly. Oral risperidone 6 mg/day was given until 26 June. She completed the trial on 26 June 2000.

On 14 April, she was hospitalized for the serious adverse events "hyperglycemia" and "hypertension crisis". During the trial, she also experienced the adverse events "headache" and "hypertension crisis".

Her medical history and concomitant medications are provided in the narrative profile. Concomitant disorders were significant for urinary tract infection and hyperuricemia as well as hypertension and diabetes that were both controlled by medication. Physical examination at baseline was normal. On 7 February, blood pressure at screening was 180/110, at baseline on 3 April, blood pressure was 145/100, on 2 May, it was 150/95 and on 26 June, was 160/105. ECG findings and clinical laboratory values are provided in the narrative profile.

The serious adverse events "hyperglycemia" and "hypertension crisis" resolved on 14 April. The investigator considered the "hyperglycemia" and "hypertension crisis" severe and not related to study treatment.

Both hypertension and diabetes were pre-existing conditions, controlled by medication. The study medication was not interrupted because of the events and the patient completed the trial. The sponsor considered a relationship with the use of risperidone unlikely.

ECG DATA

Date	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcF (ms)	QTcL (ms)
07FEB2000	TRT	SCREENING	72	170	100	400	438	425	426
03APR2000	TRT	BASELINE	80	170	80	400	462 BL	440	439
02MAY2000	TRT	WEEK 4	73	150	90	370	408	395	397
26JUN2000	TRT	WEEK 12	72	170	90	360	394	385	386

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

VITAL SIGNS DATA

Date	Phase	Time	Weight (kg)	BMI	Stand/Supine Pulse (b/min)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
07FEB2000	TRT	SCREENING	90	31	85 / 80	180 / 180	110 / 110
03APR2000	TRT	BASELINE	90	31	138 / 100	145 / 140	100 / 95
02MAY2000	TRT	WEEK 4			130 / 96	150 / 150	95 / 95
26JUN2000	TRT	WEEK 12	93	32	83 / 80	160 / 155	105 / 105

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-AUS-5

CONCOMITANT MEDICATION

Medication	Dosage	Start	End
amlodipine besilate	5 mg od po	before trial	ongoing at end of trial
diazide	1 x od po	before trial	ongoing at end of trial
enalapril	20 mg cd po	before trial	ongoing at end of trial
glimepiride	3 mg od po	before trial	ongoing at end of trial
metformin hydrochloride	850 mg od po	before trial	ongoing at end of trial
panadeine co	1 x po	13FEB2000	13FEB2000
glyceryl trinitrate	1 x 0.8 mg sl	18FEB2000	18FEB2000
insulin	8ie od sc	14APR2000	14APR2000
nifedipine	20 mg cd po	14APR2000	14APR2000

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
headache	moderate	not	13FEB00	13FEB00	run-in	-50
(headache)						
hypertension aggravated	moderate	not	18FEB00	18FEB00	run-in	-45
(hypertension crisis)						

** days after start treatment

CLINICAL LABORATORY TESTS

The following laboratory tests had results outside of normal limits during the trial:

Test (laboratory limits, unit)

alt (sgpt) (1-30 U/L)	41 at screening	54 at baseline	37 at week 12
ast (sgot) (1-32 U/L)	25 at screening	42 at baseline	23 at week 12
chloride (96-110 meq/l)	97 at screening	95 at baseline	93 at week 12
creatinine (0.4-1.5 mg/dl)	1.48 at screening	1.59 at baseline	1.59 at week 12
ggt (6-32 U/L)	44 at screening	40 at baseline	39 at week 12
lymphocytes (25-45 %)	11 at screening	17 at baseline	31 at week 12
monocytes (2-10 %)	1 at screening	2 at baseline	4 at week 12
neutrophils (50-65 %)	87 at screening	80 at baseline	65 at week 12
prolactin (2-23 ng/ml)	52.5 at baseline	17.3 at week 12	
sodium (136-148 meq/l)	134 at screening	131 at baseline	131 at week 12
urea (20-50 mg/dl)	51 at screening	54 at baseline	83 at week 12
uric acid (2.5-6 mg/dl)	7.6 at screening	8.4 at baseline	9.4 at week 12

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-AUS-5

PLASMA CONCENTRATIONS

Date	RTS, ng/ml	9-OT-RTS, ng/ml	ACTIVE METAB, ng/ml
03APR2000	1.18	28.1	29.3
17APR2000	NQ	1.66	1.7
02MAY2000	NQ	4.74	4.7
13JUN2000	NQ	2.11	2.1
15JUN2000	0.16	15.6	15.8
19JUN2000	46.5	63.6	110.1
26JUN2000	NQ	3.5	3.5

NQ=Not quantifiable(LLOQ=0.1 ng/ml) NR=No Result

CGI

Date	Phase	Time	CGI
03APR2000	TRT	BASLINE	MODERATE
06MAR2000	TRT	RUN-IN	MODERATE
07FEB2000	TRT	SCREENING	MODERATE
13JUN2000	TRT	WEEK 10	MODERATE
26JUN2000	TRT	WEEK 12	MODERATE
17APR2000	TRT	WEEK 2	MODERATE
02MAY2000	TRT	WEEK 4	MODERATE
15MAY2000	TRT	WEEK 6	MODERATE
29MAY2000	TRT	WEEK 8	MODERATE

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-AUS-5

JRF--TRIAL RIS-INT-61
SERIOUS ADVERSE EVENT SUMMARY

PATIENT #A30755

Subject: REC #A30755	Investigator: David a., MD
Age: 54 years	Trial medication: RIS 2 MG ORAL
Race: Caucasian	Run-in duration: 64 days
Sex: male	Depot duration: 71 days
Country: Great Britain	Treatment start: July 13, 2000
Diagnosis: 28 years	Treatment stop: October 4, 2000
Trial term: October 5, 2000	Term type: Completed

Trial termination reason:
treatment1=depot/oral(1), treatment2=depot/oral(2)
oral(1)=risperidone
oral(2)=risperidone for oral treatment group, placebo for depot treatment group

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbatim)	Severity	Related	Start	End	Phase	
Days** *diabetes mellitus (non insulin dependant diabetes mellitus)	moderate	doubtful	13JUL00		treatment1	1

** days after start treatment

BASELINE SUBJECT DATA

- Diagnosis: schizophrenia (undifferentiated)
- Medical and surgical history: not significant
- Concomitant disorders: dermatological: psoriasis patches on both legs; eyes: impaired acuity- needs mild bifocals; musculoskeletal: some occasional (legs) aches + pains w exercise
- Physical examination: breasts: some gynaecomastia; skin: 11 campbell de morgan's spots-trunk/ psoriasis patches both legs, mild
- Previous medications: fluphenazine decanoate (10mg 4/52)

TREATMENT DATA:

Trt. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
RUN-IN	RIS ORAL		10MAY2000	17MAY2000	2	8
RUN-IN	RIS ORAL		18MAY2000	31MAY2000	2	14
RUN-IN	RIS ORAL		01JUN2000	14JUN2000	2	14
RUN-IN	RIS ORAL		15JUN2000	12JUL2000	2	28
TREATMENT1	PLA DEPOT/RIS ORAL 1		13JUL2000	26JUL2000	3/2	14
TREATMENT1	PLA DEPOT/RIS ORAL 2		27JUL2000	32AUG2000	3/2	7
TREATMENT2	PLA DEPOT/RIS ORAL		03AUG2000	09AUG2000	3/2	7
TREATMENT2	PLA DEPOT/RIS ORAL 3		13AUG2000	23AUG2000	3/2	14
TREATMENT2	PLA DEPOT/RIS ORAL 4		24AUG2000	30SEP2000	3/2	14
TREATMENT2	PLA DEPOT/RIS ORAL 5		07SEP2000	20SEP2000	3/2	14
TREATMENT2	PLA DEPOT/RIS ORAL 6		21SEP2000	30OCT2000	3/2	14

CLINICAL NARRATIVE

RED(CRF ID A30755) was a white male with a 28-year history of undifferentiated schizophrenia. He was 54-years old at the time of trial entry. He entered the run-in period of clinical trial RIS-INT-61 on 10 May 2000 and completed the run-in on 12 July 2000. During the run-in, he received risperidone oral 0-2 mg/day for 64 days. On 13 July, he was randomized to receive double-blind treatment. He received oral risperidone 2 mg/day and placebo depot injections biweekly. Oral risperidone 2 mg/day was given until 4 October. He completed the trial on 5 October 2000.

On 13 July, the serious adverse event "non-insulin-dependent diabetes mellitus" occurred. On 15 May, at screening, glycosuria was detected on laboratory tests and on 13 July he was diagnosed with non-insulin dependent diabetes mellitus (NIDDM). He was asymptomatic during this event. He also experienced the adverse events "heartburn", "lingering taste of tablets", "morning unsteady on feet", "morning drowsiness", and "CRTI (cold)", "tight chest", "constipation" three times, and "headache" during the trial.

Prior medical history was not remarkable. Concomitant disorders and concomitant medications are listed in the narrative profile. Physical examination at baseline was unremarkable. Vital signs, ECG findings, and clinical laboratory values were not related to the serious adverse event.

The serious adverse event of "non-insulin-dependent diabetes mellitus" did not resolve. The investigator considered the adverse event moderately severe and doubtfully related to study treatment.

The NIDDM was pre-existing before the trial. The patient was randomized and completed the trial as planned. The sponsor considered a relationship with the use of risperidone highly unlikely.

ECG DATA

Date	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcF (ms)	QTcL (ms)
10MAY2000	TRT	SCREENING	60	190	90	430	430 BL	430 BL	430 BL
13JUL2000	TRT	BASELINE	60	180	90	420	420	420	420
10AUG2000	TRT	WEEK 4	65	190	100	390	406	401	402
05OCT2000	TRT	WEEK 12	69	190	100	380	408	396	400

(A=Above normal B=Below normal * =Abnormal BL=Borderline PI=Prolonged)

VITAL SIGNS DATA

Date	Phase	Time	Weight (kg)	BMI	Stand/Supine Pulse (b/min)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
10MAY2000	TRT	SCREENING	91	33	/ 69	116 / 20	80 / 80
13JUL2000	TRT	BASELINE	89	32	66 / 64	120 / 99	81 / 57
10AUG2000	TRT	WEEK 4			/	134 / 13	76 / 62
04OCT2000	TRT	WEEK 12	86	31	95 / 65	114 / 96	74 / 50

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-AUS-5

CONCOMITANT MEDICATION

Medication	Dosage	Start	End
acetylsalicylic acid (7150mg) 1 tablet		29MAY2000	30MAY2000
paracetamol 500mg		30MAY2000	31MAY2000
paracetamol 500mg		06JUN2000	07JUN2000
magnesium sulfate 5mg		26SEP2000	26SEP2000
senna fruit 2-tablets		27SEP2000	27SEP2000
senna fruit 2-tablets		02OCT2000	02OCT2000
paracetamol 250mg		03OCT2000	03OCT2000

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
dyspepsia (heartburn)	mild	possibly	18MAY00	16JUN00	run-in	-56
taste perversion (lingering taste of tablets)	mild	probable	18MAY00	16JUN00	run-in	-56
gait abnormal (morning unsteady on feet)	mild	possibly	19MAY00	06JUL00	run-in	-55
somnolence (morning drowsiness)	mild	possibly	19MAY00	06JUL00	run-in	-55
upper resp tract infection (urti(cold))	mild	not	28MAY00	31JUL00	run-in	-46
chest pain (right chest)	mild	doubtful	25JUL00	26JUL00	treatment1	13
constipation (constipation)	mild	doubtful	23SEP00	24SEP00	treatment2	73
constipation (constipation)	mild	doubtful	26SEP00	27SEP00	treatment2	76
constipation (constipation)	mild	doubtful	02OCT00	03OCT00	treatment2	82
headache (headache)	mild	doubtful	03OCT00	03OCT00	treatment2	83

** days after start treatment

CLINICAL LABORATORY TESTS

The following laboratory tests had results outside of normal limits during the trial:

Test (laboratory limits, unit)	140 at screening	131 at baseline	139 at week 12
alkaline phosphatase (31-121 U/L)			
calcium (4-5.5 meq/l)	5.4 at screening	5.6 at baseline	5.6 at week 12
ggt (10-49 U/L)	76 at screening	49 at baseline	28 at week 12
lymphocytes (25-45 %)	19.9 at screening	13.1 at baseline	17.5 at week 12
neutrophils (50-65 %)	68.4 at screening	78.3 at baseline	72.1 at week 12

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-AUS-5

PLASMA CONCENTRATIONS

Date	RIS, ng/ml	9-O4-RIS, ng/ml	ACTIVE MOIETY, ng/ml
13JUL2000	1.98	11.5	13.5
27JUL2000	1.17	10.6	11.8
10AUG2000	2.08	12.3	14.4
21SEP2000	1.62	14.5	16.1
26SEP2000	1.25	11.5	12.8
28SEP2000	0.98	6.56	7.5
05OCT2000	1.14	10.3	11.9

NQ=Not quantifiable(LQ=0.1 ng/ml) NR=No Result

CGI

Date	Phase	Time	CGI
13JUL2000	TRT	BASLINE	MILD
15JUN2000	TRT	RUN-IN	MILD
10MAY2000	TRT	SCREENING	MILD
21SEP2000	TRT	WEEK 10	MILD
04OCT2000	TRT	WEEK 12	MILD
27JUL2000	TRT	WEEK 2	MILD
10AUG2000	TRT	WEEK 4	MILD
24AUG2000	TRT	WEEK 6	MILD
07SEP2000	TRT	WEEK 8	MILD

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-85

CRF--TRIAL RIS-INT-85
SERIOUS ADVERSE EVENT SUMMARY

Subject: █ #A30272	Investigator: Sallach K., MD	
Age: 50 years	Trial medication: RIS/20C	
Race: Caucasian	Treatment start: January 10, 2002	
Sex: male	Treatment stop: March 21, 2002	
Country: Germany	Trial term: April 4, 2002	
Diagn at: 19 years	Term.type: Completed	

Trial termination reason:

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
*hyperglycaemia (significant increase of glucose)	moderate	not	10 JAN02	27 JAN02	Area.mon1	1
*hyperglycaemia (in cause of ae not hospitalisation)	severe	not	28 JAN02	13 FEB02	Area.mon1	19

** days after start of first injection

BASELINE SUBJECT DATA

- Diagnosis: (schizophrenia, paranoid)
- Medical and surgical history: not significant
- Concomitant disorders: endocrine: diabetes mellitus, increase of triglycerides (detected at visit A1)
- Physical examination: neurologic: rigidity of extremities
- Previous medications: zuclopenthixol decanoate (2ml / 2 we)

TREATMENT DATA:

Trt. Phase	Treatment	In.	Start	Stop	Dose (mg)	Duration
RUN-IN	ZUCLOPENTHIXOL	1	10DEC2001	27DEC2001	400	18
RUN-IN	ZUCLOPENTHIXOL	2	28DEC2001	09JAN2002	400	13
TREATMENT	RISPERIDONE	1	10JAN2002	23JAN2002	25	14
TREATMENT	RISPERIDONE	2	24JAN2002	06FEB2002	25	14
TREATMENT	RISPERIDONE	3	07FEB2002	20FEB2002	37.5	14
TREATMENT	RISPERIDONE	4	21FEB2002	06MAR2002	37.5	14
TREATMENT	RISPERIDONE	5	07MAR2002	20MAR2002	50	14
TREATMENT	RISPERIDONE	6	21MAR2002	21MAR2002	50	1

ORAL ADMINISTRATION DATA:

Trt. Phase	Treatment	Start	Stop	Dose (mg)	Duration
TREATMENT	RISPERIDONE	14FEB2002	07MAR2002	2	22
TREATMENT	RISPERIDONE	08MAR2002	21MAR2002	1	14

CLINICAL NARRATIVE

RED (CRF ID #A30272) was a white male with a 31-year history of paranoid schizophrenia. He was 50-years old at the time of trial entry. He entered the open-label trial RIS-INT-85 on 10 January 2002. During run-in, he received zuclopenthixol depot 400 mg injections twice. He then received treatment with

RIS-INT-85 Patient A30272 (cont.)

risperidone long acting injectable (LAI) 25 mg/biweekly twice, followed by risperidone LAI 37.5 mg/biweekly twice, followed by risperidone LAI 50 mg/biweekly twice. Supplementation with oral risperidone 2 mg/day was given for 22 days, followed by oral risperidone 1 mg/day for 14 days.

On 10 January 2002, he received his first risperidone LAI 25 mg/biweekly injection. On that same day, he experienced the serious adverse event "significant increase of glucose". His serum glucose value on 10 December 2001 (Cycle 1), prior to treatment with risperidone LAI, was 14 mmol/l (normal 3.9-6.4 mmol/l). On 10 January 2002, his serum glucose value was 25.3 mmol/l. On 24 January 2002, he received his second dose of risperidone LAI 25 mg/biweekly. On 28 January 2002, he was hospitalized due to the serious adverse event "hyperglycemia". His glucose on 24 January 2002 was 18.8 mmol/l and he was hospitalized for further investigation and insulin therapy. During the trial, the other adverse event "increased blood pressure" occurred.

Prior medical history was not significant. Concomitant disorders were remarkable for diabetes mellitus (detected at Visit A1). Concomitant medications are provided in the narrative profile as are clinical laboratory values. Physical examination at baseline was unremarkable, as were vital signs and ECG data throughout the trial.

The serious adverse event "significant increase of glucose" resolved on 27 January 2002 and was considered by the investigator as moderately severe and not related to study medication. The second serious adverse event "hyperglycemia" resolved on 13 February 2002, was considered severe and not related to the study medication by the investigator.

The patient was found to have increased glucose levels at trial entry. Dosage of the study medication was maintained at 25 mg/biweekly injection on 24 January 2002 and increased to 37.5 mg/biweekly injection on 7 February 2002. Insulin treatment was started on 22 January 2002 and the patient completed the trial on 4 April 2002 without further problems. The sponsor considered a causal relationship between the serious adverse event "hyperglycemia" and the use of the study medication unlikely.

Risperidone: Effects on Glucose Metabolism
 AE Narratives RIS-INT-85

RIS-INT-85 Patient A30272 (cont)

ECG DATA

Date	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcF (ms)	QTcL (ms)	QTcLD (ms)
10DEC2001	RI	CYCLE1	70	170	100	390	421	411	412	411
10JAN2002	TREAT	BASELINE	65	180	90	400	416	411	412	411
24JAN2002	TREAT	WEEK 2	70	190	90	340	367	358	362	361
21FEB2002	TREAT	WEEK 6	68	190	100	350	424	398	399	397
05APR2002	TREAT	WEEK 12	68	170	90	360	383	373	378	377

(R=Above normal B=Below normal * =Abnormal PL=Borderline PL=Prolonged)

ECG EVALUATIONS

Date	Phase	Time	ECG aspect	ECG evaluation
21FEB2002	TREAT	WEEK 6	MORPHOLOGY	LATE R-WAVE TRANSITION
05APR2002	TREAT	WEEK 12	MORPHOLOGY	EARLY R-WAVE TRANSITION
05APR2002	TREAT	WEEK 12	RYTHM	SINUS ARRHYTHMIA

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-85

RIS-INT-85 Patient A30272 (cont.)

VITAL SIGNS DATA

Date	Phase	Time	Stand/Supine Pulse (b/min)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
10DEC2001	RI	CYCLE1	100 / 76	130 /140	90 /100
28DEC2001	RI	CYCLE2	84 / 80	130 /130	70 / 80
10JAN2002	TREAT	BASELINE	86 / 74	140 /155	90 / 90
17JAN2002	TREAT	WEEK 1	96 / 72	140 /125	90 / 80
24JAN2002	TREAT	WEEK 2	96 / 68	130 /150	90 /100
31JAN2002	TREAT	WEEK 3	96 / 84	130 /130	85 / 85
07FEB2002	TREAT	WEEK 4	88 / 80	150 /150	105 / 90
14FEB2002	TREAT	WEEK 5	100 / 88	150 /140	100 / 80
21FEB2002	TREAT	WEEK 6	102 / 84	160 /160	100 /100
07MAR2002	TREAT	WEEK 8	96 / 84	120 /120	70 / 60
21MAR2002	TREAT	WEEK 10	80 / 88	140 /140	80 / 90
04APR2002	TREAT	WEEK 12	100 / 72	120 /135	80 / 80

WEIGHT - BMI DATA

Date	Phase	Time	Weight (kg)	BMI
10DEC2001	RI	CYCLE1	59.0	31.2
28DEC2001	RI	CYCLE2	59.0	31.2
10JAN2002	TREAT	BASELINE	59.0	31.2
24JAN2002	TREAT	WEEK 2	59.0	31.2
07FEB2002	TREAT	WEEK 4	59.0	31.2
21FEB2002	TREAT	WEEK 6	59.0	31.2
07MAR2002	TREAT	WEEK 8	58.0	30.9
21MAR2002	TREAT	WEEK 10	59.6	31.2
04APR2002	TREAT	WEEK 12	56.0	30.3

CONCOMITANT MEDICATION

Medication	Start	End
Cosaso		
'nsulin glargine sc, od	22JAN2002	24JAN2002
'nsulin glargine sc, od	25JAN2002	23JAN2002
al-irnsulin od, sc	28JAN2002	30JAN2002
'nsulin injection, isophane od, sc	28JAN2002	29JAN2002
lisinopril od, po	28JAN2002	04FEB2002
'nsulin injection, isophane sc	29JAN2002	29JAN2002
'nsulin injection, isophane sc	30JAN2002	30JAN2002
al-irnsulin od, sc	31JAN2002	31JAN2002
'nsulin injection, isophane sc	31JAN2002	03FEB2002
'nsulin injection, isophane s.c.	04FEB2002	04FEB2002
benazepril hydrochloride od, po	05FEB2002	07FEB2002
'nsulin injection, isophane s.c.	05FEB2002	05FEB2002
'nsulin injection, isophane s.c.	06FEB2002	06FEB2002
'nsulin injection, isophane s.c.	07FEB2002	07FEB2002
benazepril hydrochloride od, po	08FEB2002	ongoing at end of trial

Risperidone: Effects on Glucose Metabolism
 AE Narratives RIS-INT-85

RIS-INT-85 Patient A30272 (cont.)

Insulin injection, isophane s.c.	08FEB2002	03FEB2002
Insulin injection, isophane s.c.	09FEB2002	ongoing at end of trial

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
hypertension (increased blood pressure)	mild	not	28JAN02	10FEB02	treatment1	19

** days after start of first injection

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-85

RIS-INT-85 Patient A30272 (cont)

CLINICAL LABORATORY TESTS

The following laboratory tests had results outside of normal limits during the trial:

Test (Laboratory limits, unit)	Baseline	Week 2	Week 12
alkaline phosphatase (55-135 U/L)	100 at cycle 1	112 at week 2	73 at week 12
cholesterol (4.4-7.53 mmol/L)	7.96 at cycle 1	7.89 at week 2	5.47 at week 12
glucose (3.9-6.4 mmol/L)	9.39 at baseline	13.8 at week 2	5.5 at week 12
hemoglobin a1c (4.3-6.1 %)	14 at cycle 1	11.4 at week 2	7.5 at week 12
hdl (0.72-1.63 mmol/L)	25.3 at baseline	0.7 at week 2	0.68 at week 12
total protein (61-84 g/L)	8.5 at cycle 1	60 at week 2	64 at week 12
triglycerides (0.65-3.61 mmol/L)	10.5 at baseline	19.7 at week 2	2.31 at week 12
urea (3.8-10.7 g/ga/L)	6.57 at cycle 1	10.21 at week 2	10.89 at week 12

CGI

Date	Phase	Time	CGI
07DEC2001	R1	CYCLE1	Moderate
28DEC2001	R1	CYCLE2	Moderate
10JAN2002	TREAT	BASELINE	Moderate
24JAN2002	TREAT	WEEK 2	MILD
07FEB2002	TREAT	WEEK 4	MILD
21FEB2002	TREAT	WEEK 6	MILD
07MAR2002	TREAT	WEEK 8	MILD
21MAR2002	TREAT	WEEK 10	MILD
04APR2002	TREAT	WEEK 12	MILD

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-62

TRIAL RIS-INT-62

PREMATURE DISCONTINUATION SUMMARY

#A30358

Subject: RED #A30358	Investigator: Moctezuma J., MD
Age: 49 years	Trial medication: RIS DEPOT
Race: Caucasian	Treatment start: August 21, 2001
Sex: male	Treatment stop: April 12, 2002
Country: The Netherlands	Trial term: April 23, 2002
Diagn at: 20 years	Term type: Discontinued

Trial termination reason: Adverse event

DISCONTINUATION FROM TRIAL:

Date: April 23, 2002, 246 days from the start of treatment

Cause: hyperglycaemia

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
*hyperglycaemia (due to too high sugar, hyperglycaemia)	severe	not	11FEB02	20FEB02	treatment	175
*psychosis (worsening of psychosis)	severe	not	11FEB02	20FEB02	treatment	175
*psychosis (hospitalisation (worsening of psychosis))	severe	not	12FEB02	20FEB02	treatment	176
*psychosis (increased of psychotic sympt)	severe	possibly	09APR02		treatment	232
hyperglycaemia (significant glucose value.)	severe	possibly	23APR02		treatment	246

** days after start treatment

BASELINE SUBJECT DATA

- Diagnosis: (295.3 schizophrenia, paranoid)
- Medical and surgical history: not significant
- Concomitant disorders: endocrine: diabetic insuline injections
- Physical examination: no abnormalities
- Previous medications: zucloperthixol decanoate (150mg 2wk)

TREATMENT DATA:

Trt. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
RUN-IN	RIS ORAL		21AUG2001	27AUG2001	2	7
TREATMENT	RIS DEPOT/RIS ORAL 1		28AUG2001	10SEP2001	25/2	14
TREATMENT	RIS DEPOT/RIS ORAL 2		11SEP2001	18SEP2001	25/2	8
TREATMENT	RIS DEPOT		19SEP2001	24SEP2001	25	6
TREATMENT	RIS DEPOT	3	25SEP2001	07OCT2001	25	13
TREATMENT	RIS DEPOT	4	08OCT2001	22OCT2001	25	15
TREATMENT	RIS DEPOT	5	23OCT2001	05NOV2001	25	14
TREATMENT	RIS DEPOT	6	06NOV2001	19NOV2001	25	14
TREATMENT	RIS DEPOT	7	20NOV2001	03DEC2001	25	14
TREATMENT	RIS DEPOT	8	04DEC2001	17DEC2001	25	14
TREATMENT	RIS DEPOT	9	18DEC2001	30DEC2001	25	13
TREATMENT	RIS DEPOT	10	31DEC2001	14JAN2002	25	15
TREATMENT	RIS DEPOT	11	15JAN2002	28JAN2002	25	14
TREATMENT	RIS DEPOT	12	29JAN2002	10FEB2002	25	13
TREATMENT	RIS DEPOT/RIS ORAL		11FEB2002	11FEB2002	25/2	1
TREATMENT	RIS DEPOT/RIS ORAL 13		12FEB2002	14FEB2002	50/2	3
TREATMENT	RIS DEPOT		15FEB2002	24FEB2002	50	10
TREATMENT	RIS DEPOT/RIS ORAL 14		25FEB2002	05MAR2002	50/2	9
TREATMENT	RIS DEPOT		06MAR2002	11MAR2002	50	6
TREATMENT	RIS DEPOT	15	12MAR2002	27MAR2002	50	16
TREATMENT	RIS DEPOT	16	28MAR2002	08APR2002	50	12
TREATMENT	RIS DEPOT/RIS ORAL 17		09APR2002	09APR2002	50/2	1
TREATMENT	RIS DEPOT/RIS ORAL		10APR2002	12APR2002	0/2	3

CLINICAL NARRATIVE

RED (CRF ID A30358) was a white male with a 29-year history of paranoid schizophrenia; he was 49-years old at the time of trial entry. He entered the open-label trial RIS-INT-62 on 21 August 2001. After seven days of run-in with oral risperidone 2 mg/day, he received treatment with risperidone depot 25 mg/biweekly 12 times and risperidone depot 50 mg/biweekly 5 times. He also received supplementation with oral risperidone 2 mg/day for 39 days. He prematurely discontinued the trial on the trial on 23 April 2002 due to adverse events.

On 29 January 2002, he received a risperidone depot 25 mg/biweekly injection. On 11 February 2002, he developed "due to too high sugar, hyperglycemia" and "worsening of psychosis" and was treated with temazepam. Glucose (3.9-6.4 mmol/L) at baseline was 11.9 mmol/L, at Month 9, the glucose was 18 mmol/L. Hemoglobin A1c (4.3-6.1%) was 6.2 at baseline, 7.1 at Week 13 (20 November 2001) and 8.2 at Month 9 (23 April 2002).

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-62

On 12 February 2002, he received his first risperidone depot 50 mg/biweekly injection, on that same day he required "hospitalization (worsening of psychosis)". He became violent and threw a bench through a window. Treatment with oxazepam was initiated.

On 9 April 2002, he received his fifth risperidone depot 50 mg/biweekly injection. On 9 April 2002, he experienced "increase of psychotic symptoms" and was treated with clonazepam and oxazepam. On 23 April 2002, he again developed a "significant glucose value". During the trial, the other adverse events of "sleeplessness and "restlessness" were reported.

Prior medical history was notable for diabetes (CIOMS). Concomitant disorders included diabetic insulin injections. Concomitant medications are provided in the narrative profile. Physical examination at baseline was unremarkable. Vital signs are provided in the narrative profile, as are clinical laboratory data. Clinical Global Impression (CGI) was rated as marked at baseline, became moderate on 11 September 2001, mild on 20 November 2001, severe on 11 February 2002 and returned to marked on 23 April 2002.

The "due to too high sugar, hyperglycemia" and "worsening of psychosis" and "hospitalization (worsening of psychosis)" resolved on 20 February 2002, they were considered severe by the investigator and not related to study medication. The "significant glucose value" and "increased of psychotic symptoms had no resolution date and were considered severe by the investigator and possibly related to study medication.

Hyperglycemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment. Therefore, a causal relationship between the two episodes of "hyperglycemia" and the use of the study medication can not be excluded. The three episodes of "psychosis" in this patient were most probably due to his underlying condition. Schizophrenia is a chronic illness. The course varies, but most patients have a chronic course with frequent relapses, typically characterized by exacerbation of psychosis and hospitalization. The sponsor considered a causal relationship between these serious adverse events and the use of risperidone unlikely.

ECG DATA

Date	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTc3 (ms)	QTcF (ms)	QTcL (ms)
15AUG2001	OPEN	BASELINE	52	180	90	410	382	361	387
23APR2002	OPEN	MONTH 9	68	160	90	360	383	375	377

(A=Above normal L=Below normal * = Abnormal H=Borderline P=Prolonged)

VITAL SIGNS DATA

Date	Phase	Time	Stand/Supine Pulse (b/min.)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
15AUG2001	OPEN	BASELINE	75 / 72	125 / 125	75 / 75
23NOV2001	OPEN	WEEK 13	75 / 72	120 / 120	70 / 70
23APR2002	OPEN	MONTH 9	75 / 72	120 / 120	75 / 70

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-62

WEIGHT - BMI DATA

Date	Phase	Time	Weight (kg)	BMI
15AUG2001	OPEN	SCREENING	94.0	25.5
21AUG2001	OPEN	BASELINE	94.0	25.5
28AUG2001	OPEN	WEEK 1	95.0	25.8
11SEP2001	OPEN	WEEK 3	95.0	25.8
06OCT2001	OPEN	WEEK 7	95.0	25.8
23OCT2001	OPEN	WEEK 9	95.0	25.8
23NOV2001	OPEN	WEEK 13	95.0	25.8
11FEB2002	OPEN	MONTH 6	95.0	25.8
23APR2002	OPEN	MONTH 9	88.0	23.9

CONCOMITANT MEDICATION

Medication	Dosage	Start	End
risperidone	2 mg prn	15AUG2001	20AUG2001
temazepam	20 mg od	11FEB2002	17FEB2002
oxazepam	25 mg bid	12FEB2002	03MAR2002
oxazepam	50 mg tid	04MAR2002	21MAR2002
oxazepam	25 mg tid	22MAR2002	08APR2002
clonazepam	od	09APR2002	ongoing at end of trial
oxazepam	tid	09APR2002	ongoing at end of trial

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
insomnia (sleeplessness)	moderate	not	11FEB02	17FEB02	treatment	175
agitation (restlessness)	moderate	not	12FEB02		treatment	176

** days after start treatment

CLINICAL LABORATORY TESTS

The following laboratory tests had results outside of normal limits during the trial:

Test (laboratory limits, unit)
cholesterol (4.19-7.24 mmol/L)
4.06 at baseline 3.32 at month 9
glucose (3.9-6.4 mmol/L)
11.9 at baseline 18 at month 9
haematocrit (0.39-0.54 L)
0.42 at baseline 0.4 at week 13 0.38 at month 9
haemoglobin a1c (4.3-6.1 %)
6.2 at baseline 7.1 at week 13 8.2 at month 9
uric acid (125-488 umol/L)
196 at baseline 116 at month 9

CGI

Date	Phase	Time	CGI
21AUG2001	OPEN	BASELINE	MARKED
11FEB2002	OPEN	MONTH 6	SEVERE
23APR2002	OPEN	MONTH 9	MARKED
28AUG2001	OPEN	WEEK 1	MARKED
23NOV2001	OPEN	WEEK 13	MILD
11SEP2001	OPEN	WEEK 3	MODERATE
06OCT2001	OPEN	WEEK 7	MODERATE
23OCT2001	OPEN	WEEK 9	MODERATE

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-63

JNJPRD--TRIAL RIS-INT-63 SAFETY UPDATE (CUT-OFF MARCH 28, 2003)
DEATH SUMMARY

#A30202

Subject: ■ #A30202	Investigator: REMINGTON G., MD
Age: 43 years	Previous trial: INT-57
Race: Caucasian	Previous CRFID: A30329
Sex: male	Term.type(prev.): COMPLETED
Country: CANADA	Depot duration: 680 days
Diagnosis: years	Treatment start: November 16, 2000
Trial term: September 26, 2002	Treatment stop: September 26, 2002
	Term.type(ext.): Discontinued

Trial termination reason: Death
treatment1=depot/oral(prev. trial), treatment2=depot(prev. trial),
treatment=depot (INT-57)
follow up=depot (INT-63)
follow up1=double-blind oral ris (INT-63), follow up2=open oral ris (INT-63)
follow up1+2=double-blind+open oral ris (INT-63)

DEATH:

Date: October 8, 2002, 12 days after the end of follow up

Cause: sudden death

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
*larynx neoplasm benign Trial: INT-63 (benign neoplasm in thyroid area)	moderate	doubtful	01FEB01	20JUN01	follow up	78
*hyperglycaemia Trial: INT-63 (hyperglycemic blood sugar 33.3 pt collapsed)	moderate	doubtful	04JUL02	04JUL02	follow up	596
*sudden death Trial: INT-63 (sudden death)	severe	not	08CCT02	08OCT02	follow up	692

** days after start treatment

BASELINE SUBJECT DATA

- Diagnosis: paranoid schizophrenia
- Medical and surgical history: not significant
- Concomitant disorders: gastrointestinal: constipation; ears, nose, throat: wax accumulation, syringed q3 monthly; endocrine: diabetes (insulin dependent); psychiatric other than trial indication: mild mental retardation, agitation; neurological: mild EPS
- Physical examination:
breasts int-57 10nov1999 abnormal: gynecomastia;
breasts int-57 19may2000 abnormal;;
breasts int-57 16nov2000 abnormal: (sr, dec14 2000);
general appearance int-57 10nov1999 abnormal: obese;
general appearance int-57 19may2000 abnormal;;
general appearance int-57 16nov2000 abnormal: (sr, dec.14,2000)

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TREATMENT DATA:

Trial	Trt. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
INT-57	RUN-IN	ORAL RIS		17NCV1999	18NOV1999	1	2
INT-57	RUN-IN	ORAL RIS		19NCV1999	20NOV1999	2	2
INT-57	RUN-IN	ORAL RIS		21NCV1999	24NOV1999	4	4
INT-57	RUN-IN	ORAL RIS		25NCV1999	31DEC1999	2	7
INT-57	TREATMENT	DEPCT/ORAL RIS	1	C2DEC1999	16DEC1999	25/2	15
INT-57	TREATMENT	DEPCT/ORAL RIS	2	17DEC1999	17DEC1999	25/2	1

TREATMENT DATA:

Trial	Trt. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
INT-57	TREATMENT	DEPCT/ORAL RIS		18DEC1999	29DEC1999	25/3	12
INT-57	TREATMENT	DEPCT/ORAL RIS	3	30DEC1999	12JAN2000	25/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	4	13JAN2000	14JAN2000	50/3	2
INT-57	TREATMENT	DEPCT/ORAL RIS		15JAN2000	21JAN2000	50/2	7
INT-57	TREATMENT	DEPCT/ORAL RIS		22JAN2000	26JAN2000	50/3	5
INT-57	TREATMENT	DEPCT/ORAL RIS	5	27JAN2000	30FEB2000	75/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	6	10FEB2000	23FEB2000	75/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	7	24FEB2000	08MAR2000	75/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	8	09MAR2000	22MAR2000	75/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	9	23MAR2000	05APR2000	75/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	10	06APR2000	19APR2000	75/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	11	20APR2000	03MAY2000	75/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	12	04MAY2000	18MAY2000	75/3	15
INT-57	TREATMENT	DEPCT/ORAL RIS	13	19MAY2000	31MAY2000	75/3	13
INT-57	TREATMENT	DEPCT/ORAL RIS	14	01JUN2000	14JUN2000	75/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	15	15JUN2000	28JUN2000	75/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	16	29JUN2000	12JUL2000	75/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	17	13JUL2000	26JUL2000	75/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	18	27JUL2000	08AUG2000	75/3	13
INT-57	TREATMENT	DEPCT/ORAL RIS	19	09AUG2000	23AUG2000	75/3	15
INT-57	TREATMENT	DEPCT/ORAL RIS	20	24AUG2000	06SEP2000	75/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	21	07SEP2000	20SEP2000	75/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	22	21SEP2000	04OCT2000	75/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	23	05OCT2000	19OCT2000	75/3	15
INT-57	TREATMENT	DEPCT/ORAL RIS	24	20OCT2000	31OCT2000	75/3	12
INT-57	TREATMENT	DEPCT/ORAL RIS	25	01NOV2000	01NOV2000	75/3	1
INT-63	FOLLOW UP	RIS DEPOT		16NCV2000	27DEC2000	75	42
INT-63	FOLLOW UP	RIS DEPOT		28DEC2000	16JAN2001	0	20
INT-63	FOLLOW UP	RIS DEPOT		17JAN2001	26SEP2002	75	618

CLINICAL NARRATIVE

RED (CRF ID A30202) was a white male with a history of paranoid schizophrenia; he was 43-years old at the time of study entry. He received treatment with risperidone microspheres depot during the double-blind study, RIS-INT-57, until he completed the study. He entered the open-label extension study RIS-INT-63, on 16 November 2000. During RIS-INT-63, he received risperidone microspheres depot 75 mg/biweekly injections. The patient suddenly died on 8 October 2002.

On 1 February 2001, he was hospitalized with a "benign neoplasm in thyroid area", which occurred 78 days after the start of treatment in RIS-INT-63. Surgical removal was performed on 18 June 2001 (source: CIOMS). On 4 July 2002, after 596 days after the start of treatment in RIS-INT-63, he developed "hyperglycemic blood sugar 33.3, patient collapsed" and was hospitalized. He was stabilized and discharged home. There were no clinical laboratory data provided for this event.

On 8 October 2002, "sudden death", occurred 692 days after the start of treatment in RIS-INT-63. The patient was found dead in his bed; a myocardial infarction was suspected (source: CIOMS). During RIS-INT-63, the other adverse events of "intermittent, unsteady gait", "decreased hemoglobin", "flu symptoms", "intermittent back pain", "boils on scrotum, legs and left buttock", "thickened nails on toes" and "open lesion left large toe" occurred.

Prior medical history was insignificant. Concomitant disorders included insulin dependent diabetes mellitus and mild mental retardation. Concomitant medications are provided in the narrative profile. Physical examination is provided in the narrative profile. Clinical laboratory data, ECG data and vital signs were unrelated to the serious adverse events.

The "benign neoplasm in thyroid area" and "hyperglycemic blood sugar 33.3, patient collapsed" resolved on 20 June 2001 and 4 July 2002, respectively. The investigator considered the "benign neoplasm in thyroid area" and "hyperglycemic blood sugar 33.3, pt collapsed" as moderate in severity and doubtfully related to study treatment while the "sudden death" was considered severe and not related to study medication.

This patient had insulin-dependent diabetes. Hyperglycemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment. The sponsor considered that a causal relationship between the serious adverse event "hyperglycemic blood sugar 33.3, patient collapsed" and the use of risperidone could not be excluded. The sponsor considered a causal relationship between the serious adverse event "benign neoplasm in thyroid area" and the use of risperidone highly unlikely. The information provided on the patient's death is very sketchy. This 46-year old male with concomitant diabetes did not have a known cardiac history. Blood pressures were normal during both trials. Duration of QT interval was also normal during both trials, however, QTcB duration was borderline prolonged on two occasions. In view of this limited information, the sponsor considered a causal relationship between the serious adverse event "sudden death" and the use of risperidone doubtful.

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ECG DATA

Date	Trial	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcF (ms)	QTcI (ms)
10NOV1999	INT-57	TRT	BASELINE *	75	200	90	380	425	409	411
02DEC1999	INT-57	TRT	BASELINE	75	180	90	370	414	399	401
19MAY2000	INT-57	TRT	WEEK 24	83	200	90	340	400	379	383
16NOV2000	INT-57	TRT	WEEK 50	71	200	90	400	435 BL	423	424
15FEB2001	INT-63	FUP	MO 3(EX)	68	200	90	380	405	396	398
25MAY2001	INT-63	FUP	MO 6(EX)	80	200	100	370	427	407	409
08NOV2001	INT-63	FUP	MO 12(EX)	84	190	100	370	438 BL	414	414

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

VITAL SIGNS DATA

Date	Trial	Phase	Time	Weight(kg)	BMI	Stand/Supine Pulse (b/min)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
10NOV1999	INT-57	TRT	BASELINE	109	36	80 / 72	130 / 140	78 / 80
19MAY2000	INT-57	TRT	WEEK 24	109	36	72 / 84	100 / 124	50 / 64
16NOV2000	INT-57	TRT	WEEK 50	117	38	90 / 84	150 / 150	70 / 80
13FEB2001	INT-63	FUP	MO 3(EX)			90 / 80	124 / 143	70 / 77
24MAY2001	INT-63	FUP	MO 6(EX)	106	35	80 / 84	110 / 110	60 / 65
08NOV2001	INT-63	FUP	MO 12(EX)	125	41	80 / 90	112 / 132	59 / 70

* not included in statistical analysis

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CONCOMITANT MEDICATION

Medication Dosage	Trial	Start	End
benzotropine mesilate 2 mg po bid; 4 mg	INT-57	before trial	ongoing
diazepam 2 mg po tid; 6 mg	INT-57	before trial	ongoing
insulin novolin 70/30 30/10, 10CU/10ml, sq; 68 units qam 66 ..	INT-57	before trial	13JAN2000
lactulose po; 30 cc prn	INT-57	before trial	ongoing
metformin po; 1500 mg qam, 500 mg qpm	INT-57	before trial	31JAN2000
psyllium hydrophilic mucilloid po; as required	INT-57	before trial	ongoing
metformin po, 1500 mg qam, 1000 qpm; 2500 mg	INT-57	01JAN2000	ongoing
lorazepam 2 mg im, x 1; 2 mg	INT-57	14JAN2000	14JAN2000
insulin novolin 70/30 30/10, 10CU/10ml, sq 68 units qam, 60..	INT-57	15JAN2000	18JAN2000
paracetamol 500 mg-1000 mg po; prn	INT-57	17JAN2000	25FEB2000
insulin novolin 70/30 30/10, 60units qam 6Cu qpm; 120u	INT-57	19JAN2000	19JAN2000
insulin novolin 70/30 30/10, 20 u x 1 sq; 20 u	INT-57	20JAN2000	20JAN2000
insulin novolin 70/30 30/10, 35 u x 1 sq; 35 u	INT-57	21JAN2000	21JAN2000
insulin novolin 70/30 30/10, 25 u x 1 sq; 25 u	INT-57	22JAN2000	22JAN2000
lorazepam 2 mg im x 1; 2 mg	INT-57	22JAN2000	22JAN2000
insulin novolin 70/30 30/10, 25 u qam, qam sq; 50u	INT-57	23JAN2000	03FEB2000
insulin novolin 70/30 30/10, 35u sq qam, qam; 70u	INT-57	04FEB2000	07FEB2000
erythromycin 250 mg po; 1000 mg	INT-57	07FEB2000	14FEB2000
paracetamol 500 mg-1000 mg po; prn	INT-57	07FEB2000	14FEB2000
insulin novolin 70/30 30/10, 10CU/10ml, sq; 30 uqam	INT-57	08FEB2000	02MAR2000
insulin novolin 70/30 30/10, 10CU/10 ml, sq; 1.40 uqam, ...	INT-57	03MAR2000	22AUG2000
ramipril 2.5mg po; 2.5mg	INT-57	17MAR2000	07MAY2000
permethrin apply immed then 7 days later	INT-57	20APR2000	27APR2000

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CONCOMITANT MEDICATION

Medication	Trial	Start	End
Dosage			
ramipril			
5 mg po; 5 mg	INT-57	08MAY2000	28MAY2000
ramipril			
2.5 mg po; 2.5 mg	INT-57	29MAY2000	ongoing
insulin novolin 70/30			
30/10, 100U u/10ml/sq 60 units	INT-57	22AUG2000	ongoing
benzotropine mesilate			
2mg po bid	INT-63	before trial	07OCT2002
diazepam			
2mg po tid	INT-63	before trial	07OCT2002
insulin novolin 70/30			
1000u/10ml 30units qam 30units qpm sq	INT-63	before trial	05JUL2002
lactulose			
30cc. po prn	INT-63	before trial	07OCT2002
metformin			
1500mg qam, 1000mg qpm.	INT-63	before trial	05JUL2002
psyllium hydrophilic mucilloid			
po prn	INT-63	before trial	07OCT2002
ramipril			
2.5mg po, od	INT-63	before trial	10DEC2001
surgical procedure			
	INT-63	18JUN2001	18JUN2001
levothyroxine			
0.100 mg po od	INT-63	18JUL2001	07OCT2002
ramipril			
dosage increased 5mg od po	INT-63	10DEC2001	07OCT2002
insulin			
unknown (single dose)	INT-63	04JUL2002	04JUL2002
insulin novolin 70/30			
1000u/10m 47u qam 45u qpm sub-cutan.	INT-63	05JUL2002	07OCT2002
levothyroxine sodium			
po 250mcg od	INT-63	05JUL2002	07OCT2002
metformin			
po 500mg bid	INT-63	05JUL2002	07OCT2002
cefalixin monohydrate			
po 500mg qid	INT-63	09JUL2002	19JUL2002
polysporin drops			
topical to left toe	INT-63	16JUL2002	18JUL2002
povidone-iodine			
topical to left toe	INT-63	18JUL2002	07OCT2002

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Trial	Severity	Related	Start	End	Phase	Days**
psychosis	INT-57	severe	not	12JAN00	25FEB00	treatment	42
(increasing psychotic symptoms)							
headache	INT-57	mild	not	17JAN00	25FEB00	treatment	47
(intermittent headache)							
upper resp tract infection	INT-57	moderate	doubtful	07FEB00	14FEB00	treatment	68
(throat infection)							
gait abnormal	INT-57	mild	doubtful	20APR00		treatment	141
(unsteady gait (intermittent))							
infection parasitic	INT-57	mild	not	20APR00	27APR00	treatment	141
(head lice)							
hypotension postural	INT-57	moderate	doubtful	19MAY00	21SEP00	treatment	170
(postural hypotension)							
anaemia	INT-57	moderate	not	16NOV00		treatment	351
(decreased hbq (11.8))							

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OTHER ADVERSE EVENTS

Adverse event (verbatim)	Trial	Severity	Related	Start	End	Phase	Days**
gait abnormal (intermittent, unsteady gait)	INT-63	mild	doubtful	20A2R00		pre trial	-210
anaemia (decreased hbg)	INT-63	moderate	not	16NOV00		follow up	1
influenza-like symptoms (flu symptoms)	INT-63	mild	not	11JAN01	15JAN01	follow up	57
back pain (intermittent back pain)	INT-63	mild	not	13FEB01		follow up	90
skin disorder (boils on scrotum & legs, left buttock)	INT-63	moderate	not	01NOV01		follow up	351
nail disorder (thickened nails on toes)	INT-63	mild	not	26MAR02		follow up	496
injury (open lesion left large toe)	INT-63	mild	doubtful	01JUL02		follow up	593

** days to onset

CLINICAL LABORATORY TESTS

The following laboratory tests had results outside of normal limits during the trial:

Test (laboratory limits, unit)

chloride (96-110 meq/l)	99 at prev base	106 at base(ex)	100 at mo 6(ex)	92 at mo 12(ex)
haematocrit (39-53 %)	38.4 at prev base	34.1 at base(ex)	42.2 at mo 6(ex)	35.1 at mo 12(ex)
haemoglobin (14-18 g/dl)	13.5 at prev base	11.8 at base(ex)	12.6 at mo 6(ex)	12.2 at mo 12(ex)
lymphocytes (25-45 %)	22 at prev base	29 at base(ex)	28.6 at mo 6(ex)	18.7 at mo 12(ex)
neutrophils (50-65 %)	71 at prev base	63 at base(ex)	63.9 at mo 6(ex)	73 at mo 12(ex)
rbc (4.5-6.3 x10E6/mm3)	4.11 at prev base	3.63 at base(ex)	4.12 at mo 6(ex)	3.76 at mo 12(ex)
sodium (136-148 meq/l)	136 at prev base	140 at base(ex)	134 at mo 6(ex)	129 at mo 12(ex)
uric acid (3.5-7 mg/dl)	5.1 at prev base	5.8 at base(ex)	5.7 at mo 6(ex)	7.2 at mo 12(ex)

CGI

Date	Trial	Phase	Time	CGI
10NOV1999	INT-57	TRT	BASELINE	MILD
30DEC1999	INT-57	TRT	WEEK 4	MILD
27JAN2000	INT-57	TRT	WEEK 8	MODERATE
24FEB2000	INT-57	TRT	WEEK 12	MILD
23MAR2000	INT-57	TRT	WEEK 16	MILD
20APR2000	INT-57	TRT	WEEK 20	MILD
19MAY2000	INT-57	TRT	WEEK 24	MILD
15JUN2000	INT-57	TRT	WEEK 28	MILD
09AUG2000	INT-57	TRT	WEEK 36	MODERATE
07SEP2000	INT-57	TRT	WEEK 40	MODERATE
05OCT2000	INT-57	TRT	WEEK 44	MODERATE
01NOV2000	INT-57	TRT	WEEK 48	MODERATE
16NOV2000	INT-57	TRT	WEEK 50	MILD
30NOV2000	INT-63	FUF	WEEK 2 (EXT.)	MILD

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CGI

Date	Trial	Phase	Time	CGI
14DEC2000	INT-63	FUP	WEEK 4 (EXT.)	MILD
27DEC2000	INT-63	FUP	WEEK 6 (EXT.)	MILD
13FEB2001	INT-63	FUP	MONTH 3 (EXT.)	MILD
24MAY2001	INT-63	FUP	MONTH 6 (EXT.)	MILD
16AUG2001	INT-63	FUP	MONTH 9 (EXT.)	MILD
08NOV2001	INT-63	FUP	MONTH 12 (EXT.)	MILD
09MAY2002	INT-63	FUP	MONTH 18 (EXT.)	MILD

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UNJPRD--TRIAL RIS-INT-63 SAFETY UPDATE (CUT-OFF MARCH 28, 2003)
SERIOUS ADVERSE EVENT SUMMARY

#A30779

Subject: RED #A30779	Investigator: LILJEROS L., MD
Age: 48 years	Previous trial: INT-57
Race: Caucasian	Previous CRFID: A30091
Sex: male	Term.type(prev.): OTHER
Country: SWEDEN	Depot duration: 757 days
Diagnosis: years	Treatment start: December 14, 2000
Trial term: January 9, 2003	Treatment stop: January 9, 2003
	Term.type(ext.): Discontinued

Trial termination reason: Other
treatment1=depot/oral(prev. trial), treatment2=depot(prev. trial),
treatment=depot (INT-57)
follow up=depot (INT-63)
follow up1=double-blind oral ris(INT-63), follow up2=open oral ris(INT-63)
follow up1+2=double-blind+open oral ris(INT-63)

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbalim)	Severity	Related	Start	End	Phase	Days**
*fall Trial: INT-63 (fall)	severe	not	11AUG01	11AUG01	follow up	241
*fracture pathological Trial: INT-63 (collum femoralis fracture)	severe	not	14AUG01	01MAR02	follow up	244
*diabetes mellitus Trial: INT-63 (diabetes)	moderate	not	22AUG01	28AUG01	follow up	252
*diabetes mellitus Trial: INT-63 (diabetes)	moderate	not	29AUG01		follow up	259

** days after start treatment

BASELINE SUBJECT DATA

- Diagnosis: schizoaffective disorder
- Medical and surgical history: not significant
- Concomitant disorders: eyes: eyesight impairment - needs glasses; dermatological: psoriasis, mostly in remission; hematological: hematocrit = 0.36 v/v; neurological: eps, hypokinesia
- Physical examination:
abdomen int-57 09dec1999 abnormal: with ab. rementioned obesity;
abdomen int-57 14dec2000 abnormal: slightly more obese;
abdomen int-63 09jan2003 abnormal: adipositas;
external genitalia int-57 14dec2000 abnormal: small, no change;
eyes int-57 30jun2000 abnormal: glasses long range;
general appearance int-57 09dec1999 abnormal: with some abdominal obesity;
general appearance int-63 09jan2003 abnormal: somewhat overweight - increase;
neurological int-57 09dec1999 abnormal: hypokinesia on basis of EPS;
skin int-57 09dec1999 abnormal: light psoriatic lesions;
skin int-57 30jun2000 abnormal: psoriatic lesions no change;
skin int-63 09jan2003 abnormal: slight psoriasis - decrease

TREATMENT DATA:

Trial	Ttr. Phase	Treatment	Inj. Start	Stop	Dose (mg)	Duration
INT-57	RUN-IN	ORAL RIS	09DEC1999	12JAN2000	4	35

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TREATMENT DATA:

Trial	Trt. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
INT-57	TREATMENT	DEPCT/ORAL RIS	1	13JAN2000	26JAN2000	50/6	14
INT-57	TREATMENT	DEPCT/ORAL RIS	2	27JAN2000	27JAN2000	50/6	1
INT-57	TREATMENT	DEPCT/ORAL RIS		28JAN2000	09FEB2000	50/0	13
INT-57	TREATMENT	DEPCT/ORAL RIS	3	10FEB2000	23FEB2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	4	24FEB2000	08MAR2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	5	09MAR2000	22MAR2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	6	23MAR2000	05APR2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	7	06APR2000	19APR2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	8	20APR2000	03MAY2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	9	04MAY2000	17MAY2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	10	18MAY2000	30MAY2000	50/0	13
INT-57	TREATMENT	DEPCT/ORAL RIS	11	31MAY2000	14JUN2000	50/0	15
INT-57	TREATMENT	DEPCT/ORAL RIS	12	15JUN2000	29JUN2000	50/0	15
INT-57	TREATMENT	DEPCT/ORAL RIS	13	30JUN2000	12JUL2000	50/0	13
INT-57	TREATMENT	DEPCT/ORAL RIS	14	13JUL2000	26JUL2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	15	27JUL2000	09AUG2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	16	10AUG2000	23AUG2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	17	24AUG2000	06SEP2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	18	07SEP2000	14SEP2000	50/0	8
INT-57	TREATMENT	DEPCT/ORAL RIS		15SEP2000	20SEP2000	50/6	6
INT-57	TREATMENT	DEPCT/ORAL RIS	19	21SEP2000	04OCT2000	50/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	20	05OCT2000	12OCT2000	50/3	8
INT-57	TREATMENT	DEPCT/ORAL RIS		13OCT2000	18OCT2000	50/0	6
INT-57	TREATMENT	DEPCT/ORAL RIS	21	19OCT2000	01NOV2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	22	02NOV2000	15NOV2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	23	16NOV2000	29NOV2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	24	30NOV2000	30NOV2000	50/0	1
INT-63	FOLLOW UP	RIS DEPOT		14DEC2000	09JAN2003	50	757

CLINICAL NARRATIVE

RED (CRF ID A30779) was a white male with a history of schizoaffective disorder; he was 48-years old at the time of study entry. He received treatment during the open-label study RIS-INT-57 with risperidone microspheres depot injections 50 mg/biweekly 24 times, until he prematurely discontinued the study for other reasons than an adverse event. He entered the open-label extension study RIS-INT-63 on 14 December 2000. During RIS-INT-63, he received risperidone microspheres depot injections 50 mg/biweekly. He prematurely discontinued RIS-INT-63 on 9 January 2003 due to reasons other than an adverse event.

On 11 August 2001, after 241 days of risperidone depot use, he was hospitalized for the serious adverse event of "fall" after he fell indoors and fractured his femur. On 14 August 2001, after 244 days of risperidone depot use, he underwent a surgical repair of a "collum femoralis fracture". He received treatment with flucloxacillin sodium, heparin fraction sodium salt, paracetamol, and cefuroxime, dextran I, ketogin and tranexamic acid. He also developed a "wound infection" on 1 September 2001 that was treated with bactrim.

On 22 August 2001, after 252 days of risperidone depot use, while hospitalized for the surgical repair of his femur, the serious adverse event of "diabetes" was diagnosed. Treatment with insulin was initiated on the same day. On 29 August 2001, after 259 days of risperidone depot use, the patient again experienced the serious adverse event "diabetes".

Prior medical history was not significant. Concomitant disorders and concomitant medications are provided in the narrative profile. Physical examination is provided in the narrative profile. Vital signs, laboratory values and ECG data were unrelated to the serious adverse events.

The "fall" resolved on the same day of occurrence, the "collum femoralis fracture" resolved on 1 March 2002 and the "diabetes" of 22 August 2001 resolved on 28 August 2001, the "diabetes" of 29 August 2001 did not have a resolution date. The investigator considered the "collum femoralis fracture" and "fall" to be severe and both serious adverse events of "diabetes" to be moderate in severity. All were considered not related to study medication.

The circumstances in which the fall occurred are not specified. This patient was known with concomitant eyesight impairment. In view of this limited information, the sponsor considered a causal relationship between the serious adverse event "fall" and the use of risperidone doubtful. The sponsor considered a causal relationship between the serious adverse event "collum femoralis fracture" and the use of risperidone can be excluded.

This patient was not reported to have a history of diabetes nor were there elevated glucose levels reported during the trial. However, hyperglycemia and exacerbation of diabetes have been reported in very rare cases during risperidone treatment. The sponsor considered a causal relationship between the serious adverse event "diabetes mellitus" and the use of risperidone can not be excluded. Risperidone depot injections were continued at the same dose.

ECG DATA

Date	Trial	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcF (ms)	QTcI (ms)
09DEC1999	INT-57	TRT	BASELINE *	81	170	90	400	465 PL	442 BL	
30DEC1999	INT-57	TRT	BASELINE *	90	160	90	390	478 PL	446 BL	441 BL
13JAN2000	INT-57	TRT	BASELINE	78	160	90	420	479 PL	458 PL	456 PL
30JUN2000	INT-57	TRT	WEEK 24	73	170	80	430	474 PL	459 PL	457 PL
11DEC2000	INT-57	TRT	WEEK 48	89	170	90	350	426	399	400
09MAR2001	INT-63	FUP	MO 3 (EX)	88	170	90	380	460 PL	432 PL	429
14JUN2001	INT-63	FUP	MO 6 (EX)	86	160	90	370	440 BL	417	417
13DEC2001	INT-63	FUP	MO 12 (EX)	107	A 170	100	320	427	388	388

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

Risperidone: Effects on Glucose Metabolism
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VITAL SIGNS DATA

Date	Trial	Phase	Time	Weight(kg)	BMI	Stand/Supine Pulse (b/min)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
C9DEC1999	INT-57	TRT	BASELINE	89.8	30	72 / 90	155 /153	90 / 80
30JUN2000	INT-57	TRT	WEEK 24	96	32	92 / 79	160 /165	100 / 95
14DEC2000	INT-57	TRT	WEEK 48	99	34	98 / 96	140 /160	80 / 80
15MAR2001	INT-63	FUP	MO 3(EX)			90 / 90	140 /160	90 / 90
14JUN2001	INT-63	FUP	MO 6(EX)	93	31	74 / 66	160 /180	90 / 90
13DEC2001	INT-63	FUP	MO 12(EX)	97	33	116 /102	130 /150	75 / 80
16DEC2002	INT-63	FUP	MO 24(EX)	100	34	104 / 92	130 /135	80 / 90
C9JAN2003	INT-63	FUP	MO 24(EX) *	103	35	92 / 88	140 /140	80 / 85

* not included in statistical analysis

CONCOMITANT MEDICATION

Medication Dosage	Trial	Start	End
clomipramine 100 mg od po	INT-57	before trial	ongoing
lithium sulfate 126 mg bid po	INT-57	before trial	ongoing
clopenthixol hydrochloride 10 mg bid po	INT-57	16DEC1999	29DEC1999
zuclopenthixol acetate once, i.m.	INT-57	16DEC1999	16DEC1999
ferrous sulfate 100 mg od po	INT-57	13JUL2000	14DEC2000
diazepam 10 mg 1-3/times daily	INT-57	13SEP2000	21SEP2000
clomipramine po 100mg o.d.	INT-63	before trial	ongoing
lithium sulfate p.o. 126mg b.i.d.	INT-63	before trial	ongoing
cefuroxime 1.5g tid i.v	INT-63	14AUG2001	01SEP2001
dextran l 150mg/ml 20ml i.v	INT-63	14AUG2001	01SEP2001
flucloxacillin sodium 750mg bid	INT-63	14AUG2001	01SEP2001
heparin-fraction, sodium salt 0.2ml s.c.o.d	INT-63	14AUG2001	01SEP2001
keLogin 2.5 - 5mg i.v prn	INT-63	14AUG2001	01SEP2001
paracetamol 500mg qid	INT-63	14AUG2001	01SEP2001
tranexamic acid 100g/ml od	INT-63	14AUG2001	01SEP2001
human mixtard 12ie a.m 8ie p.m s.l	INT-63	22AUG2001	14NOV2001
bactrim bid	INT-63	01SEP2001	27DEC2002
human mixtard 16ie a.m 4ie pm	INT-63	15NOV2001	ongoing

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Trial	Severity	Related	Start	End	Phase	Days**
manic reaction (manic episode)	INT-57	moderate	possibly	16DEC99	19DEC99	run-in	-28

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OTHER ADVERSE EVENTS

Adverse event (verbatim)	Trial	Severity	Related	Start	End	Phase	Days**
anaemia (low haemoglobin)	INT-57	mild	doubtful	30JUN00	11DEC00	treatment	170
anxiety (anxiety)	INT-57	moderate	not	13SEP00	12OCT00	treatment	245
psychosis (psychotic symptoms)	INT-57	moderate	not	13SEP00	12OCT00	treatment	245
infection (wound infection)	INT-63	moderate	not	01SEP01	22DEC02	follow up	262

** days to onset

CLINICAL LABORATORY TESTS

The following laboratory tests had results outside of normal limits during the trial:

Test (laboratory limits, unit)

alkaline phosphatase (31-121 U/L)							
106 at prev base	102 at base(ex)	118 at mo 6(ex)	375 at mo 12(ex)				
121 at mo 24(ex)	121 at mo 24(ex) *						
chloride (96-110 mcg/l)							
98 at prev base	91 at base(ex)	91 at mo 6(ex)	95 at mo 12(ex)				
105 at mo 24(ex)	95 at mo 24(ex) *						
haematocrit (39-53 %)							
35.7 at prev base	40.5 at base(ex)	39.53 at mo 24(ex)					
haemoglobin (14-18 g/dl)							
11.6 at prev base	13.8 at base(ex)	13.5 at mo 24(ex)					
lymphocytes (25-45 %)							
14.9 at prev base	16.2 at base(ex)	17.8 at mo 24(ex)					
neutrophils (50-65 %)							
74.6 at prev base	75.5 at base(ex)	71.7 at mo 24(ex)					
rbc (4.5-6.3 x10E6/mm3)							
4.35 at prev base	4.58 at base(ex)	4.77 at mo 24(ex)					
sodium (136-148 meq/l)							
134 at prev base	128 at base(ex)	129 at mo 6(ex)	131 at mo 12(ex)				
141 at mo 24(ex)	133 at mo 24(ex) *						
urea (20-50 mg/dl)							
20 at prev base	27 at base(ex)	10 at mo 6(ex)	16 at mo 12(ex)				
21 at mo 24(ex)	24 at mo 24(ex) *						

CGI

Date	Trial	Phase	Time	CGI
09DEC1999	INT-57	TRT	BASELINE	MILD
10FEB2000	INT-57	TRT	WEEK 4	MODERATE
09MAR2000	INT-57	TRT	WEEK 8	VERY MILD
06APR2000	INT-57	TRT	WEEK 12	MILD
04MAY2000	INT-57	TRT	WEEK 16	MILD
31MAY2000	INT-57	TRT	WEEK 20	NOT ILL
30JUN2000	INT-57	TRT	WEEK 24	NOT ILL
27JUL2000	INT-57	TRT	WEEK 28	NOT ILL
24AUG2000	INT-57	TRT	WEEK 32	VERY MILD
21SEP2000	INT-57	TRT	WEEK 36	MILD
19OCT2000	INT-57	TRT	WEEK 40	VERY MILD
16NOV2000	INT-57	TRT	WEEK 44	VERY MILD
04DEC2000	INT-57	TRT	WEEK 46	VERY MILD
14DEC2000	INT-57	TRT	WEEK 48	MILD

Risperidone: Effects on Glucose Metabolism
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CGI

Date	Trial	Phase	Time	CGI
28DEC2000	INT-63	FUP	WEEK 2 (EXT.)	VERY MILD
11JAN2001	INT-63	FUP	WEEK 4 (EXT.)	VERY MILD
25JAN2001	INT-63	FUP	WEEK 6 (EXT.)	VERY MILD
15MAR2001	INT-63	FUP	MONTH 3 (EXT.)	VERY MILD
14JUN2001	INT-63	FUP	MONTH 6 (EXT.)	VERY MILD
06SEP2001	INT-63	FUP	MONTH 9 (EXT.)	VERY MILD
13DEC2001	INT-63	FUP	MONTH 12 (EXT.)	VERY MILD
13JUN2002	INT-63	FUP	MONTH 18 (EXT.)	VERY MILD
16DEC2002	INT-63	FUP	MONTH 24 (EXT.)	VERY MILD
09JAN2003	INT-63	FUP	MONTH 24 (EXT.)	VERY MILD

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JNCPRD--TRIAL RIS-INT-063 SAFETY UPDATE (CUT-OFF MARCH 28, 2003)
SERIOUS ADVERSE EVENT SUMMARY

#A30176

Subject: RED #A30176	Investigator: BEAUCLAIR L., MD
Age: 60 years	Previous Trial: INT-57
Race: Caucasian	Previous CRFID: A31216
Sex: male	Term.type(prev.): COMPLETED
Country: CANADA	Depot duration: 863 days
Diagnosis: years	Treatment start: November 16, 2000
Trial term: March 28, 2003	Treatment stop: March 28, 2003
	Term.type(ext.): Continued

Trial termination reason: Cut off date: 28mar2003
treatment1=depot/oral(prev. trial), treatment2=depot(prev. trial),
treatment=depot(INT-57)
follow up=depot(INT-63)
follow up1=double-blind oral ris(INT-63), follow up2=open oral ris(INT-63)
follow up1+2=double-blind+open oral ris(INT-63)

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
*diabetes mellitus trial: INT-63 (unstable diabetes)	severe	not	31NOV02	08NOV02	follow up	716

** days after start treatment

BASELINE SUBJECT DATA

- Diagnosis: paranoid schizophrenia
- Medical and surgical history: dermatological: lymphocytic vasculitis, probably drug induced stasis purpura both legs
- Concomitant disorders: endocrine: diabetes type ii hypothyroidism; eyes: ocular lens: posterior subcapsular cataract; hematological: anemia; neurological: tardive dyskinesia(moderate) akathisia; other: borderline elevated creatinine since 1988-negative investigation in the past; other: hypertension; psychiatric other than trial indication: insomnia
- Physical examination:
extremities int-57 18may2000 abnormal: Dupuytren's syndrome;
extremities int-57 16nov2000 abnormal: Dupuytren's syndrome

TREATMENT DATA:

Trial	Ttr. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
INT-57	RUN-IN	ORAL RIS		18MAY2000	19MAY2000	1	2
INT-57	RUN-IN	ORAL RIS		20MAY2000	21MAY2000	2	2
INT-57	RUN-IN	ORAL RIS		22MAY2000	31MAY2000	4	10
INT-57	TREATMENT	DEPCT/ORAL RIS	1	01JUN2000	14JUN2000	50/4	14
INT-57	TREATMENT	DEPCT/ORAL RIS	2	15JUN2000	16JUN2000	50/3	2
INT-57	TREATMENT	DEPCT/ORAL RIS		17JUN2000	18JUN2000	50/2	2
INT-57	TREATMENT	DEPCT/ORAL RIS		19JUN2000	20JUN2000	50/1	2
INT-57	TREATMENT	DEPCT/ORAL RIS		21JUN2000	28JUN2000	50/0	8
INT-57	TREATMENT	DEPCT/ORAL RIS	3	29JUN2000	12JUL2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	4	13JUL2000	26JUL2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	5	27JUL2000	30AUG2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	6	13AUG2000	23AUG2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	7	24AUG2000	06SEP2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	8	07SEP2000	20SEP2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	9	21SEP2000	04OCT2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	10	05OCT2000	18OCT2000	50/0	14

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TREATMENT DATA:

Trial	Trt. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
INT-57	TREATMENT	DEPCT/ORAL RIS	11	19OCT2000	31NOV2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	12	02NOV2000	32NOV2000	50/0	1
INT-63	FOLLOW UP	RIS DEPOT		16NOV2000	26JUN2002	50	588
INT-63	FOLLOW UP	RIS DEPOT		27JUN2002	21AUG2002	75	56
INT-63	FOLLOW UP2	RIS ORAL		27JUN2002	27JUN2002	2	1
INT-63	FOLLOW UP	RIS DEPOT		22AUG2002	30CCT2002	50	70
INT-63	FOLLOW UP	RIS DEPOT		31OCT2002	28MAR2003	75	149

CLINICAL NARRATIVE

RED(CRF ID A30176) was a white male with a history of paranoid schizophrenia; he was 60-years old at time of study entry. He received treatment with risperidone depot microspheres 50 mg/biweekly during the double-blind study, RIS-INT-57 until he completed the study. The last double-blind risperidone depot 50 mg/biweekly injection was given on 2 November 2000. He entered the open-label extension study RIS-INT-63 on 16 November 2000. During RIS-INT-63, he received varying doses of risperidone depot microspheres 50 mg/biweekly to 75 mg/biweekly.

On 1 November 2002, after 716 days of risperidone depot use during RIS-INT-63, he was hospitalized for the serious adverse event "unstable diabetes" when his caregiver was unable to arouse him. Treatment with activated human insulin, metformin and glibenclamide and oral glucose was initiated. It was found that his caregiver had been non-compliant in giving his medications. The other adverse events that occurred during RIS-INT-63 were "akathisia", "hypercholesteremia", "urinary incontinence during night" (twice), "early wake up confusion", "increased psychotic symptoms" (twice), "occasional stool incontinence", "somnolence", "unstable diabetes" and "urinary incontinence".

Prior medical history is provided in the narrative profile, as are concomitant medications. Relevant concomitant disorders included Type II Diabetes. Physical examination at baseline revealed Dupuytren's syndrome. There were no relevant clinical laboratory data provided for the unstable diabetes. Vital signs, ECG data and clinical laboratory values provided were unrelated to the serious adverse event.

The serious adverse event "unstable diabetes" resolved on 8 November 2002. The "unstable diabetes" was considered severe and not related to study medication by the investigator.

This patient had a history of Type II diabetes. Another episode of "unstable diabetes" was reported as an adverse event from 19 September to 31 October 2002. Hyperglycemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment. However, in this case it was most probably related to the non-compliance with anti-diabetic medication. As such, the sponsor considered a causal relationship between the serious adverse event and the use of risperidone rather unlikely.

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-63

ECG DATA

Date	Trial	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcF (ms)	QTcI (ms)
18MAY2003	INT-57	TRT	BASELINE *	95	180	100	330	415	385	397
01JUN2003	INT-57	TRT	BASELINE	93	170	100	350	436 BL	405	405
16NOV2003	INT-57	TRT	WEEK 24	98	160	100	340	435 BL	400	420
08FEB2001	INT-63	FUP	MO 3(EX)	111 A	180	90	320	435 BL	393	391
17MAY2001	INT-63	FUP	MO 6(EX)	113 A	140	80	340	467 PL	420	412
15NOV2001	INT-63	FUP	MO 12(EX)	96	160	90	330	417	386	388
31OCT2002	INT-63	FUP	MO 24(EX)	89	160	100	360	438 BL	411	410

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

VITAL SIGNS DATA

Date	Trial	Phase	Time	Weight(kg)	BMI	Stand/Supine Pulse (b/min)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
18MAY2003	INT-57	TRT	BASELINE	78	26	112 / 80	110 / 116	80 / 74
16NOV2003	INT-57	TRT	WEEK 24	78	26	104 / 96	104 / 128	70 / 76
08FEB2001	INT-63	FUP	MO 3(EX)			130 / 100	99 / 112	68 / 78
17MAY2001	INT-63	FUP	MO 6(EX)	77	25	138 / 120	94 / 110	64 / 74
15NOV2001	INT-63	FUP	MO 12(EX)	76	25	112 / 96	100 / 116	60 / 70
31OCT2002	INT-63	FUP	MO 24(EX)	73	24	112 / 96	104 / 118	70 / 76

* not included in statistical analysis

CONCOMITANT MEDICATION

Medication Dosage	Trial	Start	End
ferrous sulfate 300 mg tid po	INT-57	before trial	ongoing
glibenclamide 10 mg bid po	INT-57	before trial	ongoing
levolhydroxine sodium 0.075 mg am po	INT-57	before trial	ongoing
metformin hydrochloride 1000 mg bid po	INT-57	before trial	ongoing

Risperidone: Effects on Glucose Metabolism
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CONCOMITANT MEDICATION

Medication Dosage	Trial	Start	End
procyclidine hydrochloride 2.5 mg am po	INT-57	before trial	25MAY2000
valproate semisodium 750 mg hs po	INT-57	before trial	ongoing
valsartan 80 mg od po	INT-57	before trial	ongoing
olanzapine 7.5 mg hs po	INT-57	18MAY2000	19MAY2000
olanzapine 5 mg hs po	INT-57	20MAY2000	21MAY2000
procyclidine hydrochloride 1.25 mg am po	INT-57	26MAY2000	28MAY2000
procyclidine hydrochloride 2.5 mg bid po	INT-57	29JUN2000	ongoing
ferrous sulfate 300mg tid po	INT-63	before trial	30NOV2000
glibenclamide 10mg bid po	INT-63	before trial	31OCT2002
levothyroxine sodium 0.075mg am po	INT-63	before trial	20DEC2000
metformin hydrochloride 1000mg bid po	INT-63	before trial	31OCT2002
procyclidine hydrochloride 2.5mg bid po	INT-63	before trial	08JAN2002
valproate semisodium 750mg hs po	INT-63	before trial	
valsartan 80mg od po	INT-63	before trial	06SEP2001
pravastatin sodium 20mg hs po	INT-63	11DEC2000	03APR2001
levothyroxine sodium 0.088mg od po	INT-63	21DEC2000	
pravastatin 20mg hs po	INT-63	04APR2001	
valsartan 160mg od po	INT-63	07SEP2001	
procyclidine hydrochloride 2.5mg od po	INT-63	10JAN2002	10JAN2002
procyclidine hydrochloride 2.5mg bid po	INT-63	11JAN2002	21AUG2002
pioglitazone 15mg od po	INT-63	26FEB2002	18NOV2002
procyclidine hydrochloride 2.5mg od po	INT-63	22AUG2002	
glibenclamide 5mg od po	INT-63	01NOV2002	01NOV2002
glucose 40 g od po	INT-63	01NOV2002	01NOV2002
metformin 1000mg od po	INT-63	01NOV2002	02NOV2002
glibenclamide 10mg od po	INT-63	02NOV2002	03NOV2002
insulin human 8 u od sc	INT-63	02NOV2002	02NOV2002
insulin human 12 u od sc	INT-63	03NOV2002	03NOV2002
lorazepam 1mg od po	INT-63	03NOV2002	03NOV2002
metformin 1000mg bid po	INT-63	03NOV2002	04NOV2002

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CONCOMITANT MEDICATION

Medication	Trial	Start	End
Dosage			
insulin human			
4 u od sc	INT-63	04NOV2002	04NOV2002
lorazepam			
0.5mg od po	INT-63	04NOV2002	04NOV2002
glibenclamide			
10mg od po	INT-63	05NOV2002	07NOV2002
insulin human			
10u od sc	INT-63	05NOV2002	05NOV2002
metformin			
1000mg am & 500mg pm po	INT-63	05NOV2002	05NOV2002
metformin			
1000mg am & 250mg hs po	INT-63	06NOV2002	06NOV2002
insulin human			
10 u od sc	INT-63	07NOV2002	07NOV2002
metformin			
750mg am & 250mg hs po	INT-63	07NOV2002	07NOV2002
glibenclamide			
7.5mg od po	INT-63	08NOV2002	29DEC2002
metformin			
1000mg am & 250mg hs po	INT-63	08NOV2002	09DEC2002
ferrous gluconate			
324mg bid po	INT-63	16NOV2002	16DEC2002
pioglitazone			
30mg od po	INT-63	19NOV2002	08DEC2002
pioglitazone			
15mg od po	INT-63	09DEC2002	
metformin			
1000mg od po	INT-63	10DEC2002	
glibenclamide			
5mg od po	INT-63	30DEC2002	

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Trial	Severity	Related	Start	End	Phase	Days**
hyperkinesia	INT-57	mild	possibly	02JUN00		treatment	2
(akathisia)							
hyperkinesia	INT-63	mild	possibly	02JUN00		pre trial	-167
(akathisia)							
hypercholesterolaemia	INT-63	mild	not	11DEC00		follow up	26
(hypercholesterolemia)							
urinary incontinence	INT-63	moderate	not	20JUN02	07JUL02	follow up	582
(urinary incontinence during night)							
insomnia	INT-63	moderate	not	27JUN02	05JUL02	follow up	589
(early wake up confusion)							
psychosis	INT-63	mild	not	27JUN02	02JUL02	follow up	589
(increased psychotic symptoms)							
urinary incontinence	INT-63	mild	not	12JUL02	08NOV02	follow up	604
(occasional urinary incontinence during night)							
faecal incontinence	INT-63	mild	not	17AUG02	08NOV02	follow up	640
(occasional stool incontinence)							
somnolence	INT-63	moderate	possibly	17AUG02	05SEP02	follow up	640
(somnolence)							
diabetes mellitus	INT-63	moderate	not	19SEP02	31OCT02	follow up	673
(unstable diabetes)							
psychosis	INT-63	moderate	not	31OCT02	28NOV02	follow up	715
(increased psychotic symptoms)							
urinary incontinence	INT-63	mild	not	18NOV02	18NOV02	follow up	733
(urinary incontinence)							

** days to onset

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CLINICAL LABORATORY TESTS

The following laboratory tests had results outside of normal limits during the trial:

Test (laboratory limits, unit)

alt (sgpt) (1-39 U/L)			
31 at prev base	49 at base(ex)	24 at mo 6(ex)	19 at mo 12(ex)
21 at mo 24(ex)			
creatinine (0.4-1.5 mg/dl)			
1.63 at prev base	1.78 at base(cx)	1.6 at mo 6(cx)	1.7 at mo 12(cx)
1.5 at mo 24(ex)			
eosinophils (0-6 %)			
9 at prev base	1 at base(ex)	1 at mo 6(ex)	0.3 at mo 12(ex)
0.9 at mo 24(ex)			
eggt (10-49 U/L)			
47 aL prev base	63 aL base(ex)	41 aL mo 6(ex)	33 aL mo 12(ex)
20 at mo 24(cx)			
haemoglobin (14-18 g/dl)			
13.7 at prev base	13.7 at base(ex)	13.2 at mo 6(ex)	12.8 at mo 12(ex)
12.6 at mo 24(ex)			
lymphocytes (25-45 %)			
32 at prev base	17 at base(ex)	17.8 at mo 6(ex)	12.8 at mo 12(ex)
24.7 at mo 24(ex)			
monocytes (2-10 %)			
10 at prev base	7 at base(ex)	11.3 at mo 6(ex)	8.2 at mo 12(ex)
10.2 at mo 24(ex)			
neutrophils (50-65 %)			
48 at prev base	75 at base(ex)	69.7 at mo 6(ex)	78.7 at mo 12(ex)
63.9 at mo 24(ex)			
rbc (4.5-6.3 x10E6/mm3)			
4.59 at prev base	4.52 at base(cx)	4.56 at mo 6(cx)	4.42 at mo 12(cx)
4.31 at mo 24(ex)			
urea (20-50 mg/dl)			
47 at prev base	41 at base(ex)	41 at mo 6(ex)	47 at mo 12(ex)
58 at mo 24(ex)			
uric acid (3.5-7 mg/dl)			
4.4 aL prev base	8.3 aL base(ex)	7.6 aL mo 6(ex)	8.7 aL mo 12(ex)
7 at mo 24(cx)			

CGI

Date	Trial	Phase	Time	CGI
18MAY2000	INT-57	TRT	BASELINE	MILD
29JUN2000	INT-57	TRT	WEEK 4	MILD
27JUL2000	INT-57	TRT	WEEK 8	VERY MILD
24AUG2000	INT-57	TRT	WEEK 12	VERY MILD
21SEP2000	INT-57	TRT	WEEK 16	MILD
19OCT2000	INT-57	TRT	WEEK 20	VERY MILD
16NOV2000	INT-57	TRT	WEEK 24	VERY MILD
30NOV2000	INT-63	FUP	WEEK 2 (EXT.)	VERY MILD
14DEC2000	INT-63	FUP	WEEK 4 (EXT.)	VERY MILD
28DEC2000	INT-63	FUP	WEEK 6 (EXT.)	MILD
08FEB2001	INT-63	FUP	MONTH 3 (EXT.)	VERY MILD
17MAY2001	INT-63	FUP	MONTH 6 (EXT.)	VERY MILD
09AUG2001	INT-63	FUP	MONTH 9 (EXT.)	VERY MILD
15NOV2001	INT-63	FUP	MONTH 12 (EXT.)	VERY MILD
02MAY2002	INT-63	FUP	MONTH 18 (EXT.)	VERY MILD
31OCT2002	INT-63	FUP	MONTH 24 (EXT.)	MODERATE

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-63

JNJPRD--TRIAL RIS-INT-63 SAFETY UPDATE (CUT-OFF MARCH 28, 2003)
SERIOUS ADVERSE EVENT SUMMARY

#A30184

Subject: █ #A30184	Investigator: MANCHANDA R., MD
Age: 35 years	Previous trial: INT-57
Race: Caucasian	Previous CRFID: A30316
Sex: male	Term.type(prev.): COMPLETED
Country: CANADA	Depot duration: 913 days
Diagnosis: years	Treatment start: September 27, 2000
Trial term: March 28, 2003	Treatment stop: March 28, 2003
	Term.type(ext.): Continued

Trial termination reason: Cut off date: 28mar2003
treatment1=depot/oral(prev. trial), treatment2=depot(prev. trial),
treatment=depot (INT-57)
follow up=depot (INT-63)
follow up1=double-blind oral ris (INT-63), follow up2=open oral ris (INT-63)
follow up1+2=double-blind+open oral ris (INT-63)

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbalim)	Severity	Related	Start	End	Phase	Days**
*hyperglycaemia Trial: INT-63 (high glucose / diabetes)	moderate	doubtful	21SEP01	15OCT01	follow up	360
*diverticulitis Trial: INT-63 (diverticulitis)	severe	doubtful	09SEP02	11SEP02	follow up	713

** days after start treatment

BASELINE SUBJECT DATA

- Diagnosis: disorganized schizophrenia
- Medical and surgical history: not significant
- Concomitant disorders: hematological: elevated LFT's 1997
- Physical examination:
abdomen int-57 27sep2000 abnormal: obese;
eyes int-57 20sep1999 abnormal: moderate squint r eye- lifelong;
eyes int-57 28mar2000 abnormal: squint lifelong;
general appearance int-57 28mar2000 abnormal: heavy set, overweight;
general appearance int-57 27sep2000 abnormal: obese

TREATMENT DATA:

Trial	Trt. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
INT-57	RUN-IN	ORAL RIS		23SEP1999	27OCT1999	4	15
INT-57	RUN-IN	ORAL RIS		08OCT1999	13OCT1999	4	6
INT-57	TREATMENT	DEPCT/ORAL RIS	1	14OCT1999	14OCT1999	50/4	1
INT-57	TREATMENT	DEPCT/ORAL RIS		15OCT1999	27OCT1999	50/4	13
INT-57	TREATMENT	DEPCT/ORAL RIS	2	28OCT1999	28OCT1999	50/4	1
INT-57	TREATMENT	DEPCT/ORAL RIS		29OCT1999	30NOV1999	50/0	12
INT-57	TREATMENT	DEPCT/ORAL RIS	3	10NOV1999	24NOV1999	50/0	15
INT-57	TREATMENT	DEPCT/ORAL RIS	4	25NOV1999	27DEC1999	50/0	13
INT-57	TREATMENT	DEPCT/ORAL RIS	5	08DEC1999	22DEC1999	50/0	15
INT-57	TREATMENT	DEPCT/ORAL RIS	6	23DEC1999	30JAN2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	7	06JAN2000	20JAN2000	50/0	15
INT-57	TREATMENT	DEPCT/ORAL RIS	8	21JAN2000	31JAN2000	50/0	11
INT-57	TREATMENT	DEPCT/ORAL RIS	9	01FEB2000	16FEB2000	50/0	16
INT-57	TREATMENT	DEPCT/ORAL RIS	10	17FEB2000	29FEB2000	50/0	13
INT-57	TREATMENT	DEPCT/ORAL RIS	11	01MAR2000	15MAR2000	50/0	15

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-63

TREATMENT DATA:

Trial	Trt. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
INT-57	TREATMENT	DEPCT/ORAL RIS	12	16MAR2000	27MAR2000	50/3	12
INT-57	TREATMENT	DEPCT/ORAL RIS	13	28MAR2000	12APR2000	50/3	16
INT-57	TREATMENT	DEPCT/ORAL RIS	14	13APR2000	25APR2000	50/3	13
INT-57	TREATMENT	DEPCT/ORAL RIS	15	26APR2000	10MAY2000	50/3	15
INT-57	TREATMENT	DEPCT/ORAL RIS	16	11MAY2000	23MAY2000	50/3	13
INT-57	TREATMENT	DEPCT/ORAL RIS	17	24MAY2000	37JUN2000	50/3	15
INT-57	TREATMENT	DEPCT/ORAL RIS	18	08JUN2000	20JUN2000	50/3	13
INT-57	TREATMENT	DEPCT/ORAL RIS	19	21JUN2000	35JUL2000	50/3	15
INT-57	TREATMENT	DEPCT/ORAL RIS	20	06JUL2000	19JUL2000	50/3	14
INT-57	TREATMENT	DEPCT/ORAL RIS	21	20JUL2000	31JUL2000	50/3	12
INT-57	TREATMENT	DEPCT/ORAL RIS	22	01AUG2000	16AUG2000	50/3	16
INT-57	TREATMENT	DEPCT/ORAL RIS	23	17AUG2000	34SEP2000	50/3	19
INT-57	TREATMENT	DEPCT/ORAL RIS	24	05SEP2000	14SEP2000	50/3	10
INT-57	TREATMENT	DEPCT/ORAL RIS	25	15SEP2000	15SEP2000	50/3	1
INT-63	FOLLOW UP	RIS DEPOT		27SEP2000	28MAR2003	50	913

CLINICAL NARRATIVE

RED(CRF ID A30184) was a white male with a history of disorganized schizophrenia; he was 35-years old at the time of study entry. He received treatment with risperidone microspheres depot 50 mg/biweekly during the double-blind study, RIS-INT-57, until he completed the study. The last double-blind risperidone depot was given on 15 September 2000. He entered the open-label extension study on 27 September 2000. During RIS-INT-63, he received risperidone depot 50 mg/biweekly injections.

On 21 September 2001, while receiving risperidone depot 50 mg/biweekly injection, he was hospitalized with "high glucose/diabetes". Treatment with insulin human injection isophane was initiated. Glucose values at this time were not available. This serious adverse event occurred 360 days after the start of treatment with risperidone depot injections in RIS-INT-63.

On 9 September 2002, while receiving risperidone depot 50 mg/biweekly injection, he was hospitalized with "diverticulitis". Treatment with metronidazole, paracetamol, ciprofloxacin and cloxacillin was initiated. This serious adverse event occurred 713 days after the start of treatment with risperidone injections in RIS-INT-63.

Prior medical history was unremarkable. Concomitant disorders are provided in the narrative profile. Concomitant medications are provided in the narrative profile. Physical examination at baseline revealed obesity. Clinical laboratory data and vital signs were unrelated to the serious adverse event.

The serious adverse event of "high glucose/diabetes" resolved on 15 October 2001. It was considered by the investigator to be moderate in severity and doubtfully related to study treatment. The second serious adverse event "diverticulitis" was considered severe and doubtfully related to study treatment.

This patient was not known to have a history of diabetes. Hyperglycemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment. The sponsor considered a causal relationship between the serious adverse event "high glucose/diabetes" and the use of risperidone can not be excluded. The sponsor considered a causal relationship between the serious adverse event "diverticulitis" and the use of risperidone highly unlikely. Risperidone depot injections were continued at the same dose.

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-63

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Date	Trial	Phase	Time	FR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcF (ms)	QTcI (ms)
20SEP1999	INT-57	TRT	BASELINE *	51	180	120	* 420	387	398	393
14OCT1999	INT-57	TRT	BASELINE	60	170	120	* 410	410	410	410
28MAR2000	INT-57	TRT	WEEK 24	65	160	120	* 350	364	359	362
18JAN2001	INT-63	FUP	MO 6(EX) *	53	190	120	* 390	367	374	370
27MAR2001	INT-63	FUP	MO 6(EX)	55	170	110	370	354	359	356
12SEP2001	INT-63	FUP	MO 12(EX)	60	170	110	380	380	380	380
11SEP2002	INT-63	FUP	MO 24(EX)	51	190	120	* 420	387	398	393

(A=Above normal B=Below normal *=Abnormal BL=Borderline PI=Prolonged).

VITAL SIGNS DATA

Date	Trial	Phase	Time	Weight(kg)	BMI	Stand/Supine Pulse (b/min)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
20SEP1999	INT-57	TRT	BASELINE	138	42	68 / 72	130 / 128	80 / 78
28MAR2000	INT-57	TRT	WEEK 24	146	44	88 / 88	128 / 128	76 / 78
27SEP2000	INT-57	TRT	WEEK 50	150	45	84 / 80	140 / 140	76 / 80
20DEC2000	INT-63	FUP	MO 3(EX)			72 / 68	128 / 130	76 / 72
27MAR2001	INT-63	FUP	MO 6(EX)	149	45	72 / 64	140 / 144	80 / 82
12SEP2001	INT-63	FUP	MO 12(EX)	148	45	/ 64	158 / 140	100 / 80
11SEP2002	INT-63	FUP	MO 24(EX)	137	41	60 / 60	150 / 148	74 / 90

* not included in statistical analysis

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-63

CONCOMITANT MEDICATION

Medication Dosage	Trial	Start	End
sertraline hydrochloride 200 mg po od	INT-57	before trial	ongoing
amoxicillin 500 mg tid	INT-57	18DEC1999	28DEC1999
sertraline hydrochloride 200mg po od	INT-63	before trial	
ceftiofur 250mg tid	INT-63	06APR2001	16APR2001
insulin human injection, isophane 36u. hs.sc	INT-63	01OCT2001	13DEC2001
novolin 20/80 s.c. sliding scale	INT-63	04OCT2001	05OCT2001
bisacodyl tabst prn	INT-63	05OCT2001	08OCT2001
insulin lispro s.c. sliding scale	INT-63	05OCT2001	24NOV2001
fenclofenac tabs 1 od	INT-63	06OCT2001	
insulin human injection, isophane 20 u.s.c.,h.s.	INT-63	06OCT2001	06OCT2001
insulin human injection, isophane 26 u.s.c.,h.s.	INT-63	07OCT2001	09OCT2001
ramipril 2.5mg od po	INT-63	08OCT2001	
insulin human injection, isophane 30u hs.sc	INT-63	09OCT2001	11OCT2001
glibenclamide 5mg bid	INT-63	25NOV2001	10JAN2002
metformin 500mg bid	INT-63	25NOV2001	12MAR2002
insulin human injection, isophane 20 u hs	INT-63	14DEC2001	27DEC2001
glibenclamide	INT-63	11JAN2002	05FEB2002
metformin 500mg od	INT-63	13MAR2002	
phenoxymethylpenicillin	INT-63	23APR2002	01MAY2002
tooth extraction	INT-63	23APR2002	21MAY2002
lylenol no 3 q4hrs	INT-63	23APR2002	05MAY2002
ciprofloxacin	INT-63	09SEP2002	
metronidazole	INT-63	09SEP2002	10SEP2002
paracetamol Tabs 2 - qid po	INT-63	09SEP2002	09SEP2002
ciprofloxacin 400mg iv q 12h	INT-63	10SEP2002	11SEP2002
cloxacillin 500mg bid	INT-63	11SEP2002	16SEP2002
metronidazole	INT-63	11SEP2002	16SEP2002

Risperidone: Effects on Glucose Metabolism
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OTHER ADVERSE EVENTS

Adverse event (verbatim)	Trial	Severity	Related	Start	End	Phase	Days**
lab values abnormal (elevated lab results)	INT-57	moderate	possibly	21SEP99	12OCT99	pre trial	-23
upper resp tract infection (upper respiratory infection)	INT-57	mild	not	18DEC99	28DEC99	treatment	66
dizziness (dizziness)	INT-57	mild	possibly	06JAN00	06JAN00	treatment	85
hepatomegaly (enlarged liver)	INT-57	mild	possibly	01FEB00		treatment	111
hepatomegaly (enlarged fatty liver)	INT-63	mild	not	01FEB00		pre trial	-239
bundle branch block (ecg-left posterior hemi block)	INT-63	mild	not	18JAN01		follow up	114
ecg abnormal (right axis deviation)	INT-63	mild	not	18JAN01		follow up	114
hypertension: pulmonary (pulmonary hypertension)	INT-63	mild	not	18JAN01		follow up	114
rhinitis (cold symptoms)	INT-63	mild	not	03APR01	15APR01	follow up	189
hypertension (exercise induced hypertension)	INT-63	moderate	not	20AUG01	20AUG01	follow up	328
vision abnormal (elevated vision (long distance))	INT-63	mild	not	05SEP01	24OCT01	follow up	344
glycosuria (glucosuria)	INT-63	moderate	not	27SEP01	31OCT01	follow up	366
hypercholesterolaemia (elevated cholesterol)	INT-63	mild	not	01CCT01		follow up	370
tooth disorder (cracked tooth)	INT-63	mild	not	23APR02	21MAY02	follow up	574
gastritis (stomach flu)	INT-63	mild	not	10JAN03	18JAN03	follow up	836
rhinitis (head cold)	INT-63	mild	not	11JAN03	18JAN03	follow up	837

** days to onset

Risperidone: Effects on Glucose Metabolism
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CLINICAL LABORATORY TESTS

The following laboratory tests had results outside of normal limits during the trial:

Test (laboratory limits, unit)

alt (agpt) (1-39 U/L)			
108 at prev base	158 at base(ex)	117 at mo 6(ex)	128 at mo 12(ex)
59 at mo 24(ex)			
ast (agot) (1-39 U/L)			
44 at prev base	86 at base(ex)	52 at mo 6(ex)	69 at mo 12(ex)
39 at mo 24(ex)			
chloride (96-110 meq/l)			
101 at prev base	130 at base(ex)	102 at mo 6(ex)	94 at mo 12(ex)
101 at mo 24(ex)			
eosinophils (0-6 %)			
7 at prev base	6 at base(ex)	4.8 at mo 6(ex)	4.4 at mo 12(ex)
5.8 at mo 24(ex)			
lymphocytes (20-45 %)			
20 at prev base	17 at base(ex)	20.7 at mo 6(ex)	15.1 at mo 12(ex)
19.4 at mo 24(ex)			
monocytes (2-10 %)			
8 at prev base	4 at base(ex)	10.1 at mo 6(ex)	6.8 at mo 12(ex)
9.6 at mo 24(ex)			
neutrophils (50-65 %)			
64 at prev base	73 at base(ex)	64.1 at mo 6(ex)	72.9 at mo 12(ex)

The following laboratory tests had results outside of normal limits during the trial:

Test (laboratory limits, unit)

64.8 at mo 24(ex)			
sodium (136-148 meq/l)			
135 at prev base	136 at base(ex)	137 at mo 6(ex)	131 at mo 12(ex)
135 at mo 24(ex)			

CGI

Date	Trial	Phase	Time	CGI
20SEP1999	INT-57	TRT	BASELINE	MILD
10NOV1999	INT-57	TRT	WEEK 4	VERY MILD
08DEC1999	INT-57	TRT	WEEK 8	VERY MILD
06JAN2000	INT-57	TRT	WEEK 12	VERY MILD
01FEB2000	INT-57	TRT	WEEK 16	VERY MILD
01MAR2000	INT-57	TRT	WEEK 20	VERY MILD
28MAR2000	INT-57	TRT	WEEK 24	VERY MILD
26APR2000	INT-57	TRT	WEEK 28	VERY MILD
24MAY2000	INT-57	TRT	WEEK 32	VERY MILD
21JUN2000	INT-57	TRT	WEEK 36	VERY MILD
20JUL2000	INT-57	TRT	WEEK 40	VERY MILD
17AUG2000	INT-57	TRT	WEEK 44	VERY MILD
15SEP2000	INT-57	TRT	WEEK 48	VERY MILD
27SEP2000	INT-57	TRT	WEEK 50	VERY MILD
13OCT2000	INT-63	FUF	WEEK 2 (EXT.)	VERY MILD
25OCT2000	INT-63	FUF	WEEK 4 (EXT.)	VERY MILD
08NOV2000	INT-63	FUF	WEEK 6 (EXT.)	VERY MILD
20DEC2000	INT-63	FUF	MONTH 3 (EXT.)	VERY MILD
27MAR2001	INT-63	FUF	MONTH 6 (EXT.)	VERY MILD
20JUN2001	INT-63	FUF	MONTH 9 (EXT.)	VERY MILD
12SEP2001	INT-63	FUF	MONTH 12 (EXT.)	VERY MILD
27MAR2002	INT-63	FUF	MONTH 18 (EXT.)	VERY MILD
11SEP2002	INT-63	FUF	MONTH 24 (EXT.)	VERY MILD
25MAR2003	INT-63	FUF	MONTH 30 (EXT.)	VERY MILD

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-63

JNJPRD--TRIAL RIS-INT-63 SAFETY UPDATE (CUT-OFF MARCH 28, 2003)
SERIOUS ADVERSE EVENT SUMMARY

#A30468

Subject: RED #A30468	Investigator: WESTERS L., MD
Age: 48 years	Previous Trial: INT-57
Race: Caucasian	Previous CRFID: A30493
Sex: female	Term.type(prev.): COMPLETED
Country: GERMANY	Depot duration: 1E3 days
Diagnosis: years	Treatment start: April 23, 2000
Trial term: January 21, 2003	Treatment stop: January 21, 2003
	Term.type(ext.): Completed

Trial termination reason:
treatment1=depot/oral(prev. trial), treatment2=depot(prev. trial),
treatment=depot(INT-57)
follow up=depot(INT-63)
follow up1=double-blind oral ris(INT-63), follow up2=open oral ris(INT-63)
follow up1+2=double-blind+open oral ris(INT-63)

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
*hyperglycaemia	mild	not	22JUL02	01AUG02	follow up	824
trial: INT-63 (planned hospitalization, new insulin plan long term regulation of the diabetes)						

** days after start treatment

BASELINE SUBJECT DATA

- Diagnosis: schizoaffective disorder
- Medical and surgical history: musculoskeletal: spondylosis deformans cervical spine;
gastrointestinal: cholecystectomy, data not available
- Concomitant disorders: cardiovascular: hypertension; endocrine: diabetes mellitus,
hypercholesterinaemia; musculoskeletal: hip malformation left; osteoporosis; psychiatric
other than trial indication: depression, sleeping disorder
- Physical examination:
general appearance int-57 04may1999 abnormal: obesitas;
general appearance int-57 21oct1999 abnormal: obesitas;
general appearance int-57 20apr2000 abnormal: obesitas;
general appearance int-63 21jan2003 abnormal: adipositas;
musculoskeletal int-57 04may1999 abnormal: hip malformation left;
musculoskeletal int-57 21oct1999 abnormal: hip malformation left side;
musculoskeletal int-57 20apr2000 abnormal;;
musculoskeletal int-63 21jan2003 abnormal: hip malformation left side

TREATMENT DATA:

Trial	Treat. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
INT-57	RUN-IN	ORAL RIS		04MAY1999	05MAY1999	4	2
INT-57	TREATMENT	DEPCT/ORAL RIS	1	06MAY1999	19MAY1999	50/4	14
INT-57	TREATMENT	DEPCT/ORAL RIS	2	20MAY1999	20MAY1999	50/4	1
INT-57	TREATMENT	DEPCT/ORAL RIS		21MAY1999	02JUN1999	50/0	13
INT-57	TREATMENT	DEPCT/ORAL RIS	3	03JUN1999	16JUN1999	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	4	17JUN1999	30JUN1999	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	5	01JUL1999	14JUL1999	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	6	15JUL1999	28JUL1999	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	7	29JUL1999	11AUG1999	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	8	12AUG1999	25AUG1999	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	9	26AUG1999	08SEP1999	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	10	09SEP1999	22SEP1999	50/0	14

Risperidone: Effects on Glucose Metabolism
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TREATMENT DATA:

Trial	Trt. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
INT-57	TREATMENT	DEPCT/ORAL RIS	11	23SEP1999	06CCT1999	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	12	07OCT1999	20CCT1999	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	13	21OCT1999	03NOV1999	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	14	01NOV1999	17NOV1999	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	15	18NOV1999	01DEC1999	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	16	02DEC1999	15DEC1999	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	17	16DEC1999	29DEC1999	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	18	30DEC1999	12JAN2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	19	13JAN2000	26JAN2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	20	27JAN2000	09FEB2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	21	10FEB2000	23FEB2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	22	24FEB2000	08MAR2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	23	09MAR2000	22MAR2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	24	23MAR2000	05APR2000	50/0	14
INT-57	TREATMENT	DEPCT/ORAL RIS	25	06APR2000	06APR2000	75/0	1
INT-63	FOLLOW UP	RIS DEPOT		20APR2000	21JAN2003	50	1007

CLINICAL NARRATIVE:

RED (CRF ID #A30468) was a white female with a history of schizoaffective disorder; she was 48-years old at time of study entry. She received treatment during the open-label study RIS-INT-57 with risperidone microspheres depot injections 50mg/biweekly 24 times and risperidone depot injection 75 mg/biweekly once, until she completed the study. She entered the open-label extension study RIS-INT-63 on 20 April 2000. During RIS-INT-63, she received risperidone depot injection 50 mg/biweekly. The patient completed the study on 21 January 2003.

On 22 July 2002, after 824 days of risperidone depot use, a planned hospitalization for a "new insulin plan long term regulation of the diabetes" occurred. She had a history of obesity (grade II) and had insulin dependent diabetes for seven years. Her concomitant insulins were discontinued and she received furosemide, insulin aspart and insulin human isophane. The other adverse event reported during RIS-INT-63 was "worsening blood sugar-insulin necessary".

Prior medical history, concomitant disorders and concomitant medications are provided in the narrative profile. Physical examination is provided in the narrative profile. Vital signs and clinical laboratory values were unrelated to the serious adverse event, ECG findings were unremarkable.

The serious adverse event "planned hospitalization, new insulin plan long term regulation of the diabetes" resolved on 1 August 2002. It was considered by the investigator to be mild and not related to study medication.

This patient was known with concomitant insulin dependent diabetes. Hyperglycemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment. The sponsor considered a causal relationship between the serious adverse event and the use of risperidone can not be excluded.

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-63

ECG DATA

Date	Trial	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcF (ms)	QTcL (ms)
21OCT1999	INT-57	TRT	WEEK 24	100 A	170	90	370	478 PL	439	432
20APR2000	INT-57	TRT	WEEK 50	90	170	90	330	404	378	381
25JUL2000	INT-63	FUP	MO 3 (EX)	85	180	90	370	440	416	415
19OCT2000	INT-63	FUP	MO 6 (EX)	95	190	100	350	440	408	407
17APR2001	INT-63	FUP	MO 12 (EX)	78	170	90	380	433	415	416
16APR2002	INT-63	FUP	MO 24 (EX)	88	170	100	340	412	386	389
21JAN2003	INT-63	FUP	MO 36 (EX)	95	190	90	340	428	396	397

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

VITAL SIGNS DATA

Date	Trial	Phase	Time	Weight(kg)	BMI	Stand/Supine Pulse (b/min)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
04MAY1999	INT-57	TRT	BASELINE	95	39	100 / 88	110 / 110	70 / 70
21OCT1999	INT-57	TRT	WEEK 24	100	41	74 / 72	130 / 140	90 / 90
20APR2000	INT-57	TRT	WEEK 50	101	42	74 / 72	135 / 145	90 / 90
25JUL2000	INT-63	FUP	MO 3 (EX)			88 / 80	115 / 130	100 / 100
19OCT2000	INT-63	FUP	MO 6 (EX)	100	41	98 / 130	135 / 140	80 / 80
17APR2001	INT-63	FUP	MO 12 (EX)	97	40	88 / 68	130 / 140	90 / 75
16APR2002	INT-63	FUP	MO 24 (EX)	99	41	80 / 130	140 / 190	90 / 130
21JAN2003	INT-63	FUP	MO 36 (EX)	99	41	90 / 84	125 / 150	80 / 90

* not included in statistical analysis

Risperidone: Effects on Glucose Metabolism
 AE Narratives RIS-INT-63

CONCOMITANT MEDICATION

Medication Dosage	Trial	Start	End
atorvastatin calcium 10 mg od po	INT-57	before trial	ongoing
bisoprolol fumarate 5 mg od po	INT-57	before trial	ongoing
cyclo-progyrova 1 dragee od po	INT-57	before trial	ongoing
dibenzepin hydrochloride 480 mg od po	INT-57	before trial	ongoing
enalapril maleate 10 mg od po	INT-57	before trial	ongoing
fluvoxamine maleate 100 mg od po	INT-57	before trial	ongoing
furosemide 40 mg bid po	INT-57	before trial	ongoing
moxonidine 0.3 mg bid po	INT-57	before trial	ongoing
nifedipine 20 mg od po	INT-57	before trial	ongoing
zopiclone 15 mg od po	INT-57	before trial	ongoing
phenoxymethylpenicillin 1.2 me bid po	INT-57	25JUN1999	30JUN1999
doxycycline monohydrate 200 mg od po	INT-57	09AUG1999	18AUG1999
diclofenac 25 mg im od	INT-57	18AUG1999	23AUG1999
atorvastatin calcium 10mg od po	INT-63	before trial	ongoing
bisoprolol fumarate 5mg od po	INT-63	before trial	ongoing
cyclo-progyrova 1 drag od po	INT-63	before trial	ongoing
dibenzepin hydrochloride 480mg od po	INT-63	before trial	ongoing
enalapril maleate 10mg od po	INT-63	before trial	01AUG2002
fluvoxamine maleate 100mg od po	INT-63	before trial	ongoing
furosemide 40mg bid po	INT-63	before trial	22JUL2002
moxonidine 0.3mg bid po	INT-63	before trial	ongoing
nifedipine 20mg od po	INT-63	before trial	ongoing
zopiclone 15mg od po	INT-63	before trial	ongoing
insulin human 1x20e sc	INT-63	23JUN2000	31JUL2002
insulin human injection, isophane 1x42e sc	INT-63	23JUN2000	31JUL2002
furosemide 60mg po	INT-63	23JUL2002	ongoing
enalapril 10mg od po	INT-63	01AUG2002	ongoing
insulin aspart 10u-0-38u sc bid	INT-63	01AUG2002	ongoing
insulin isophane human semisynthetic sc	INT-63	01AUG2002	ongoing

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-63

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Trial	Severity	Related	Start	End	Phase	Days**
pharyngitis (tonsillitis)	INT-57	mild	not	23JUN99	03JUL99	treatment	49
skin disorder (infection ad area after insectbite right leg)	INT-57	mild	not	08AUG99	17AUG99	treatment	95
back pain (backache)	INT-57	moderate	not	18AUG99	23AUG99	treatment	105
injection site pain (induration and pain right buttock)	INT-57	mild	not	23AUG99	06OCT99	treatment	110
injection site pain (induration and pain right buttock)	INT-57	mild	doubtful	09MAR00	22MAR00	treatment	309
hyperglycaemia (worsening blood sugar levels -> insulin necessary)	INT-63	mild	not	23JUN00		follow up	65

** days to onset

CLINICAL LABORATORY TESTS

The following laboratory tests had results outside of normal limits during the trial:

Test (laboratory limits, unit)

alkaline phosphatase (31-121 U/L)			
280 at prev base	156 at base(ex)	214 at mo 6(ex)	192 at mo 12(ex)
220 at mo 24(ex)	121 at mo 36(ex)		
alt (sgpt) (1-30 U/L)			
44 at prev base	35 at base(ex)	33 at mo 6(ex)	35 at mo 12(ex)
44 at mo 24(ex)	31 at mo 36(ex)		
ast (sgot) (1-32 U/L)			
26 at prev base	44 at base(ex)	19 at mo 6(ex)	21 at mo 12(ex)
28 at mo 24(ex)	21 at mo 36(ex)		
chloride (96-110 meq/l)			
95 at prev base	97 at base(ex)	103 at mo 6(ex)	102 at mo 12(ex)
97 at mo 24(ex)	104 at mo 36(ex)		
eosinophils (0-6 %)			
3.3 at prev base	3.2 at base(ex)	7.3 at mo 6(ex)	4 at mo 12(ex)
2.2 at mo 24(ex)	3 at mo 36(ex)		
cgt (6-32 U/L)			
126 at prev base	137 at base(ex)	109 at mo 6(ex)	98 at mo 12(ex)
135 at mo 24(ex)	60 at mo 36(ex)		
lactate dehydrogenase (77-296 U/L)			
182 at prev base	433 at base(ex)	162 at mo 6(ex)	149 at mo 12(ex)
176 at mo 24(ex)	185 at mo 36(ex)		
lymphocytes (25-45 %)			
21.5 at prev base	19.4 at base(ex)	22.2 at mo 6(ex)	22.4 at mo 12(ex)
21.8 at mo 24(ex)	12.9 at mo 36(ex)		
neutrophils (50-65 %)			
70.4 at prev base	73.6 at base(ex)	66.7 at mo 6(ex)	68.8 at mo 12(ex)
67.7 at mo 24(ex)	79.4 at mo 36(ex)		
sodium (136-148 meq/l)			
136 at prev base	133 at base(ex)	140 at mo 6(ex)	139 at mo 12(ex)
139 at mo 24(ex)	160 at mo 36(ex)		
uric acid (2.5-6 mg/dl)			
7.4 at prev base	5.8 at base(ex)	6.7 at mo 6(ex)	5.8 at mo 12(ex)
6.7 at mo 24(ex)	6.8 at mo 36(ex)		

Risperidone: Effects on Glucose Metabolism
 AE Narratives RIS-INT-63

CGI

Date	Trial	Phase	Time	CGI
C4MAY1999	INT-57	TRT	BASELINE	VERY MILD
C3JUN1999	INT-57	TRT	WEEK 4	NOT ILL
C1JUL1999	INT-57	TRT	WEEK 8	NOT ILL
29JUL1999	INT-57	TRT	WEEK 12	VERY MILD
26AUG1999	INT-57	TRT	WEEK 16	NOT ILL
23SEP1999	INT-57	TRT	WEEK 20	NOT ILL
21OCT1999	INT-57	TRT	WEEK 24	VERY MILD
18NOV1999	INT-57	TRT	WEEK 28	NOT ILL
16DEC1999	INT-57	TRT	WEEK 32	NOT ILL
13JAN2000	INT-57	TRT	WEEK 36	NOT ILL
10FEB2000	INT-57	TRT	WEEK 40	NOT ILL
C9MAR2000	INT-57	TRT	WEEK 44	NOT ILL
C6APR2000	INT-57	TRT	WEEK 48	NOT ILL
20APR2000	INT-57	TRT	WEEK 50	NOT ILL
C2MAY2000	INT-63	FUP	WEEK 2 (EXT.)	NOT ILL
16MAY2000	INT-63	FUP	WEEK 4 (EXT.)	VERY MILD
30MAY2000	INT-63	FUP	WEEK 6 (EXT.)	VERY MILD
25JUL2000	INT-63	FUP	MONTH 3 (EXT.)	VERY MILD
19OCT2000	INT-63	FUP	MONTH 6 (EXT.)	VERY MILD
C6FEB2001	INT-63	FUP	MONTH 9 (EXT.)	VERY MILD
17APR2001	INT-63	FUP	MONTH 12 (EXT.)	VERY MILD
16OCT2001	INT-63	FUP	MONTH 18 (EXT.)	VERY MILD
16APR2002	INT-63	FUP	MONTH 24 (EXT.)	VERY MILD
C6AUG2002	INT-63	FUP	MONTH 30 (EXT.)	VERY MILD
21JAN2003	INT-63	FUP	MONTH 36 (EXT.)	VERY MILD

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-63

JNC PRD--TRIAL RIS-INT-063 SAFETY UPDATE (CUT-OFF MARCH 28, 2003)
SERIOUS ADVERSE EVENT SUMMARY

#A30767

Subject: RED #A30767	Investigator: ERIKSSON L., MD
Age: 63 years	Previous Trial: INT-61
Race: Caucasian	Previous CRFID: A30947
Sex: female	Term.type(prev.): SUBJECT WITHDREW CONSENT
Country: SWEDEN	Depot duration: 911 days
Diagnosis: 34 years	Treatment start: September 29, 2000
Trial term: March 28, 2003	Treatment stop: March 28, 2003
	Term.type(ext.): Continued

Trial termination reason: Cut off date: 28mar2003
treatment1=depot/oral(prev. trial), treatment2=depot(prev. trial),
treatment=depot (INT-57)
follow up=depot (INT-63)
follow up1=double-blind oral ris (INT-63), follow up2=open oral ris (INT-63)
follow up1+2=double-blind+open oral ris (INT-63)

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbalim)	Severity	Related	Start	End	Phase	Days**
*hyperglycemia trial: INT-63 (hyperglycemia)	moderate	doubtful	26JAN02	29JAN02	follow up	485

** days after start treatment

BASELINE SUBJECT DATA

- Diagnosis: undifferentiated schizophrenia
- Medical and surgical history: musculoskeletal: back pain; gastrointestinal: gallstones
; psychiatric other than trial indication: anxiety
- Concomitant disorders: neurological: slight EPS; cardiovascular: hypertension;
allergic/immunologic: cat; psychiatric other than trial indication: insomnia
- Physical examination:
abdomen int-61 24may2000 abnormal: old scar after operation;
general appearance int-61 24may2000 abnormal: obese;
general appearance int-61 29sep2000 abnormal: obese;
heart int-61 24may2000 abnormal: hypertension;
heart int-61 29sep2000 abnormal: hypertension;
neurological int-61 29sep2000 abnormal: slight EPS;
other int-61 24may2000 abnormal: slight EPS

TREATMENT DATA:

Trial	Ttl. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
INT-61	RUN-IN	RIS ORAL		24MAY2000	04JUN2000	2	12
INT-61	RUN-IN	RIS ORAL		05JUN2000	19JUN2000	2	15
INT-61	RUN-IN	RIS ORAL		20JUN2000	17JUL2000	2	28
INT-61	TREATMENT1	PL DEP/RIS ORAL	1	18JUL2000	31JUL2000	0/2	14
INT-61	TREATMENT1	PL DEP/RIS ORAL	2	01AUG2000	07AUG2000	0/2	7
INT-61	TREATMENT2	PL DEP/RIS ORAL		08AUG2000	14AUG2000	0/2	7
INT-61	TREATMENT2	PL DEP/RIS ORAL	3	15AUG2000	28AUG2000	0/2	14
INT-61	TREATMENT2	PL DEP/RIS ORAL	4	29AUG2000	10SEP2000	0/2	13
INT-61	TREATMENT2	PL DEP/RIS ORAL	5	11SEP2000	17SEP2000	0/2	7
INT-61	TREATMENT2	PL DEP/RIS ORAL		18SEP2000	20SEP2000	0/0	3
INT-61	TREATMENT2	PL DEP/RIS ORAL		21SEP2000	26SEP2000	0/2	6
INT-63	FOLLOW UP	RIS DEPOT		29SEP2000	16CCT2000	50	18
INT-63	FOLLOW UP1	RIS ORAL		29SEP2000	16CCT2000	2	18
INT-63	FOLLOW UP	RIS DEPOT		17OCT2000	28MAR2003	25	893

CLINICAL NARRATIVE

RED (CRF ID A30767) was a white female with a 34-year history of undifferentiated schizophrenia; she was 63-years old at the time of study entry. She received treatment with placebo injections five times during the double blind study, RIS-INT-61, until she discontinued the study when she withdrew her consent. She entered the open-label extension study RIS-INT-63 on 29 September 2000. During RIS-INT-63, she received risperidone microspheres depot injections 50 mg/biweekly followed by risperidone depot 25 mg/biweekly.

On 26 January 2002, after 485 days of risperidone depot use, the serious adverse event "hyperglycemia" occurred that required her hospitalization. Glucose values at the time are not available; no elevated glucose values were reported during the trial. During RIS-INT-63, the other adverse events "low value of potassium", "increased creatine level", "flu", "cold", "high cholesterol" and "diabetes" occurred as well as the event "increased psychotic symptoms" that had not resolved prior to the start of RIS-INT-63.

Prior medical history, concomitant disorders and concomitant medications are provided in the narrative profile. According to the CIOMS, the patient was known to have a diagnosis of diabetes mellitus. Physical examination is provided in the narrative profile. Vital signs and ECG data were unremarkable.

The serious adverse event of "hyperglycemia" resolved on 29 January 2002. The "hyperglycemia" was considered moderate in severity by the investigator and doubtfully related to study medication.

According to the CIOMS, this patient was reported to have a diagnosis of diabetes mellitus, and a mild episode of "diabetes mellitus" was reported as an adverse event with start date 13 August 2001. No end date was provided for this adverse event.

Hyperglycemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment. The sponsor considered a causal relationship between this serious adverse event and the use of risperidone can not be excluded. Risperidone depot injections were continued at the same dose.

ECG DATA

Date	Trial	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcF (ms)	QTcI (ms)
24MAY2000	INT-61	TRT	SCREENING	66	210	A 80	400	420	413	414
18JUN2000	INT-61	TRT	BASELINE	63	220	A 110	360	369	366	367
15AUG2000	INT-61	TRT	WEEK 4	61	200	80	430	434	432	433
29SEP2000	INT-61	TRT	WEEK 10	75	180	80	390	436	420	421
19DEC2000	INT-63	FUP	MO 3 (EX)	57	200	90	450	439	442	442
28MAR2001	INT-63	FUP	MO 6 (EX)	66	200	90	410	430	423	424
25SEP2001	INT-63	FUP	MO 12 (EX)	68	130	90	420	447	438	438

(A=Above normal H=Below normal *=Abnormal BL=Borderline PL=Prolonged)

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-63

VITAL SIGNS DATA

Date	Trial	Phase	Time	Weight (kg)	BMI	Stand/Supine Pulse (b/min)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
24MAY2003	INT-61	TRT	SCREENING	92	30	96 / 68	160 / 210	90 / 95
18JUL2003	INT-61	TRT	BASELINE	88	29	78 / 72	165 / 210	120 / 120
15AUG2003	INT-61	TRT	WEEK 4			72 / 68	170 / 180	105 / 110
29SEP2003	INT-61	TRT	WEEK 10	87	29	88 / 72	180 / 185	85 / 110
19DEC2003	INT-63	FUP	MO 3(EX)			61 / 58	193 / 225	106 / 110
28MAR2001	INT-63	FUP	MO 6(EX)	92	30	75 / 69	190 / 215	105 / 93
25SEP2001	INT-63	FUP	MO 12(EX)	92	30	78 / 70	185 / 205	95 / 95
10OCT2002	INT-63	FUP	MO 24(EX)	93	31	80 / 68	140 / 135	80 / 80

* not included in statistical analysis

CONCOMITANT MEDICATION

Medication Dosage	Trial	Start	End
hydroxyzine hydrochloride 25 mg prn	INT-61	before trial	ongoing
losartan potassium 50 mg od	INT-61	before trial	ongoing
orphenadrine hydrochloride 100 mg prn	INT-61	before trial	ongoing
propranolol 160 mg, od	INT-61	before trial	ongoing
zopiclone 5 mg, od	INT-61	before trial	ongoing
hydroxyzine hydrochloride 25mg prn	INT-63	before trial	26MAR2002
losartan potassium 50mg o.d	INT-63	before trial	17SEP2001
orphenadrine hydrochloride 100mg prn	INT-63	before trial	
propiomazine maleate 25mg 2st od	INT-63	before trial	
propranolol hydrochloride 160mg o.d.	INT-63	before trial	
zopiclone 5mg o.d	INT-63	before trial	

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-63

CONCOMITANT MEDICATION

Medication Dosage	Trial	Start	End
metformin hydrochloride 500mg bid	INT-63	13AUG2001	08JUL2002
candesartan cilexetil 8mg od	INT-63	18SEP2001	01APR2002
furosemide 30mg od bid	INT-63	18SEP2001	
potassium chloride 750 mg bid	INT-63	10OCT2001	16APR2002
acetylsalicylic acid 75mg od	INT-63	31OCT2001	
glimepiride 1mg od	INT-63	08FEB2002	
candesartan cilexetil 8mg bid	INT-63	02APR2002	22APR2002
felodipine 10mg od	INT-63	16APR2002	
candesartan cilexetil tablet 8mg od	INT-63	08JUL2002	
rosiglitazone maleate tablet 4mg od	INT-63	03OCT2002	
atorvastatin 10mg xl	INT-63	28OCT2002	11NOV2002
atorvastatin 20mg xl	INT-63	12NOV2002	

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Trial	Severity	Related	Start	End	Phase	Days**
gastritis (gastric influenza)	INT-61	mild	not	29MAY00	05JUN00	run-in	-50
headache (headache)	INT-61	mild	not	06JUL00	09JUL00	run-in	-12
tachycardia (tachycardia)	INT-61	mild	not	09JUL00	09JUL00	run-in	-9
tachycardia supraventricular (auricular flutter)	INT-61	mild	not	09JUL00	09JUL00	run-in	-9
hypertension (high blood pressure)	INT-61	mild	not	03SEP00	03SEP00	treatment2	48
psychosis (increased psychotic symptoms)	INT-61	severe	possibly	18SEP00		treatment2	63
psychosis (increased psychotic symptoms)	INT-63	severe	possibly	18SEP00	19DEC00	pre trial	-11
diabetes mellitus (diabetes)	INT-63	mild	possibly	13AUG01		follow up	319
hypokalaemia (low value of potassium)	INT-63	mild	not	25SEP01	11OCT02	follow up	362
rpm increased (increased creatinine level)	INT-63	mild	not	01MAR02	11OCT02	follow up	519
influenza-like symptoms (flu)	INT-63	severe	not	30APR02	05MAY02	follow up	579
rhinitis (cold)	INT-63	mild	not	21OCT02	04NOV02	follow up	753
hypercholesterolaemia (high cholesterol)	INT-63	moderate	not	28OCT02		follow up	760

** days to onset

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-INT-63

CLINICAL LABORATORY TESTS

The following laboratory tests had results outside of normal limits during the trial:

Test (laboratory limits, unit)

alkaline phosphatase (31-121 U/L)

172 at mo 6(ex) 132 at mo 12(ex) 158 at mo 24(ex)

sgt (6-32 U/L)

71 at mo 6(ex) 49 at mo 12(ex) 47 at mo 24(ex)

hemoglobin (12-16 g/dl)

13.3 at prev base 13.3 at base(ex) 12.8 at mo 6(ex) 11.9 at mo 12(ex)

12.8 at mo 24(ex)

lymphocytes (25-45 %)

23.3 at prev base 23.3 at base(ex) 18.3 at mo 6(ex) 22 at mo 12(ex)

22 at mo 24(ex)

neutrophils (50-65 %)

68.9 at prev base 68.9 at base(ex) 75.1 at mo 6(ex) 69.4 at mo 12(ex)

68.7 at mo 24(ex)

potassium (3.5-5.5 meq/l)

4 at mo 6(ex) 3 at mo 12(ex) 3.5 at mo 24(ex)

rbc (4.2-5.8 x10⁶/mm³)

4.51 at prev base 4.51 at base(ex) 4.43 at mo 6(ex) 3.96 at mo 12(ex)

4.29 at mo 24(ex)

total protein (6.6-8.7 g/dl)

6.5 at mo 6(ex) 5.8 at mo 12(ex) 6.2 at mo 24(ex)

urea (20-50 mg/dl)

42 at mo 6(ex) 53 at mo 12(ex) 47 at mo 24(ex)

CGI

Date	Trial	Phase	Time	CGI
24MAY2003	INT-61	TRT	SCREENING	MILD
20JUN2003	INT-61	TRT	RUN-IN	VERY MILD
18JUL2003	INT-61	TRT	BASELINE	VERY MILD
01AUG2003	INT-61	TRT	WEEK 2	MILD
15AUG2003	INT-61	TRT	WEEK 4	MILD
29AUG2003	INT-61	TRT	WEEK 6	MILD
11SEP2003	INT-61	TRT	WEEK 8	MODERATE
26SEP2003	INT-61	TRT	WEEK 10	MARKED
29SEP2003	INT-61	TRT	WEEK 10 *	MODERATE
17OCT2003	INT-63	FUP	WEEK 4 (EXT.)	MODERATE
31OCT2003	INT-63	FUP	WEEK 6 (EXT.)	MILD
21NOV2003	INT-63	FUP	MONTH 3 (EXT.) *	MODERATE
19DEC2003	INT-63	FUP	MONTH 3 (EXT.)	MILD
28MAR2001	INT-63	FUP	MONTH 6 (EXT.)	VERY MILD
19JUN2001	INT-63	FUP	MONTH 9 (EXT.)	VERY MILD
25SEP2001	INT-63	FUP	MONTH 12 (EXT.)	VERY MILD
26MAR2002	INT-63	FUP	MONTH 18 (EXT.)	VERY MILD
10OCT2002	INT-63	FUP	MONTH 24 (EXT.)	VERY MILD
24MAR2003	INT-63	FUP	MONTH 30 (EXT.)	VERY MILD

Risperidone: Effects on Glucose Metabolism
 AE Narratives REDACTED

JNJPRD--TRIAL REDACTED SAFETY UPDATE(CUT-OFF MARCH 28, 2003)
 SERIOUS ADVERSE EVENT SUMMARY

#A30240

Subject: RED #A30240	Investigator: PANDURANGI A., MD
Age: 48 years	Previous trial: USA-121
Race: Black	Previous CRFID: A30299
Sex: female	Term.type(prev.): COMPLETED
Country: USA	Depot duration: 1E3 days
Diagnosis: 28 years	Treatment start: June 8, 2000
Trial term: March 28, 2003	Treatment stop: March 28, 2003
	Term.type(ext.): Continued

Trial termination reason: Cut off date: 28mar-2003
 treatment1=depot/oral(prev. trial), treatment2=depot(prev. trial),
 follow up=depot(extension)

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
*depression aggravated Trial: REDACTED (increased sadness of mood - depressed mood)	severe	not	19OCT00	01NOV00	follow up	134
*depression Trial: REDACTED (depression)	severe	not	23AUG01	24SEP01	follow up	442
*diabetes mellitus Trial: REDACTED (diabetes)		possibly	28AUG01		follow up	447

** days after start treatment

BASELINE SUBJECT DATA

- Diagnosis: paranoid schizophrenia
 - Medical and surgical history: allergic/immunologic: sinus allergies to pollen.;
 ears, nose, throat: sinus allergies; genito-urinary: hysterectomy, bilateral oophorectomy,
 yeast infection
 - Concomitant disorders: endocrine: hormone replacement therapy.; gastrointestinal:
 irritable bowel syndrome, occasional nausea, diarrhea; musculoskeletal: aches in both
 knees and lower back; other: 1+ pitting edema in both legs; depression
 - Physical examination: extremities: positive non-pitting edema in both legs

TREATMENT DATA:

Trial	Trt. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
USA-121	SCREENING	NONE		08MAR2000	10MAR2000		3
USA-121	RUN-IN	CRAL RIS		11MAR2000	13MAR2000	2	3
USA-121	RUN-IN	CRAL RIS		14MAR2000	16MAR2000	4	3
USA-121	TREATMENT1	DEPOT/ORAL PLAC	1	17MAR2000	17MAR2000	0/4	1
USA-121	TREATMENT1	DEPOT/ORAL PLAC		18MAR2000	29MAR2000	0/0	12
USA-121	TREATMENT1	DEPOT/ORAL PLAC	2	30MAR2000	06APR2000	0/0	8
USA-121	TREATMENT2	DEPOT PLACEBO		07APR2000	12APR2000	0	6
USA-121	TREATMENT2	DEPOT PLACEBO	3	13APR2000	26APR2000	0	14
USA-121	TREATMENT2	DEPOT PLACEBO	4	27APR2000	10MAY2000	0	14
USA-121	TREATMENT2	DEPOT PLACEBO	5	11MAY2000	24MAY2000	0	14
USA-121	TREATMENT2	DEPOT PLACEBO	6	25MAY2000	25MAY2000	0	1
REDACTED	FOLLOW UP	RIS DEPOT	7	08JUN2000	22JUN2000	25	15
	FOLLOW UP	RIS CRAL		09JUN2000	11JUN2000	2	3
	FOLLOW UP	RIS DEPOT	8	23JUN2000	05JUL2000	50	13
	FOLLOW UP	RIS DEPOT	9	06JUL2000	19JUL2000	50	14
	FOLLOW UP	RIS DEPOT	10	20JUL2000	02AUG2000	50	14

Risperidone: Effects on Glucose Metabolism
 AE Narratives REDACTED

TREATMENT DATA:

Trial	Ttr. Phase	Treatment	Inj. Start	Stop	Dose (mg)	Duration
REDACTED						
	FOLLOW UP	RIS DEPOT	11 03AUG2000	16AUG2000	50	14
	FOLLOW UP	RIS DEPOT	12 17AUG2000	29AUG2000	50	13
	FOLLOW UP	RIS DEPOT	13 30AUG2000	14SEP2000	50	16
	FOLLOW UP	RIS DEPOT	14 15SEP2000	28SEP2000	50	14
	FOLLOW UP	RIS DEPOT	15 29SEP2000	11OCT2000	50	13
	FOLLOW UP	RIS DEPOT	16 12OCT2000	25OCT2000	50	14
	FOLLOW UP	RIS DEPOT	17 26OCT2000	08NOV2000	75	14
	FOLLOW UP	RIS DEPOT	18 09NOV2000	28NOV2000	75	20
	FOLLOW UP	RIS DEPOT	19 29NOV2000	13DEC2000	75	15
	FOLLOW UP	RIS DEPOT	20 14DEC2000	27DEC2000	75	14
	FOLLOW UP	RIS DEPOT	21 28DEC2000	10JAN2001	75	14
	FOLLOW UP	RIS DEPOT	22 11JAN2001	21JAN2001	75	11
	FOLLOW UP	RIS DEPOT	23 22JAN2001	05FEB2001	75	15
	FOLLOW UP	RIS DEPOT	24 06FEB2001	22FEB2001	75	17
	FOLLOW UP	RIS DEPOT	25 23FEB2001	07MAR2001	75	13
	FOLLOW UP	RIS DEPOT	26 08MAR2001	21MAR2001	75	14
	FOLLOW UP	RIS DEPOT	27 22MAR2001	04APR2001	75	14
	FOLLOW UP	RIS DEPOT	28 05APR2001	18APR2001	75	14
	FOLLOW UP	RIS DEPOT	29 19APR2001	09MAY2001	75	21
	FOLLOW UP	RIS DEPOT	30 10MAY2001	20MAY2001	50	11
	FOLLOW UP	RIS DEPOT	31 21MAY2001	31MAY2001	50	11
	FOLLOW UP	RIS DEPOT	32 01JUN2001	13JUN2001	50	13
	FOLLOW UP	RIS DEPOT	33 14JUN2001	28JUN2001	50	15
	FOLLOW UP	RIS DEPOT	34 29JUN2001	12JUL2001	25	14
	FOLLOW UP	RIS DEPOT	35 13JUL2001	25JUL2001	25	13
	FOLLOW UP	RIS DEPOT	36 26JUL2001	08AUG2001	25	14
	FOLLOW UP	RIS DEPOT	37 09AUG2001	22AUG2001	25	14
	FOLLOW UP	RIS DEPOT	38 23AUG2001	05SEP2001	25	14
	FOLLOW UP	RIS DEPOT	39 06SEP2001	23SEP2001	25	18
	FOLLOW UP	RIS DEPOT	40 24SEP2001	03OCT2001	25	10
	FOLLOW UP	RIS DEPOT	41 04OCT2001	18OCT2001	25	15
	FOLLOW UP	RIS DEPOT	42 19OCT2001	01NOV2001	25	17
	FOLLOW UP	RIS DEPOT	43 05NOV2001	14NOV2001	25	10
	FOLLOW UP	RIS DEPOT	44 15NOV2001	28NOV2001	25	14
	FOLLOW UP	RIS DEPOT	45 29NOV2001	09DEC2001	25	11
	FOLLOW UP	RIS DEPOT	46 10DEC2001	20DEC2001	25	11
	FOLLOW UP	RIS DEPOT	47 21DEC2001	06JAN2002	25	17
	FOLLOW UP	RIS DEPOT	48 07JAN2002	21JAN2002	25	15
	FOLLOW UP	RIS DEPOT	49 22JAN2002	03FEB2002	25	13
	FOLLOW UP	RIS DEPOT	50 04FEB2002	17FEB2002	25	14
	FOLLOW UP	RIS DEPOT	51 18FEB2002	28FEB2002	25	11
	FOLLOW UP	RIS DEPOT	52 01MAR2002	13MAR2002	25	13
	FOLLOW UP	RIS DEPOT	53 14MAR2002	27MAR2002	25	14
	FOLLOW UP	RIS DEPOT	54 28MAR2002	10APR2002	25	14
	FOLLOW UP	RIS DEPOT	55 11APR2002	24APR2002	25	14
	FOLLOW UP	RIS DEPOT	56 25APR2002	09MAY2002	25	15
	FOLLOW UP	RIS DEPOT	57 10MAY2002	23MAY2002	25	14
	FOLLOW UP	RIS DEPOT	58 24MAY2002	05JUN2002	25	13
	FOLLOW UP	RIS DEPOT	59 06JUN2002	19JUN2002	25	14
	FOLLOW UP	RIS DEPOT	60 20JUN2002	01JUL2002	25	12
	FOLLOW UP	RIS DEPOT	61 02JUL2002	18JUL2002	25	17
	FOLLOW UP	RIS DEPOT	62 19JUL2002	01AUG2002	25	14
	FOLLOW UP	RIS DEPOT	63 02AUG2002	14AUG2002	25	13
	FOLLOW UP	RIS DEPOT	64 15AUG2002	26AUG2002	25	12
	FOLLOW UP	RIS DEPOT	65 27AUG2002	10SEP2002	25	15
	FOLLOW UP	RIS DEPOT	66 11SEP2002	27SEP2002	25	17
	FOLLOW UP	RIS DEPOT	67 28SEP2002	10OCT2002	25	13
	FOLLOW UP	RIS DEPOT	68 11OCT2002	23OCT2002	25	13
	FOLLOW UP	RIS DEPOT	69 24OCT2002	07NOV2002	25	15
	FOLLOW UP	RIS DEPOT	70 08NOV2002	18NOV2002	25	11

Risperidone: Effects on Glucose Metabolism
AE Narratives **REDACTED**

TREATMENT DATA:

Trial	Treat. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
REDACTED	FOLLOW UP	RIS DEPOT	71	19NOV2002	05DEC2002	25	17
	FOLLOW UP	RIS DEPOT	72	06DEC2002	18DEC2002	25	13
	FOLLOW UP	RIS DEPOT	73	19DEC2002	01JAN2003	25	14
	FOLLOW UP	RIS DEPOT	74	02JAN2003	14JAN2003	25	13
	FOLLOW UP	RIS DEPOT	75	15JAN2003	29JAN2003	25	15
	FOLLOW UP	RIS DEPOT	76	30JAN2003	12FEB2003	25	14
	FOLLOW UP	RIS DEPOT	77	13FEB2003	26FEB2003	25	14
	FOLLOW UP	RIS DEPOT	78	27FEB2003	13MAR2003	25	15
	FOLLOW UP	RIS DEPOT	79	14MAR2003	28MAR2003	25	15

CLINICAL NARRATIVE

RED (CRF ID A30240) was a black female with a 28-year history of paranoid schizophrenia; she was 48-years old at time of study entry. She received treatment with placebo during the double-blind study, RIS-USA-121 until completion on 25 May 2000. She entered the open-label extension study **REDACTED** on 8 June 2000. During **REDACTED**, she received varying doses of 25 mg, 50 mg, and 75 mg of risperidone microspheres depot injection.

On 12 October 2000, risperidone depot 50 mg/biweekly was administered. On 19 October 2000, she experienced the serious adverse event "increased sadness of mood-depressed mood" that resulted in her hospitalization after she developed increasing sadness, low energy and crying spells. This sadness was attributed to the stresses of a limited income and dependency on her sister. Risperidone depot was increased from 50 mg/biweekly to 75 mg/biweekly on 26 October 2000.

On 23 August 2001, risperidone depot 25 mg/biweekly was administered. On the same day, she experienced the serious adverse event "depression". She was hospitalized and was treated with lorazepam and paroxetine. On 28 August 2001, she was diagnosed with new onset "diabetes". She received varying doses of insulin and oral metformin. She was discharged on oral medications and also received counseling. Additionally, the adverse events "heartburn" three times, "sadness of mood-depressed mood" twice, "constipation" three times, "indigestion" twice, and "vomiting" twice, "nervousness", "nausea", "headache", "urinary incontinence", "yeast infection", "high blood pressure", "numbness in hands", "runny nose", "first degree AV block", "wrist pain", "toe nail fungus", "inflamed bunion", "increased anxiety", "swelling in feet and ankles", "swollen ankles and wrist", "increase in vivid dreams", "middle insomnia", "increase in blood pressure", "low potassium", "dizziness", "insomnia", "low energy", "crying spells", "swelling in feet", "weight gain", "akinesia" and "tremors" also occurred during **REDACTED**.

Prior medical history and concomitant medications are provided in the narrative profile. Concomitant disorders were remarkable for depression. Physical examination at baseline showed non-pitting edema in both legs. Vital signs, ECG findings and clinical laboratory values were unremarkable throughout the study.

The serious adverse event "increased sadness of mood-depressed mood" resolved on 1 November 2000; the event was considered severe by the investigator and not related to study medication. The serious adverse event "depression" resolved on 24 September 2001, the serious adverse event "diabetes" did not have a resolution date. The "depression" was considered severe by the investigator and not related to study medication. The "diabetes" was not rated in severity by the investigator and was considered possibly related to study medication.

Depression is listed as a possible side-effect of risperidone. In this subject, the depression apparently was triggered by the patient's limited income and dependency on her sister. However, the sponsor considered a causal relationship between this serious adverse event and the use of risperidone can not totally be excluded. Hyperglycemia and exacerbation of existing diabetes have been reported with risperidone. The patient had risk factors for diabetes including race, obesity, and age. The sponsor considered a causal relationship between the diabetes mellitus and the use of risperidone could not be excluded.

Risperidone: Effects on Glucose Metabolism
 AE Narratives **REDACTED**

KCG JATA

Date	Trial	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcF (ms)	QTcL (ms)
08MAR2003	USA-121	TRT	SCREENING	73	180	90	400	441	427	427
17MAR2003	USA-121	TRT	BASELINE	74	190	100	340	378	365	369
24MAR2003	USA-121	TRT	WEEK 1	74	170	100	400	444	429	429
06APR2003	USA-121	TRT	WEEK 3	62	200	90	410	417	415	415
18APR2003	USA-121	TRT	WEEK 5	68	190	80	370	394	386	388
19MAY2003	USA-121	TRT	WEEK 9	74	190	100	390	433	418	419
08JUN2003	USA-121	TRT	WEEK 12	60	180	100	370	370	370	370
30AUG2003	REDACTED	FUP	MO 3 (EX)	67	200	100	410	433	425	426
29NOV2003		FUP	MO 6 (EX)	77	190	100	390	442	424	424
01JUN2001		FUP	MO 12 (EX)	70	200	90	380	410	400	402
10MAY2002		FUP	MO 24 (EX)	74	210	A 90	370	411	397	399

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

VITAL SIGNS DATA

Date	Trial	Phase	Time	Weight (kg)	BMI	Stand/Supine Pulse (b/min)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
08MAR2003	USA-121	TRT	SCREENING	93	32	81 / 75	122 / 128	85 / 86
17MAR2003	USA-121	TRT	BASELINE	91.6	32	80 / 71	122 / 133	91 / 92
24MAR2003	USA-121	TRT	WEEK 1			78 / 75	146 / 132	103 / 83
30MAR2003	USA-121	TRT	WEEK 2			70 / 68	161 / 151	99 / 95
06APR2003	USA-121	TRT	WEEK 3			75 / 66	142 / 123	93 / 75
13APR2003	USA-121	TRT	WEEK 4			72 / 68	132 / 112	85 / 74
18APR2003	USA-121	TRT	WEEK 5			76 / 71	144 / 136	86 / 77
27APR2003	USA-121	TRT	WEEK 6			77 / 71	135 / 111	93 / 76
11MAY2003	USA-121	TRT	WEEK 8			71 / 65	134 / 110	88 / 75
15MAY2003	USA-121	TRT	WEEK 8 *			67 / 66	138 / 123	92 / 81
25MAY2003	USA-121	TRT	WEEK 10			70 / 68	113 / 114	70 / 71
08JUN2003	USA-121	TRT	WEEK 12	90.7	31	69 / 71	138 / 136	97 / 84

Risperidone: Effects on Glucose Metabolism
 AE Narratives **REDACTED**

VITAL SIGNS DATA

Date	Trial	Phase	Time	Weight (kg)	BMI	Stand/Supine Pulse (b/min)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
23JUN2003	REDACTED	FUP	WK 2 (EX)	92.1	32	75 / 74	168 / 145	99 / 73
06JUL2003	REDACTED	FUP	WK 4 (EX)	94.8	33	83 / 81	152 / 128	98 / 84
20JUL2003	REDACTED	FUP	WK 6 (EX)	95.3	33	89 / 76	152 / 142	101 / 90
30AUG2003	REDACTED	FUP	MO 3 (EX)	93.4	32	74 / 70	123 / 112	77 / 65
29NOV2003	REDACTED	FUP	MO 6 (EX)	93.4	32	85 / 80	142 / 129	84 / 83
08MAR2001	REDACTED	FUP	MO 9 (EX)	104	36	/ /	/ /	/ /
21MAY2001	REDACTED	FUP	MO 12 (EX)	105	36	85 / 80	102 / 101	59 / 53
15NOV2001	REDACTED	FUP	MONTH 18 (E)	99.3	34	92 / 86	142 / 123	91 / 79
10MAY2002	REDACTED	FUP	MO 24 (EX)	103	35	122 / 109	175 / 143	93 / 89
08NOV2002	REDACTED	FUP	MONTH 30 (E)	104	36	65 / 65	188 / 176	84 / 107

* not included in statistical analysis

CONCOMITANT MEDICATION

Medication	Trial	Start	End
estrogen nos	USA-121	before trial	ongoing
0.625mg od po	USA-121	before trial	ongoing
ibuprofen	USA-121	before trial	ongoing
200mg prn po	USA-121	before trial	ongoing
paroxetine	USA-121	before trial	08MAR2000
20mg od po	USA-121	before trial	ongoing
lorazepam	USA-121	14MAR2000	ongoing
1mg bid prn po	USA-121	24MAR2000	29MAR2000
maalox plus	USA-121	24MAR2000	29MAR2000
30ml tid po	USA-121	24MAR2000	29MAR2000
prochlorperazine	USA-121	24MAR2000	29MAR2000
5mg prn po q 8 hr	USA-121	29MAR2000	30MAR2000
zolpidem	USA-121	29MAR2000	30MAR2000
10mg od prn po	USA-121	06APR2000	ongoing
multivitamins	USA-121	14APR2000	22APR2000
1 tablet od po	USA-121	23APR2000	05MAY2000
psyllium hydrophilic mucilloid	REDACTED	before trial	01NOV2001
1tbsp qam po	REDACTED	before trial	16JUN2000
cotlenol	REDACTED	before trial	28OCT2000
2tablets qd po	REDACTED	before trial	01AUG2001
estrogen nos	REDACTED	before trial	16JUN2000
0.625mg od po	REDACTED	before trial	19JUL2000
ibuprofen	REDACTED	before trial	19JUL2000
200mg prn po	REDACTED	before trial	20JUL2000
lorazepam	REDACTED	before trial	29NOV2000
1mg bid prn po	REDACTED	before trial	09AUG2000
multivitamins	REDACTED	before trial	07MAY2001
1 tablet q.d. po	REDACTED	before trial	18SEP2000
naproxen sodium	REDACTED	before trial	01AUG2001
2 tabs q.d. prn	REDACTED	before trial	18SEP2000
sodium bicarbonate	REDACTED	before trial	29SEP2000
1 tablet	REDACTED	before trial	11JAN2001
hydrochlorothiazide	REDACTED	before trial	
1/2 tablet (25mg) po q.d.	REDACTED	before trial	
psyllium hydrophilic mucilloid	REDACTED	before trial	
1 tbs q.d. prn	REDACTED	before trial	
calcium	REDACTED	before trial	
1 tablet po q.d. prn	REDACTED	before trial	
tocopherol	REDACTED	before trial	
1 tablet po q.d. prn	REDACTED	before trial	
potassium chloride	REDACTED	before trial	
1 tablet po q.d.	REDACTED	before trial	

Risperidone: Effects on Glucose Metabolism
 AE Narratives **REDACTED**

CONCOMITANT MEDICATION

Medication	Trial	Start	End
Dosage	REDACTED		
zolpidem tartrate	REDACTED	05OCT2000	12OCT2000
10mg (1 or 2) po q.h.s.	REDACTED		
chloral hydrate	REDACTED	12OCT2000	29OCT2000
(500mg) x 2 q.h.s. po	REDACTED		
paroxetine	REDACTED	20OCT2000	23OCT2000
20mg q.d. po	REDACTED		
psyllium hydrophilic mucilloid	REDACTED	20OCT2000	29OCT2000
3.5gm bid po	REDACTED		
paroxetine	REDACTED	24OCT2000	10JAN2001
(20mg) x 2 q.d. po	REDACTED		
maalox	REDACTED	25OCT2000	25OCT2000
30ml q.d. po	REDACTED		
serena	REDACTED	27OCT2000	27OCT2000
2 tablets bid po	REDACTED		
docusate	REDACTED	28OCT2000	28OCT2000
100mg po bid	REDACTED		
docusate	REDACTED	29OCT2000	29OCT2000
100mg po q.d.	REDACTED		
lorazepam	REDACTED	29OCT2000	29OCT2000
1mg q.d. po bid	REDACTED		
psyllium hydrophilic mucilloid	REDACTED	29OCT2000	29OCT2000
3.5gm po q.d.	REDACTED		
chloral hydrate	REDACTED	30OCT2000	11JAN2001
1500mg po q.d.	REDACTED		
docusate	REDACTED	30OCT2000	01NOV2000
100mg bid. po	REDACTED		
lorazepam	REDACTED	30OCT2000	23AUG2001
1mg bid po	REDACTED		
psyllium hydrophilic mucilloid	REDACTED	30OCT2000	01NOV2000
3.5gm bid po	REDACTED		
sorbitol	REDACTED	31OCT2000	01NOV2000
30ml q.d. po	REDACTED		
benzotropine mesilate	REDACTED	01NOV2000	05FEB2001
2mg po q.d.	REDACTED		
hydrochlorothiazide	REDACTED	30NOV2000	14DEC2000
25mg po q.d.	REDACTED		
furosemide	REDACTED	14DEC2000	11JAN2001
20mg po q.d.	REDACTED		
paroxetine	REDACTED	11JAN2001	28JUN2001
20mg po	REDACTED		
chloral hydrate	REDACTED	12JAN2001	06FEB2001
(500mg) x 2 po q.d.	REDACTED		
furosemide	REDACTED	12JAN2001	23AUG2001
30mg po q.d.	REDACTED		
benzotropine mesilate	REDACTED	06FEB2001	19OCT2001
2mg po bid	REDACTED		
psyllium hydrophilic mucilloid	REDACTED	08MAY2001	30APR2002
2tsp bid prn	REDACTED		
chloral hydrate	REDACTED	29JUN2001	25JUL2001
(500mg)x2 po q.d.	REDACTED		
paroxetine	REDACTED	29JUN2001	08AUG2001
40mg po	REDACTED		
chloral hydrate	REDACTED	26JUL2001	01AUG2001
500mg/tsp 1tsp	REDACTED		
paroxetine	REDACTED	09AUG2001	23AUG2001
20mg po	REDACTED		
fluconazole	REDACTED	10AUG2001	10AUG2001
1 dose 150mg p.o.	REDACTED		
rystatin	REDACTED	10AUG2001	09NOV2001
external application	REDACTED		

Risperidone: Effects on Glucose Metabolism
 AE Narratives **REDACTED**

CONCOMITANT MEDICATION

Medication	Trial	Start	End
Dosage			
lorazepam	REDACTED	23AUG2001	24AUG2001
.5mg qd			
paroxetine		23AUG2001	24AUG2001
30mg			
potassium		23AUG2001	23AUG2001
10meq 2po			
insulin		25AUG2001	25AUG2001
4 units in; sc			
paracetamol		25AUG2001	25AUG2001
650mg po			
paroxetine		25AUG2001	19NOV2002
40mg po			
insulin		26AUG2001	26AUG2001
2 units in; sc			
magnesium hydroxide		26AUG2001	26AUG2001
16ml po			
insulin		27AUG2001	27AUG2001
8 units in; sc			
acetylsalicylic acid		28AUG2001	03OCT2001
81mg one qid			
metformin		28AUG2001	06SEP2001
500mg tab 1qid			
acetylsalicylic acid		29AUG2001	30AUG2001
81mg lpo			
insulin		29AUG2001	29AUG2001
8 units in; sc			
lorazepam		29AUG2001	06SEP2001
.5mg po bid			
insulin		30AUG2001	30AUG2001
6 units in; sc			
lorazepam		07SEP2001	
1mg bid			
metformin		07SEP2001	18DEC2002
500mg 1bid			
omeprazole		03OCT2001	13DEC2001
20mg one qid			
acetylsalicylic acid		04OCT2001	
325mg one qid			
antacid		14DEC2001	30DEC2001
40mg po qd			
omeprazole		31DEC2001	18DEC2002
20mg			
enalapril maleate		18FEB2002	14AUG2002
5mc 1qd			
cetylenol		10MAR2002	13MAR2002
525mg qd			
diflunisal		03JUN2002	09JUN2002
250mg one bid			
celecoxib		10JUN2002	15AUG2002
200mg			
fexofenadine hydrochloride		24JUL2002	01SEP2002
1qd			
terbinafine hydrochloride		02AUG2002	02OCT2002
1qd			
triamcinolone acetonide		02AUG2002	18AUG2002
2 puffs each nostril bid			
enalapril		15AUG2002	17SEP2002
10mg			
propranolol hydrochloride		11SEP2002	
10mg bid			

Risperidone: Effects on Glucose Metabolism
 AE Narratives **REDACTED**

CONCOMITANT MEDICATION

Medication	Trial	Start	End
Dosage			
enalapril	REDACTED	18SEP2002	18DEC2002
20mg			
cortisone		11OCT2002	11OCT2002
50mg/ml			
influenza virus vaccine polyvalent			
single injection		16OCT2002	16OCT2002
vaccinco			
single injection		16OCT2002	16OCT2002
penicillin ros			
500mg unk		22OCT2002	
terbinafine hydrochloride			
250mg qd		11NOV2002	03JAN2003
paroxetine hydrochloride			
25mg-2tabs qd		20NOV2002	
metoclopramide			
250mg bid		19DEC2002	19FEB2003
oral antidiabetics			
10mg qid		19DEC2002	29JAN2003
quinapril hydrochloride			
40mg tabs 1 qd		19DEC2002	
torasemide			
20mg qd		30DEC2002	03JAN2003
glibenclamide			
500mg bid		01FEB2003	
metformin			
500mg bid		01FEB2003	
general nutrients			
onc qd		10FEB2003	
omeprazole			
20mg qd		20FEB2003	

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Trial	Severity	Related	Start	End	Phase	Days**
nervousness	USA-121	moderate	possibly	14MAR00	21APROC	run-in	-3
(nervousness)							
nausea	USA-121	moderate	possibly	19MAR00	29MAR00	treatment1	3
(nausea - increased)							
vomiting	USA-121	mild	possibly	19MAR00	28MAR00	treatment1	3
(vomiting)							
diarrhoea	USA-121	mild	doubtful	20MAR00	27MAR00	treatment1	4
(diarrhea - increased)							
oedema peripheral	USA-121	mild	doubtful	20MAR00	12APROC	treatment1	4
(swelling in both hands)							
anxiety	USA-121	moderate	possibly	27MAR00	31MAR00	treatment1	11
(increased stress)							
apathy	USA-121	moderate	possibly	27MAR00	31MAR00	treatment1	11
(emotional withdrawal)							
insomnia	USA-121	mild	not	29MAR00	30MAR00	treatment1	13
(insomnia)							
nausea	USA-121	mild	doubtful	09APR00	24APROC	treatment2	24
(nausea - increased)							
rhinitis	USA-121	mild	not	23APR00	04MAY00	treatment2	38
(head cold)							
nervousness	USA-121	mild	not	05MAY00		treatment2	50
(nervousness)							
oedema peripheral	USA-121	mild	possibly	11MAY00	13MAY00	treatment2	56
(swelling in ankles)							

Risperidone: Effects on Glucose Metabolism
AE Narratives REDACTED

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Trial	Severity	Related	Start	End	Phase	Days**
nervousness (nervousness)	REDACTED	mild	not	05MAY00		pre trial	-34
vomiting (vomiting)		mild	probable	10JUN00	12JUN00	follow up	3
dreaming abnormal (increase in vivid dreams)		mild	not	16JUN00	06JUL00	follow up	9
oedema peripheral (swollen ankles & wrists)	REDACTED	moderate	not	16JUN00	04JUL00	follow up	9
hypertension (increase in blood pressure)	REDACTED	mild	doubtful	23JUN00	03AUG00	follow up	16
insomnia (middle insomnia)	REDACTED	mild	not	02JUL00	16AUG00	follow up	25
oedema peripheral (swelling in feet & ankles)		moderate	doubtful	10JUL00	03AUG00	follow up	33
dyspepsia (indigestion)	REDACTED	mild	not	19JUL00	20JUL00	follow up	42
constipation (constipation)		mild	doubtful	09AUG00	22SEP00	follow up	63
hypokalaemia (low potassium)		mild	not	30AUG00	11JAN01	follow up	84
dizziness (dizziness)		mild	possibly	11SEP00	29SEP00	follow up	96
insomnia (insomnia)		moderate	not	05OCT00	09NOV00	follow up	120
depression (sadness of mood - depressed mood)		moderate	not	06OCT00	18OCT00	follow up	121
crying abnormal (crying spells)	REDACTED	moderate	not	19OCT00	01NOV00	follow up	134
fatigue (low energy)		severe	not	19OCT00	30NOV00	follow up	134
constipation (constipation)		mild	doubtful	20OCT00	01NOV00	follow up	135
dyspepsia (indigestion)		mild	doubtful	25OCT00	25OCT00	follow up	140
hypokinesia (akinesia)		moderate	probable	01NOV00	08MAR01	follow up	147
tremor (tremors)		mild	probable	01NOV00	14JUN01	follow up	147
depression (sadness of mood - depressed mood)		moderate	not	02NOV00	14DEC00	follow up	148
weight increase (weight gain)	REDACTED			11JAN01		follow up	218
nausea (nausea)		mild	possibly	03MAY01	01JUL01	follow up	330
headache (headache)		mild	possibly	06MAY01	18MAY01	follow up	333
constipation (constipation)		moderate	doubtful	08MAY01	20DEC01	follow up	335
oedema peripheral (swelling in feet)		moderate	doubtful	15MAY01	23AUG01	follow up	342
urinary incontinence (urinary incontinence)		moderate	doubtful	18JUL01	20DEC01	follow up	406
infection fungal (yeast infection)		moderate	not	08AUG01	24SEP01	follow up	427
dyspepsia (heartburn)		mild	doubtful	24SEP01	20DEC01	follow up	474
vomiting (vomiting)		mild	not	12NOV01	12NOV01	follow up	523
dyspepsia (heartburn)		mild	doubtful	31DEC01	04FEB02	follow up	572
dyspepsia (heartburn)		moderate	not	05FEB02		follow up	608

Risperidone: Effects on Glucose Metabolism
 AE Narratives REDACTED

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Trial	Severity	Related	Start	End	Phase	Days**
hypertension (high blood pressure)	REDACTED	mild	not	18FEB02		follow up	621
hypoesthesia (numbness in hands)	REDACTED	mild	possibly	18FEB02	11APR02	follow up	621
rhinitis (runny nose)	REDACTED	mild	not	01MAR02	14MAR02	follow up	632
av block (first degree av block)	REDACTED	mild	not	10MAY02		follow up	702
arthralgia (wrist pain)	REDACTED	mild	not	12MAY02		follow up	704
infection fungal (toe nail fungus)	REDACTED	moderate	not	24JUL02		follow up	777
arthritis (inflamed bunion)	REDACTED	moderate	not	05OCT02	07NOV02	follow up	850
anxiety (increased anxiety)	REDACTED	moderate	not	12NOV02		follow up	888

** days to onset

CLINICAL LABORATORY TESTS

The following laboratory tests had results outside of normal limits during the trial:

Test (laboratory limits, unit)

ast (sgot) (9-34 U/L)				
22 at prev base	22 at base(ex)	28 at mo 3(ex)	25 at mo 3(ex)	*
25 at mo 6(ex)	37 at mo 12(ex)	32 at mo 24(ex)		
ggt (4-49 U/L)				
18 at prev base	18 at base(ex)	24 at mo 3(ex)	24 at mo 3(ex)	*
26 at mo 6(ex)	50 at mo 12(ex)	29 at mo 24(ex)		
platelet count (140-400 GT/L)				
337 at prev base	337 at base(ex)	380 at mo 3(ex)	457 at mo 6(ex)	
391 at mo 12(ex)	455 at mo 24(ex)			
potassium (3.4-5.4 mmol/L)				
3.6 at prev base	3.6 at base(ex)	3 at mo 3(ex)	3.1 at mo 3(ex)	*
3.7 at mo 6(ex)	4.1 at mo 12(ex)	4.2 at mo 24(ex)		
rbc (4.1-5.6 TI/L)				
4.1 at prev base	4.1 at base(ex)	4.1 at mo 3(ex)	3.9 at mo 6(ex)	
4.3 at mo 12(ex)	4.6 at mo 24(ex)			

CGI

Date	Trial	Phase	Time	CGI
17MAR2003	USA-121	TRT	BASELINE	MODERATE
30MAR2003	USA-121	TRT	WEEK 2	MODERATE
06APR2003	USA-121	TRT	WEEK 3	MODERATE
13APR2003	USA-121	TRT	WEEK 4	MODERATE
20APR2003	USA-121	TRT	WEEK 5	MODERATE
27APR2003	USA-121	TRT	WEEK 6	MILD
05MAY2003	USA-121	TRT	WEEK 7	MILD
11MAY2003	USA-121	TRT	WEEK 8	MILD
19MAY2003	USA-121	TRT	WEEK 9	MILD
25MAY2003	USA-121	TRT	WEEK 10	MILD
02JUN2003	USA-121	TRT	WEEK 11	MILD
08JUN2003	USA-121	TRT	WEEK 12	MILD
08JUN2003	REDACTED	FUP	BASE (EXT.)	MILD

Risperidone: Effects on Glucose Metabolism
AE Narratives REDACTED

CGI

Date	Trial	Phase	Time	CGI
23JUN2003	REDACTED	FUP	WEEK 2 (EXT.)	MILD
06JUL2003	REDACTED	FUP	WEEK 4 (EXT.)	MILD
20JUL2003	REDACTED	FUP	WEEK 6 (EXT.)	MILD
30AUG2003	REDACTED	FUP	MONTH 3 (EXT.)	MILD
29NOV2003	REDACTED	FUP	MONTH 6 (EXT.)	MILD
08MAR2001	REDACTED	FUP	MONTH 9 (EXT.)	MILD
21MAY2001	REDACTED	FUP	MONTH 12 (EXT.)	VERY MILD
15NOV2001	REDACTED	FUP	MONTH 18 (EXT.)	MILD
10MAY2002	REDACTED	FUP	MONTH 24 (EXT.)	VERY MILD
08NOV2002	REDACTED	FUP	MONTH 30 (EXT.)	MILD

Risperidone: Effects on Glucose Metabolism
AE Narratives **REDACTED**

UNJPRD--TRIAL: **REDACTED** SAFETY UPDATE (CUT-OFF: MARCH 28, 2003)
PREMATURE DISCONTINUATION SUMMARY

#A30361

Subject: RED #A30361	Investigator: LAURIELLO J., MD
Age: 33 years	Previous Trial: USA-121
Race: Caucasian	Previous CRFID: A30595
Sex: male	Term.type(prev.): COMPLETED
Country: USA	Depot duration: 590 days
Diagnosis: 12 years	Treatment start: November 20, 2000
Trial term: July 2, 2002	Treatment stop: July 2, 2002
	Term.type(ext.): Discontinued

Trial termination reason: Adverse event
treatment1=depot/oral(prev. trial), treatment2=depot(prev. trial),
follow up=depot(extension)

DISCONTINUATION FROM TRIAL:
Date: July 2, 2002, 590 days from the start of treatment
Cause: glycosuria, hyperglycaemia
SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbalim)	Severity	Related	Start	End	Phase	Days**
*glycosuria Trial: REDACTED (elevated glucose in urine (diabetes))	severe	possibly	26JUN02		follow up	584
*hyperglycaemia Trial: REDACTED (elevated blood sugar (diabetes))	severe	possibly	26JUN02		follow up	584

** days after start treatment

BASELINE SUBJECT DATA

- Diagnosis: undifferentiated schizophrenia
- Medical and surgical history: allergic/immunologic: neomycin and tetracycline.
- Concomitant disorders: cardiovascular: htn (tx with medications); other: anxiety (agitation) insomnia
- Physical examination: eyes: wears glasses; abdomen: mildly - moderately obese

TREATMENT DATA:

Trial	Tr. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
USA-121	SCREENING	NONE		15AUG2000	16AUG2000		2
USA-121	RUN-IN	CRAL RIS		17AUG2000	20AUG2000	2	4
USA-121	RUN-IN	CRAL RIS		21AUG2000	24AUG2000	4	4
USA-121	TREATMENT1	DEPOT/ORAL RIS	1	25AUG2000	31AUG2000	50/4	7
USA-121	TREATMENT1	DEPOT/ORAL RIS		01SEP2000	10SEP2000	50/4	10
USA-121	TREATMENT1	DEPOT/ORAL RIS		11SEP2000	11SEP2000	50/C	1
USA-121	TREATMENT1	DEPOT/ORAL RIS	2	12SEP2000	18SEP2000	50/4	7
USA-121	TREATMENT2	DEPOT RIS		19SEP2000	24SEP2000	50	6
USA-121	TREATMENT2	DEPOT RIS	3	25SEP2000	09OCT2000	50	15
USA-121	TREATMENT2	DEPOT RIS	4	10OCT2000	22OCT2000	50	13
USA-121	TREATMENT2	DEPOT RIS	5	23OCT2000	05NOV2000	50	14
USA-121	TREATMENT2	DEPOT RIS	6	06NOV2000	06NOV2000	50	1
REDACTED	FOLLOW UP	RIS DEPOT	7	20NOV2000	03DEC2000	25	14
REDACTED	FOLLOW UP	RIS CRAL		20NOV2000	04DEC2000	2	15
REDACTED	FOLLOW UP	RIS DEPOT	8	04DEC2000	17DEC2000	50	14
REDACTED	FOLLOW UP	RIS CRAL		05DEC2000	13FEB2001	2	71
REDACTED	FOLLOW UP	RIS DEPOT	9	18DEC2000	01JAN2001	50	15
REDACTED	FOLLOW UP	RIS DEPOT	10	02JAN2001	15JAN2001	50	14
REDACTED	FOLLOW UP	RIS DEPOT	11	16JAN2001	29JAN2001	75	14

Risperidone: Effects on Glucose Metabolism
 AE Narratives **REDACTED**

TREATMENT DATA:

Trial	Trt. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
REDACTED	FOLLOW UP	RIS DEPOT	12	30JAN2001	12FEB2001	75	14
	FOLLOW UP	RIS DEPOT	13	13FEB2001	27FEB2001	75	15
	FOLLOW UP	RIS DEPOT	14	28FEB2001	12MAR2001	75	13
	FOLLOW UP	RIS DEPOT	15	13MAR2001	26MAR2001	75	14
	FOLLOW UP	RIS DEPOT	16	27MAR2001	09APR2001	75	14
	FOLLOW UP	RIS DEPOT	17	1CAPR2001	22APR2001	75	13
	FOLLOW UP	RIS DEPOT	18	23APR2001	07MAY2001	75	15
	FOLLOW UP	RIS DEPOT	19	08MAY2001	21MAY2001	75	14
	FOLLOW UP	RIS DEPOT	20	22MAY2001	04JUN2001	75	14
	FOLLOW UP	RIS DEPOT	21	05JUN2001	18JUN2001	75	14
	FOLLOW UP	RIS DEPOT	22	19JUN2001	02JUL2001	75	14
	FOLLOW UP	RIS DEPOT	23	03JUL2001	16JUL2001	75	14
	FOLLOW UP	RIS DEPOT	24	17JUL2001	30JUL2001	75	14
	FOLLOW UP	RIS DEPOT	25	31JUL2001	12AUG2001	75	13
	FOLLOW UP	RIS DEPOT	26	13AUG2001	13AUG2001	25	1
	FOLLOW UP	RIS DEPOT	27	14AUG2001	27AUG2001	50	14
	FOLLOW UP	RIS DEPOT	28	28AUG2001	09SEP2001	75	13
	FOLLOW UP	RIS DEPOT	29	1CSEP2001	24SEP2001	75	15
	FOLLOW UP	RIS DEPOT	30	25SEP2001	08OCT2001	75	14
	FOLLOW UP	RIS DEPOT	31	09OCT2001	23OCT2001	75	15
	FOLLOW UP	RIS DEPOT	32	24OCT2001	04NOV2001	75	12
	FOLLOW UP	RIS DEPOT	33	05NOV2001	05NOV2001	25	1
	FOLLOW UP	RIS DEPOT	34	06NOV2001	19NOV2001	50	14
	FOLLOW UP	RIS DEPOT	35	2CNOV2001	03DEC2001	75	14
	FOLLOW UP	RIS DEPOT	36	04DEC2001	17DEC2001	75	14
	FOLLOW UP	RIS DEPOT	37	18DEC2001	01JAN2002	75	15
	FOLLOW UP	RIS DEPOT	38	02JAN2002	14JAN2002	75	13
	FOLLOW UP	RIS DEPOT	39	15JAN2002	28JAN2002	75	14
	FOLLOW UP	RIS DEPOT	40	29JAN2002	11FEB2002	75	14
	FOLLOW UP	RIS DEPOT	41	12FEB2002	25FEB2002	75	14
	FOLLOW UP	RIS DEPOT	42	26FEB2002	11MAR2002	75	14
	FOLLOW UP	RIS DEPOT	43	12MAR2002	25MAR2002	75	14
	FOLLOW UP	RIS DEPOT	44	26MAR2002	08APR2002	75	14
	FOLLOW UP	RIS DEPOT	45	09APR2002	22APR2002	75	14
	FOLLOW UP	RIS DEPOT	46	23APR2002	06MAY2002	75	14
	FOLLOW UP	RIS DEPOT	47	07MAY2002	21MAY2002	75	15
	FOLLOW UP	RIS DEPOT	48	22MAY2002	04JUN2002	75	14
	FOLLOW UP	RIS DEPOT	49	05JUN2002	19JUN2002	75	15
	FOLLOW UP	RIS DEPOT	50	20JUN2002	02JUL2002	75	13

CLINICAL NARRATIVE

RED (CRF ID A30361) was a white male with a 12-year history of undifferentiated schizophrenia; he was 33-years old at time of study entry. He received treatment with risperidone microspheres depot during the double-blind study, RIS-USA-121 and completed the study. He entered the open-label extension study **REDACTED** on 20 November 2000. During **REDACTED**, he received varying doses of 25 mg, 50 mg and 75 mg risperidone microspheres depot injection biweekly. He prematurely discontinued the study on 2 July 2002 due to serious adverse events.

On 20 June 2002, he received risperidone depot 75 mg/biweekly. On 26 June 2002, he was treated as an outpatient and eventually hospitalized in diabetic ketoacidosis with "elevated glucose in urine (diabetes)" and "elevated blood sugar (diabetes)" related to new onset of diabetes. The patient had a two-week history of nausea and vomiting, abdominal pain, "sticky urine", dry heaves, polydipsia and a 10-pound weight loss in the previous four to six weeks. Laboratory results on 26 June 2002 (outpatient visit) revealed a capillary blood glucose of 496 and an anion gap of 20. He was treated with insulin and intravenous normal saline and sent home. Upon admission to the hospital on 27 June 2002, his glucose level was 237 with an anion gap of 17.5. He was treated with an intravenous insulin drip. The patient was discharged from the hospital on 1 July 2002 on a diet and with insulin treatment (source: CIOMS). Treatment with risperidone depot was permanently discontinued. Additionally, the other adverse events of "ear infection" and "insomnia" occurred during **REDACTED**.

Prior medical history was not significant and concomitant disorders included anxiety and insomnia. Concomitant medications are provided in the narrative profile. Physical examination at baseline revealed obesity. Clinical laboratory values, ECG findings and vital signs were not relevant to the serious adverse events.

The "elevated glucose in urine (diabetes)" and "elevated blood sugar (diabetes)" were considered not resolved. The serious adverse events were considered severe by the investigator and possibly related to study medication.

A diagnosis of new onset diabetes was made. The patient had a risk factor of obesity with a BMI up to 42 during the study. Hyperglycemia has been reported in very rare cases during risperidone treatment. Therefore the sponsor considered that a causal relationship between the serious adverse event and the use of risperidone cannot be excluded.

Risperidone: Effects on Glucose Metabolism
AE Narratives **REDACTED**

ECG DATA

Date	Trial	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcF (ms)	QTcL (ms)
15AUG2000	USA-121	TRT	SCREENING	64	19C	100	420	434 BL	429	43C BL
25AUG2000	USA-121	TRT	BASELINE	52	19C	100	410	382	391	386
01SEP2000	USA-121	TRT	WEEK 1	50 B	19C	90	430	393	405	399
19SEP2000	USA-121	TRT	WEEK 4	51	19C	100	460	424	436 PI	433 PI
29SEP2000	USA-121	TRT	WEEK 5	43 B	20C	90	450	381	403	389
27OCT2000	USA-121	TRT	WEEK 9	48 B	18C	90	430	385	399	392
20NOV2000	USA-121	TRT	WEEK 12	60	18C	100	390	390	390	39C
13FEB2001	REDACTED	FUP	MO 3 (EX)	50 B	19C	90	420	383	395	389
22MAY2001	REDACTED	FUP	MO 6 (EX)	63	18C	90	400	410	407	407
24OCT2001	REDACTED	FUP	MO 12 (EX)	65	19C	90	390	406	401	402
02JUL2002	REDACTED	FUP	MO 24 (EX)	72	18C	90	370	405	393	396

(A=Above normal B=Below normal *Abnormal BL=Borderline PI=Prolonged)

VITAL SIGNS DATA

Date	Trial	Phase	Time	Weight (kg)	BMI	Stand/Supine Pulse (b/min)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
15AUG2000	USA-121	TRT	SCREENING	131	4C	80 / 72	124 / 118	90 / 92
25AUG2000	USA-121	TRT	BASELINE	132	41	70 / 76	128 / 126	96 / 98
01SEP2000	USA-121	TRT	WEEK 1			68 / 64	122 / 124	88 / 88
12SEP2000	USA-121	TRT	WEEK 3			/ 72	/ 148	/ 80
19SEP2000	USA-121	TRT	WEEK 4 *			72 / 80	110 / 116	80 / 88
25SEP2000	USA-121	TRT	WEEK 4			70 / 68	118 / 109	68 / 60
29SEP2000	USA-121	TRT	WEEK 5			68 / 64	120 / 122	88 / 88
10OCT2000	USA-121	TRT	WEEK 7			76 / 64	118 / 100	88 / 80
23OCT2000	USA-121	TRT	WEEK 8			72 / 64	108 / 112	76 / 74
27OCT2000	USA-121	TRT	WEEK 9			72 / 64	118 / 124	78 / 82
06NOV2000	USA-121	TRT	WEEK 10			80 / 76	120 / 124	72 / 80
20NOV2000	USA-121	TRT	WEEK 12			80 / 72	118 / 120	84 / 80
04DEC2000	REDACTED	FUP	WK 2 (EX)	130	4C	72 / 72	124 / 128	84 / 70
18DEC2000	REDACTED	FUP	WK 4 (EX)	133	41	68 / 60	110 / 106	84 / 84
02JAN2001	REDACTED	FUP	WK 6 (EX)			90 / 92	122 / 124	80 / 78
13FEB2001	REDACTED	FUP	MO 3 (EX)	131	4C	76 / 68	118 / 128	88 / 94
22MAY2001	REDACTED	FUP	MO 6 (EX)	132	41	80 / 72	110 / 110	82 / 79
13AUG2001	REDACTED	FUP	MO 9 (EX)	131	4C	/	/	/
24OCT2001	REDACTED	FUP	MO 12 (EX)	134	41	80 / 80	128 / 124	84 / 80
09APR2002	REDACTED	FUP	MONTH 18 (E)	137	42	100 / 92	130 / 140	94 / 90
02JUL2002	REDACTED	FUP	MONTH 18 (E)	122	37	92 / 96	104 / 122	72 / 78

* not included in statistical analysis

CONCOMITANT MEDICATION

Medication	Trial	Start	End
Dosage atenolol 50mg	USA-121	before trial	ongoing
Hydrochlorothiazide 12.5mg	USA-121	before trial	ongoing
lorazepam 2mg	USA-121	before trial	25AUG2000
lorazepam 2mg prn	USA-121	25AUG2000	ongoing
temazepam 15mg hs prn	USA-121	25AUG2000	ongoing
antipyrine w/benzocaine 8-12 gtt	REDACTED	before trial	08DEC2000

Risperidone: Effects on Glucose Metabolism
 AE Narratives [REDACTED]

CONCOMITANT MEDICATION

Medication	Trial	Start	End
Dosage			
atenolol	[REDACTED]	before trial	ongoing
50mg			
cefalexin	[REDACTED]	before trial	08DEC2000
500mg tid			
hydrochlorothiazide	[REDACTED]	before trial	ongoing
12.5mg			
lorazepam	[REDACTED]	before trial	ongoing
2mg p.r.n.			
temazepam	[REDACTED]	before trial	ongoing
15mg hs p.r.n.			
insulin	[REDACTED]	27JUN2002	ongoing
.8 sq bid			
insulin injection, isophane	[REDACTED]	27JUN2002	ongoing
24u			
oxazepam	[REDACTED]	27JUN2002	ongoing
25mg			
potassium chloride	[REDACTED]	27JUN2002	30JUN2002
20meq			

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Trial	Severity	Related	Start	End	Phase	Days**
dyspepsia	USA-121	mild	not	25AUG00	25AUG00	treatment1	1
(upset stomach)							
insomnia	USA-121	mild	possibly	25AUG00		treatment1	1
(insomnia)							
nervousness	USA-121	moderate	possibly	07OCT00	16OCT00	treatment2	44
(increased irritability)							
agitation	USA-121	moderate	possibly	24OCT00	06NOV00	treatment2	61
(increased agitation)							
insomnia	[REDACTED]	mild	possibly	25AUG00		pre trial	-87
(insomnia)							
infection	[REDACTED]	mild	not	28NOV00	08DEC00	follow up	9
(ear infection)							

** days to onset

CLINICAL LABORATORY TESTS

The following laboratory tests had results outside of normal limits during the trial:

Test (laboratory limits, unit)			
alkaline phosphatase (31-110 U/L)			
102 at prev base	103 at base(ex)	96 at mo 3(ex)	99 at mo 6(ex)
85 at mo 12(ex)	120 at mo 24(ex)		
alt (sgpt) (6-43 U/L)			
118 at prev base	107 at base(ex)	95 at mo 3(ex)	90 at mo 6(ex)
117 at mo 12(ex)	43 at mo 24(ex)		
ast (sgot) (11-36 U/L)			
39 at prev base	32 at base(ex)	35 at mo 3(ex)	30 at mo 6(ex)
44 at mo 12(ex)	46 at mo 24(ex)		
uric acid (196-446 umol/L)			
577 at prev base	535 at base(ex)	523 at mo 3(ex)	506 at mo 6(ex)
595 at mo 12(ex)	143 at mo 24(ex)		

Risperidone: Effects on Glucose Metabolism
 AE Narratives **REDACTED**

CGI

Date	Trial	Phase	Time	CGI
25AUG2000	USA-121	TRT	BASELINE	MODERATE
12SEP2000	USA-121	TRT	WEEK 3	MODERATE
19SEP2000	USA-121	TRT	WEEK 4 *	MODERATE
25SEP2000	USA-121	TRT	WEEK 4	MODERATE
03OCT2000	USA-121	TRT	WEEK 6	MODERATE
10OCT2000	USA-121	TRT	WEEK 7 *	MODERATE
16OCT2000	USA-121	TRT	WEEK 7	MODERATE
23OCT2000	USA-121	TRT	WEEK 8	MODERATE
30OCT2000	USA-121	TRT	WEEK 9	MODERATE
06NOV2000	USA-121	TRT	WEEK 10	MODERATE
13NOV2000	USA-121	TRT	WEEK 11	MODERATE
20NOV2000	USA-121	TRT	WEEK 12	MODERATE
20NOV2000	REDACTED	FUP	BASE (EXT.)	MODERATE
04DEC2000	REDACTED	FUP	WEEK 2 (EXT.)	MODERATE
18DEC2000	REDACTED	FUP	WEEK 4 (EXT.)	MODERATE
02JAN2001	REDACTED	FUP	WEEK 6 (EXT.)	MODERATE
13FEB2001	REDACTED	FUP	MONTH 3 (EXT.)	MODERATE
22MAY2001	REDACTED	FUP	MONTH 6 (EXT.)	MODERATE
13AUG2001	REDACTED	FUP	MONTH 9 (EXT.)	MODERATE
24OCT2001	REDACTED	FUP	MONTH 12 (EXT.)	MODERATE
09APR2002	REDACTED	FUP	MONTH 18 (EXT.) *	MODERATE
02JUL2002	REDACTED	FUP	MONTH 18 (EXT.)	MODERATE

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-USA-259

JRF--TRIAL RIS-USA-259

SERIOUS ADVERSE EVENT SUMMARY

#A30322

Subject: RED #A30322	Investigator: Brenner E., MD
Age: 81 years	Trial medication: RIS/HAL
Race: Black	Treatment start: February 14, 2002
Sex: male	Treatment stop: April 25, 2002
Country: USA	Trial term: May 9, 2002
Diagn at: 23 years	Term type: Completed

Trial termination reason:

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
*diabetes mellitus (NIDDM)	mild	not	19FEB02		treatment	6
*ketosis (diabetic ketoacidosis)	moderate	not	19FEB02	26FEB02	treatment	6

** days after start of first injection

BASELINE SUBJECT DATA

- Diagnosis: (schizophrenia, undifferentiated)
- Medical and surgical history: musculoskeletal: osteoarthritis; respiratory: COPD
- Concomitant disorders: cardiovascular: hypertension; genitourinary: prostatic cancer; neurological: eps; psychiatric other than trial indication: mood swings
- Physical examination: no abnormalities
- Previous medications: haloperidol (10mg po)

TREATMENT DATA:

Trt. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
RUN-IN	HALOPERIDOL		17JAN2002	13FEB2002	10	28
TREATMENT	RISPERIDONE	1	14FEB2002	27FEB2002	25	14
TREATMENT	RISPERIDONE	2	28FEB2002	13MAR2002	25	14
TREATMENT	RISPERIDONE	3	14MAR2002	26MAR2002	37.5	13
TREATMENT	RISPERIDONE	4	27MAR2002	10APR2002	37.5	15
TREATMENT	RISPERIDONE	5	11APR2002	24APR2002	50	14
TREATMENT	RISPERIDONE	6	25APR2002	25APR2002	50	1

ORAL ADMINISTRATION DATA:

Trt. Phase	Treatment	Start	Stop	Dose (mg)	Duration
RUN-IN	HALOPERIDOL	17JAN2002	13FEB2002	10	28
RUN-IN	RISPERIDONE	31JAN2002	01FEB2002	2	2
TREATMENT	HALOPERIDOL	14FEB2002	28FEB2002	10	15
TREATMENT	HALOPERIDOL	01MAR2002	06MAR2002	5	6
TREATMENT	RISPERIDONE	07MAR2002	11APR2002	2	36
TREATMENT	RISPERIDONE	12APR2002	08MAY2002	1	27

CLINICAL NARRATIVE

RED (CRF ID #A30322) was a black male with a 58-year history of undifferentiated schizophrenia; he was 81-years old at the time of trial entry. He entered the open-label trial RIS-USA-259 on 14 February 2002. During 28 days of run-in, he received haloperidol 10 mg/day as well as two days of oral risperidone 2 mg/day. He received treatment with risperidone depot microspheres 25 mg/biweekly injection twice, risperidone depot microspheres 37.5 mg/biweekly injection twice, risperidone depot microspheres 50 mg/biweekly injection twice and supplementation with haloperidol 5-10 mg/day for 21 days and oral risperidone 1-2 mg/day for 63 days. He completed the trial on 9 May 2002.

On 14 February 2002, he received risperidone depot microspheres 25 mg/biweekly injection and 10 mg/day of haloperidol. On 19 February 2002 he was hospitalized with the serious adverse event "NIDDM" and "diabetic ketoacidosis. He was lethargic and hyperglycemic and diagnosed as a new onset diabetic. He was treated with IV solution additives and insulin. Risperidone depot microspheres injections were continued at 25 mg/biweekly on 28 February 2002 and increased to 37.5 mg/biweekly on 14 and 27 March 2002 and further increased to 50 mg/biweekly on 11 and 25 April 2002. During the trial, the other adverse events of "volume depletion", "hypercholesterolemia", "hyperpotassemia" twice, "acute renal failure", "coryza" twice and a mild episode of "hyperglycemia" occurred.

Prior medical history, concomitant disorders, and concomitant medications are provided in the narrative profile. Physical examination at baseline was unremarkable. Vital signs and ECG data were unremarkable. Relevant clinical laboratory data included glucose at 11.9 mmol/L (reference range 3.9-6.7 mmol/L) at Week -4, 5.0 mmol/L at baseline, 8.1 mmol/L at Week 2 and 9.0 mmol/L at Week 12 and haemoglobin A1c at 7.9 (reference range 4.3-6.1%) at Week -4, 12.3 at baseline, 14.2 at Week 2 and 12.6 at Week 12. Additional clinical laboratory abnormalities are provided in the narrative profile. Clinical Global Impression (CGI) was moderate to mild during run-in and remained mild throughout the trial.

The serious adverse event "diabetic ketoacidosis" resolved on 26 February 2002, and was considered moderately severe by the investigator and not related to the study medication. The serious adverse event "NIDDM" had no resolution date listed, it was considered mild by the investigator and not related to study medication.

Risperidone is not known to cause diabetes although hyperglycemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment. The sponsor considered it is unlikely there is a causal relationship between study medication and the serious adverse events.

ECG DATA

Date	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTc3 (ms)	QTcF (ms)	QTcL (ms)
17JAN2002	RI	WEEK -4	65	170	90	380	396	390	392
14FEB2002	TREAT	BASELINE	64	160	70	400	413	409	410
28FEB2002	TREAT	WEEK 2	78	160	70	310	353	338	346
27MAR2002	TREAT	WEEK 6	85	160	90	360	428	404	405
09MAY2002	TREAT	WEEK 12	90	160	80	330	404	378	381

(N-Above normal B-Below normal *-Abnormal BL-Borderline PL-Prolonged)

ECG EVALUATIONS

Date	Phase	Time	ECG aspect	ECG evaluation
17JAN2002	RI	WEEK -4	MORPHOLOGY	EARLY R-WAVE TRANSITION
14FEB2002	TREAT	BASELINE	MORPHOLOGY	EARLY R-WAVE TRANSITION
27MAR2002	TREAT	WEEK 6	MORPHOLOGY	L.A.E.
27MAR2002	TREAT	WEEK 6	MORPHOLOGY	RA ENLARGEMENT

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-USA-259

VITAL SIGNS DATA

Date	Phase	Time	Stand/Supine Pulse (b/min.)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
17JAN2002	RI	WEEK -4	71 / 65	120 / 123	70 / 80
31JAN2002	RI	WEEK -2	79 / 72	122 / 126	80 / 80
14FEB2002	TREAT	BASELINE	70 / 65	126 / 130	76 / 80
23FEB2002	TREAT	WEEK 2	81 / 77	130 / 133	76 / 76
07MAR2002	TREAT	WEEK 3	77 / 70	126 / 130	72 / 70
14MAR2002	TREAT	WEEK 4	68 / 66	140 / 143	76 / 78
21MAR2002	TREAT	WEEK 5	70 / 68	128 / 130	68 / 68
27MAR2002	TREAT	WEEK 6	80 / 76	130 / 132	70 / 70
11APR2002	TREAT	WEEK 8	81 / 77	136 / 140	80 / 80
25APR2002	TREAT	WEEK 10	77 / 71	126 / 130	78 / 76
09MAY2002	TREAT	WEEK 12	91 / 88	134 / 130	72 / 70

WRIGHT - BMI DATA

Date	Phase	Time	Weight (kg)	BMI
17JAN2002	RI	WEEK -4	72.0	26.4
31JAN2002	RI	WEEK -2	72.0	26.4
14FEB2002	TREAT	BASELINE	68.0	24.9
23FEB2002	TREAT	WEEK 2	67.0	24.6
14MAR2002	TREAT	WEEK 4	72.0	26.4
27MAR2002	TREAT	WEEK 6	71.0	26.0
11APR2002	TREAT	WEEK 8	71.0	26.0
25APR2002	TREAT	WEEK 10	71.0	26.0
09MAY2002	TREAT	WEEK 12	74.0	27.1

CONCOMITANT MEDICATION

Medication	Start	End
Dosage		
benzatropine mesilate	before trial	ongoing at end of trial
0.5mg bid		
bicalutamide	before trial	ongoing at end of trial
50mg od		
captopril	before trial	30APR2002
25mg tid		
carbamazepine	before trial	ongoing at end of trial
400mg bid		
clonidine	before trial	ongoing at end of trial
0-2mg tid		
goserelin	before trial	06MAY2002
45mg sc q 3 months		
propranolol hydrochloride	before trial	ongoing at end of trial
10mg bid		
i.v. solution additives	19FEB2002	25FEB2002
insulin		
12 'u' am & 8 'u' pm	20FEB2002	07MAY2002
pravastatin sodium		
20mg op	20FEB2002	ongoing at end of trial
insulin		
2 'u' sc	30APR2002	30APR2002
sodium polystyrene sulfonate		
30cc	30APR2002	30APR2002
goserelin		
10.8 'u' every three months	07MAY2002	ongoing at end of trial
insulin		
18 units am & pm	07MAY2002	ongoing at end of trial

Risperidone: Effects on Glucose Metabolism
AE Narratives RIS-USA-259

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
dehydration (volume depletion)	mild	not	19FEB02	26FEB02	treatment1	6
hypercholesterolaemia (hypercholesterolemia)	mild	not	19FEB02		treatment1	6
hyperkalaemia (hyperpotassemia)	mild	not	19FEB02	26FEB02	treatment1	6
renal failure acute (acute renal failure)	mild	not	19FEB02	26FEB02	treatment1	6
rinitis (coryza)	mild	not	13MAR02	17MAR02	treatment1	28
hyperglycemia (hyperglycemia)	mild	not	30APR02	30APR02	treatment2	76
hyperkalaemia (hyperpotassemia)	mild	not	30APR02	30APR02	treatment2	76
rinitis (coryza)	mild	not	03MAY02		treatment2	79

** days after start of first injection

CLINICAL LABORATORY TESTS

The following laboratory tests had results outside of normal limits during the trial:

Test (laboratory limits, unit)

alt (sgpt) (6-35 U/L)	22 at week -4	14 at baseline	45 at week 2	20 at week 12
ast (sgot) (11-36 U/L)	16 at week -4	12 at baseline	39 at week 2	14 at week 12
cholesterol (4.56-7.76 mmol/L)	6.28 at week -4	4.01 at baseline	4.55 at week 2	5.84 at week 12
glucose (3.9-6.7 mmol/L)	11.9 at week -4	5 at baseline	8.1 at week 2	9 at week 12
haematocrit (0.37-0.51 l)	0.37 at week -4	0.39 at baseline	0.33 at week 2	0.39 at week 12
haemoglobin (125-170 g/l)	119 at week -4	127 at baseline	105 at week 2	127 at week 12
haemoglobin alc (4.3-6.1 %)	7.9 at week -4	12.3 at baseline	14.2 at week 2	12.6 at week 12
lactate dehydrogenase (53-234 U/L)	170 at week -4	161 at baseline	278 at week 2	160 at week 12
neutrophils (40.5-75 %)	66.8 at week -4	78.2 at baseline	71.5 at week 2	65.8 at week 12
prolactin (1.61-19.77 ng/ml)	25.87 at week -4	10.96 at baseline	14.55 at week 2	30.2 at week 12
triglycerides (0.65-2.94 mmol/L)	6.3 at week -4	1.4 at baseline	1.76 at week 2	2.38 at week 12
uric acid (149-434 umol/L)	297 at week -4	220 at baseline	137 at week 2	202 at week 12

CGI

Date	Phase	Time	CGI
17JAN2002	RI	WEEK -4	MODERATE
31JAN2002	RI	WEEK -2	MILD
14FEB2002	TREAT	BASELINE	MILD
28FEB2002	TREAT	WEEK 2	MILD
14MAR2002	TREAT	WEEK 4	MILD
27MAR2002	TREAT	WEEK 6	MILD
11APR2002	TREAT	WEEK 8	MILD
25APR2002	TREAT	WEEK 10	MILD
09MAY2002	TREAT	WEEK 12	MILD

Differential Risk of Diabetic Ketoacidosis with Exposure to Atypical Antipsychotics

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ABSTRACT

Objective: To assess the risk of diabetic ketoacidosis (DKA) in patients using atypical antipsychotics.

Methods: Retrospective cohorts were evaluated for presence of DKA diagnosis (ICD-9-CM 250.10) using California Medicaid data. "Potentially atypical" patients were defined as those appearing within 45 days following an antipsychotic dispensation. Medication use data were obtained using endocrine analysis.

Results: The rate of DKA per 10,000 persons was 109.2 in diabetes, 12.8 in those with schizophrenia/bipolar disorder, 35.4 in atypical antipsychotic users and 43.1 in total antipsychotic users (i.e., first prescription claim occurred after the first 6 months of the study period). Of 10,537 patients who were at least once exposed to atypical agents, 5,999 were in comparison for "potentially atypical" cases were identified (31 exposures and 10,537 patients). The relative risk of developing DKA for atypical versus typical antipsychotic users was 1.41 (95% CI 1.17-1.69). Treatment group, age, race (African American patients) and the presence of other chronic or diabetic conditions as significant predictors of DKA using a logistic model.

Conclusions: The rate of DKA was significantly greater for patients exposed to atypical antipsychotics. Additional study is needed to confirm these findings.

INTRODUCTION

Atypical antipsychotics have been associated with impaired glucose metabolism, exacerbation of existing diabetes, new-onset type 2 diabetes and diabetic ketoacidosis (DKA), a rare but potentially fatal metabolic complication.¹ However, evidence suggests that the strength of these associations varies between agents. Chlorzazine and clozapine, in particular, have been implicated in a large number of published case reports.²⁻¹¹ The purpose of the present study was to assess the risk of DKA associated with use of atypical antipsychotics in a large population of Medicaid recipients.

METHODS

- This was a retrospective, cohort study based on California Medicaid data.
- Hospital claims were evaluated for the presence of DKA diagnosis, as defined by the International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM).
- The study was conducted in two phases.
 - Phase I: 20% random sample from 1993-2001
 - Phase II: Preliminary results from the 20% data supported further analysis using a larger 100% dataset (study period: July 1997-September 2000)

In Phase I

- The period prevalence of DKA was estimated from the 20% random sample as follows:
 - Number of DKA cases identified during the study period (1993-2001)
 - Total population of interest during study period (1993-2001)

- Period prevalence on antipsychotics were performed for the following non mutually exclusive patient populations:
 - Med-Cal general population
 - All Medicaid recipients with at least one medical claim
 - Diabetic patients
 - Patients with at least one claim for an ICD-9-CM code of "250" in either of the two recorded diagnosis fields
 - Patients exposed to atypical antipsychotics
 - Patients with at least one claim for atypical antipsychotic (e.g., "256.0", "256.1", "256.2", "256.3", "256.4", "256.5", "256.6", "256.7", "256.8", "256.9" or "256.9") in either of the two recorded diagnosis fields
 - Patients with schizophrenia or bipolar disorder
 - Identified based on presence of at least one prescription claim for any combination of atypical antipsychotic medication. ADD criteria were therefore for these medications using the Medicaid "diagnosis" database.
 - Patients with atypical antipsychotic prescription claims
 - Identified based on presence of at least one prescription claim for any atypical antipsychotic medication
 - Patients with initial atypical antipsychotic prescription claims
 - Identified based on 1) that the first prescription claim occurred after the first 6 months of the study period (i.e., at least 6 months with no prescription claim for an atypical)

These populations define the different denominators for the period prevalence estimates.

In Phase II (100% Medicaid population)

- "Potentially atypical" cases of DKA were defined as those occurring after the initial prescription claim for an atypical agent, where there are at least one antipsychotic prescription claim within 45 days prior to the event.
- The relative risk of DKA for linked cases of atypical versus atypical versus typical antipsychotic medication was estimated.
- A logistic model was developed to predict the odds of DKA and to estimate the association with atypical antipsychotics.

RESULTS

Phase I

- Although the prevalence of DKA was slightly lower in patients using atypical antipsychotics than in patients with schizophrenia/bipolar disorder, it was more than 3 times greater than in the general population (Table 1). As expected, the prevalence of DKA was higher in patients with diabetes in schizophrenia/bipolar disorder than in the general population (Table 1).

Table 1. Period prevalence of diabetes and diabetic ketoacidosis (DKA) in selected patient populations using California Medicaid (CA) from July 1997 to September 2000

Population	N	Diabetes (%)	DKA per 10,000 persons	95% CI	Prevalence ratio
All patients	1,053,700	7.2	12.8	11.7-13.9	1.0
Med-Cal general population	1,053,700	7.2	12.8	11.7-13.9	1.0
Diabetic patients	105,370	72.0	109.2	98.5-120.0	8.5
Schizophrenia/bipolar disorder	105,370	18.0	35.4	31.5-39.4	2.8
Atypical antipsychotic users	10,537	4.0	43.1	38.2-48.0	3.4
Total antipsychotic users	10,537	4.0	43.1	38.2-48.0	3.4
DKA cases	1,053,700	0.1	10.9	9.8-12.0	0.8

DKA cases were identified from the 20% random sample.

Phase II

- Figure 1 shows the primary outcome for identifying "potentially atypical" cases of DKA in the 100% dataset. 31 and 55 cases of DKA were identified among the linked cases of schizophrenia and bipolar disorder, respectively (Table 2). An outcome similar to that observed in Phase I of the study.
- The unadjusted relative risk of DKA was 1.78 for those greater with exposure versus schizophrenia (p=0.0006, Table 3).
- Treatment group, age, race (African American race) and the presence of schizophrenia or bipolar disorder were identified as significant predictors of DKA using a logistic model (Table 4). The logistic model showed that the odds of DKA was 1.82 times greater for patients treated with atypical versus typical antipsychotics (p<0.001, Table 4).

Figure 1. Diagram of possible outcomes seen in the study design.

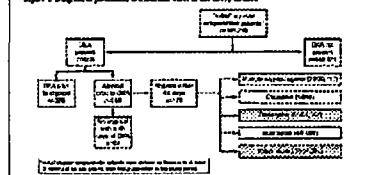


Table 2. Incidence rates of diabetic ketoacidosis (DKA) by drug treatment (95% CI). Cases were not necessarily attributable to exposure antipsychotic agents but are reported per Figure 1 for details

Population	N	DKA (%)	DKA per 10,000 persons	95% CI
Schizophrenia/bipolar disorder	105,370	0.03	3.1	2.0-4.2
Atypical antipsychotic users	10,537	0.03	3.1	2.0-4.2
Total antipsychotic users	10,537	0.03	3.1	2.0-4.2
DKA cases	10,900	0.03	10.9	9.8-12.0

LIMITATIONS

- Family history of diabetes and weight change over time was not available.
- Underreporting of diabetes might be minimal, as few of these data were.
- Potential bias of duration of exposure to antipsychotics will be presented in a subsequent publication.

Table 3. Unadjusted risk of diabetic ketoacidosis (DKA) with exposure and schizophrenia (95% CI)

Population	N	Diabetes (%)	DKA per 10,000 persons	95% CI
Schizophrenia/bipolar disorder	105,370	18.0	35.4	31.5-39.4
Atypical antipsychotic users	10,537	4.0	43.1	38.2-48.0
Total antipsychotic users	10,537	4.0	43.1	38.2-48.0

Table 4. Odds of developing DKA by logistic model (95% CI) showing

Variable	OR	95% CI
Age (years)	1.02	1.01-1.03
Gender (male)	1.01	0.99-1.03
Race (African American)	1.01	0.99-1.03
Diagnosis (schizophrenia/bipolar disorder)	1.78	1.62-1.94
Atypical antipsychotic users	1.82	1.62-2.02

CONCLUSIONS

- The period prevalence of DKA was estimated to be greater in patients with schizophrenia/bipolar disorder, in patients with prescriptions for any antipsychotic or any atypical antipsychotic agents, and in patients with diabetes compared with the general Med-Cal population.
- The unadjusted incidence rate of DKA appears to be different across the different antipsychotics. However, low rates for quetiapine and risperidone precluded further statistical testing.
- The adjusted risk of DKA was significantly greater in patients using atypical versus typical antipsychotics, after accounting for factors such as age, sex, race, major psychiatric diagnosis, prior diagnosis of diabetes, and history of atypicality in Med-Cal.
- While further study is needed using data that provide more detail concerning clinical variables, it would be prudent to exercise caution when making prescribing choices among atypical antipsychotics for patients with preexisting factors for DKA.

REFERENCES

1. Hsu CY, Mendenhall CL. Hyperglycemia and antipsychotic medications. J Clin Psychiatry 2001;62(suppl 2):18-28.
2. Arora A, Mendenhall CL, Ruzynski K, et al. Atypical antipsychotics and new-onset diabetes mellitus. J Clin Psychiatry 2002;63:254-258.
3. Arora A, Mendenhall CL, Ruzynski K, et al. Atypical antipsychotics and new-onset diabetes mellitus: a retrospective analysis of new-onset diabetes mellitus in patients with schizophrenia. Am J Psychiatry 2002;159:664.
4. <http://www.medicare.gov> access here.

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Clozapine-associated Diabetes

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PURPOSE: Clozapine is a potent antipsychotic agent that has been marketed since 1990. Several published reports of diabetes mellitus occurring with clozapine therapy have appeared during the past 5 years. Because the risk and characteristics of clozapine-associated diabetes mellitus remain unclear, we conducted a descriptive epidemiologic study of spontaneous adverse event reports of hyperglycemia occurring in clozapine-treated patients.

MATERIAL AND METHODS: The Food and Drug Administration MedWatch surveillance program was queried (January 1990 through February 2001), and the results were pooled with published cases. Parameters assessed included documentation of diabetes, clinical severity, new-onset diabetes versus exacerbation of preexisting disease, demographic characteristics of patients, time to onset of hyperglycemia, and effect of drug discontinuation and rechallenge.

RESULTS: We identified 384 reports. Of these, new-onset dia-

betes was diagnosed definitively in 242 patients, and 54 patients had exacerbation of preexisting disease. The mean ($\pm$ SD) age was 40 ± 12 years (range, 13 to 77). The male:female ratio was 2:0. Most cases appeared within 6 months of initiating clozapine therapy. One patient developed diabetes following a single 500-mg dose. There were 80 cases of metabolic acidosis or ketosis. Twenty-five patients died during hyperglycemic episodes. Forty-six patients had improved glycemic control after discontinuation or dose reduction of the drug.

CONCLUSIONS: A causal relationship between clozapine and diabetes is suggested by the number of reports, the temporal relation to clozapine initiation, the relatively young age of the affected patients, and the prompt reversibility on withdrawal of the drug in some patients. The severity of reported cases ranged from mild glucose intolerance to diabetic ketoacidosis or hyperosmolar coma. *Am J Med.* 2001;111:716-723. © 2001 by Excerpta Medica, Inc.

Clozapine was approved in the United States in 1989 for the management of schizophrenia. The major advantages of clozapine over conventional neuroleptics are greater efficacy and a reduced incidence of extrapyramidal side effects and tardive dyskinesia (1). Adverse reactions to clozapine include agranulocytosis, orthostatic hypotension, seizures, hypersalivation, sedation, and weight gain. Because of the risk of agranulocytosis, refills are initially obtained weekly, although recent changes permit biweekly prescriptions for patients who have been stable for 6 months. Between 1994 and 2000, there have been approximately 1.5 to 2 million clozapine prescriptions per year in the United States (2).

Since 1995, there have been several published reports of diabetes mellitus occurring in association with clozapine therapy (3-27). The spectrum of reported illness has ranged from mild glucose intolerance to diabetic ketoacidosis and nonketotic hyperosmolar coma. In 1998, Hagg et al. (8) reported an increased incidence of glucose intolerance or diabetes in clozapine-treated patients, as compared with patients treated with conventional neuroleptics. Stronger evidence was recently provided in a 5-year observational study (28); of 82 clozapine-treated

patients, 30 (36%) were diagnosed with new-onset diabetes by 60 months of treatment, including 22 (27%) who required treatment with oral agents or insulin. There was no correlation between weight gain and development of diabetes. The mean ($\pm$ SD) age of patients with diabetes was 36 ± 8 years.

To gain further insight into the clinical characteristics of diabetes reported in association with clozapine, we attempted to identify all such cases submitted to the Food and Drug Administration (FDA) MedWatch surveillance program.

MATERIAL AND METHODS

We identified cases by querying the MedWatch Drug Surveillance System from January 1990 to February 2001. Published cases were identified via Medline (January 1985 to February 2001). We also reviewed selected abstracts from national endocrinology and diabetes meetings. We combined multiple reports of the same cases. Drug utilization data were obtained through the IMS Health *National Prescription Audit Plus* and the IMS Health *National Disease and Therapeutic Index* (2,29).

We assessed documentation of diabetes, severity of illness, whether the hyperglycemia was new onset, demographic features, time to onset of hyperglycemia, and effect of drug discontinuation. We arbitrarily defined "documentation" of new-onset diabetes as a fasting glucose level ≥ 126 mg/dL, a random glucose level ≥ 200 mg/dL, or an elevated glycosylated hemoglobin A_{1c} (HbA_{1c}) level; the presence of metabolic acidosis or ketosis; or phy-

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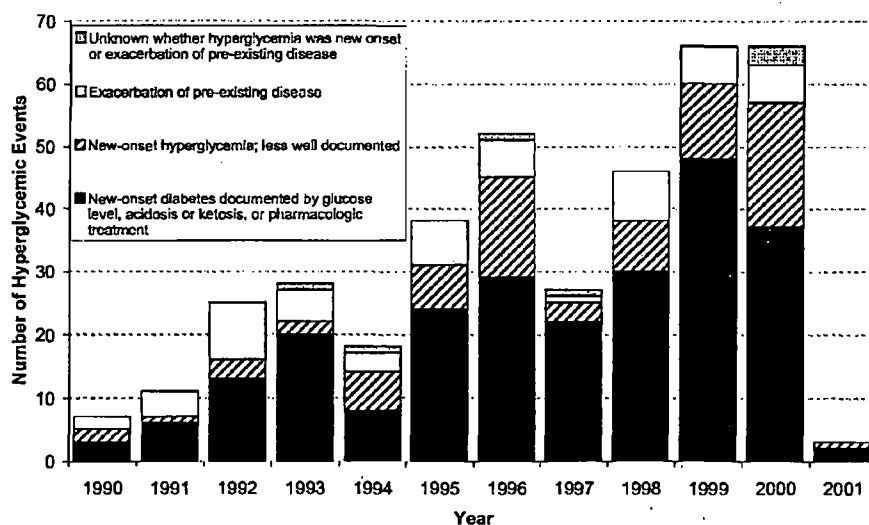


Figure 1. Hyperglycemic adverse event reports by year. Hyperglycemic events were categorized by the nature of their documentation and the year of their occurrence. If the date of occurrence was unavailable, events were posted to the time of the adverse event report or the date of publication.

sician institution of antidiabetic medication. Patients without definitive documentation were classified separately.

RESULTS

We identified 384 cases of clozapine-associated diabetes or hyperglycemia (238 originating in the United States and 146 from international sources), including 39 cases in 24 publications (3–27). The number of cases reported per year increased over time, in parallel with drug utilization (Figure 1).

There were 323 reports of new-onset “hyperglycemia.” Of these, 171 patients fit the criteria for the diagnosis of diabetes (Figure 1). Of the patients whose diabetes was determined by fasting blood glucose levels, all but 4 had levels ≥ 140 mg/dL. Among the 152 patients whose reports lacked definitive laboratory data for the diagnosis of diabetes, 49 received antidiabetic drug therapy. Seven of these 49 were also reported to have had acidosis or ketosis. Another 22 patients had acidosis or ketosis at the time of hyperglycemia, but lacked additional diagnostic data.

In addition to these 323 cases, there were 54 reports in which metabolic control in patients with preexisting diabetes worsened following clozapine initiation. In 7 additional cases, it was unclear whether the diabetes was new onset or preexistent.

Demographic Features

The 171 cases of new-onset diabetes documented by serum glucose or HbA_{1c} levels had a mean age of 39 ± 11 years (range, 13 to 74 years), with at least 40% ($n = 68$) of patients presenting in the fourth decade of life (Table 1). The male:female ratio in this subgroup was 2:9 (Table 1). Of the 54 patients with exacerbation of diabetes, the average age was 48 ± 14 years (range, 17 to 77), with a male:female ratio of 1:3. For the remaining subgroups, the age and sex distributions were similar to those of the better-documented cases. Racial information was provided for only 36 patients: African descent ($n = 21$), white ($n = 8$), Asian ($n = 3$), Caribbean ($n = 3$), and African-Asian ($n = 1$).

Time to Onset

Adequate information was available for 141 of the 171 patients with new-onset diabetes documented by glucose levels. In 38 patients (27%), diabetes was diagnosed within the first month of clozapine therapy and in 79 (56%) within the first 3 months (Figure 2). One patient developed diabetes immediately after a single accidental clozapine dose of 500 mg.

Information was available for 47 of the 54 patients with exacerbation of preexisting diabetes. The exacerbation was observed within the first month of initiation of clozapine in 38% ($n = 18$) and within the first 3 months in 64% ($n = 30$) of patients.

Table 1. Characteristics of Patients with Clozapine-associated Hyperglycemia

Category of Hyperglycemic Report	Age (years)			Distribution by Age (Years)			Sex Ratio (Male:Female)		Dose of Clozapine (mg)		
	Mean $\pm$ SD	Range	% Known	11-30	31-50	50+	Ratio (% Known)	% Known	Mean $\pm$ SD	Range	% Known
New-onset hyperglycemia (n = 323)	39 $\pm$ 11	13-74	88	56	192	38	2:2 (9:1)	82	369 $\pm$ 202	25-1350	82
Documented by glucose level (n = 171)	39 $\pm$ 11	13-74	94	32	108	21	2:9 (97)	88	360 $\pm$ 195	25-1000	88
Documented by pharmacologic therapy (n = 49)	42 $\pm$ 12	16-67	94	6	30	10	1:3 (100)	96	366 $\pm$ 168	75-900	96
Documented by acidosis or ketosis (n = 22)	36 $\pm$ 10	22-57	91	6	12	2	2:5 (95)	82	325 $\pm$ 234	25-900	82
Less well documented (n = 81)	38 $\pm$ 11	17-70	73	12	42	5	1:7 (73)	63	413 $\pm$ 234	125-1350	63
Exacerbation of preexisting disease (n = 54)	48 $\pm$ 14	17-77	93	6	22	22	1:3 (96)	87	342 $\pm$ 246	25-1000	87
Unknown if new onset or exacerbation of preexisting disease (n = 7)	35 $\pm$ 11	15-52	100	1	5	1	1:3 (100)	100	239 $\pm$ 131	100-400	100
Total (n = 384)	40 $\pm$ 12	13-77	89	63	219	61	2:0 (92)	83	362 $\pm$ 208	25-1350	83

In the majority of cases (175 of the 293 with data), the time to diagnosis of hyperglycemia was 6 months or less (range, 2 days to >5 years). However, in 37 of the 81 patients with hyperglycemia but insufficient diagnostic data, the time to onset was unknown.

Dosage

The average clozapine dose (362 ± 208 mg; data available for 83% [n = 320] of cases) was similar for all categories of hyperglycemia (Table 1). There was no association between dose and severity of hyperglycemia, presence of acidosis, or time to onset of hyperglycemia (cumulative exposure). The correlation coefficients between dose and time to onset were 0.27 for all cases (n = 275), 0.27 for new-onset cases (n = 225), 0.23 for cases of exacerbation of diabetes (n = 44), and 0.41 for cases in which it was unknown whether the hyperglycemia was new onset or preexisting (n = 6). Drug levels were not available.

Concomitant Medications

No patient received systemic glucocorticoids, although 1 patient received megestrol acetate. One patient had used niacin, and 2 had used hydrochlorothiazide. The most frequent concurrent medications were valproic acid, lithium, benzatropine, major tranquilizers, thyroid hormone, histamine (H_2) blockers, and proton pump inhibitors.

Reversibility

Clozapine was discontinued in 110 cases. Of these, follow-up data were available in 54 cases: 42 were reported to have improved and 11 had no change in metabolic status. One patient died before further data could be acquired. Of the patients who improved, 26 no longer required hypoglycemic drug therapy; in some of these patients (n = 18), glucose levels returned to normal. The clozapine dose was reduced in at least 14 cases. Of these, follow-up data were available in 5 cases: 4 improved (1 with a normal glucose level), and 1 continued to require insulin. For patients who continued clozapine therapy, there were insufficient data to determine the course of their diabetes.

Twelve patients were rechallenged with clozapine. Of these, 9 experienced deterioration in glycemic control (within 3 days of rechallenge for 2 patients), 1 did not deteriorate, and the responses of 2 are unknown. Glycemic control improved again after clozapine discontinuation in 4 of the patients who were rechallenged.

Serious Outcomes

Metabolic abnormalities ranged from mild glucose intolerance to ketoacidosis and hyperosmolar coma. In 51 cases, primarily patients with new-onset diabetes (n = 45), the blood glucose level was ≥ 700 mg/dL (Table 2). At least 63% (n = 32) of these cases occurred within 3 months of the initiation of clozapine therapy.

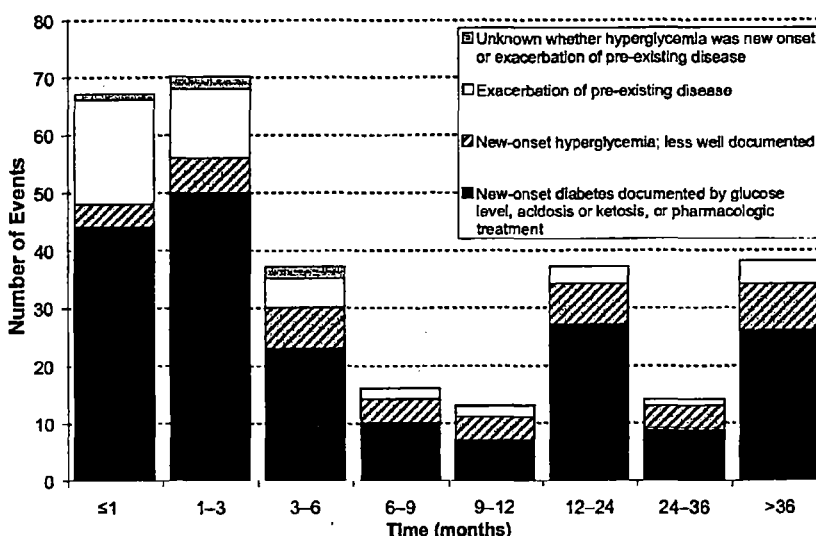


Figure 2. Time to hyperglycemic event. Hyperglycemic events were categorized by the time to occurrence after initiation of therapy. Data were available for 293 patients (76%). Most hyperglycemic events were identified within the first 6 months of clozapine treatment, but several cases had delayed onset.

In 80 cases, metabolic acidosis or ketosis accompanied the hyperglycemia; 91% ($n = 73$) were patients with new-onset diabetes. Although the acidosis was generally mild, the glucose level at presentation was often >500 mg/dL. Of the 51 patients with glucose levels >700 mg/dL, 26 had acidosis or ketosis.

Twenty-five patients died during hyperglycemic episodes. Sixteen of these were reported to have had acidosis or ketosis. Often, these patients had multiple medical problems at the time of death, making it difficult to determine whether the hyperglycemia played a primary or ancillary role. In some cases, however, there were few confounding medical problems. One euglycemic hospitalized patient, aged 54 years, died unexpectedly, with ketoacidosis identified postmortem.

There were 17 reports of pancreatitis or hyperamylasemia in association with hyperglycemia. Of the 12 patients with concomitant acidosis or ketosis, 2 had elevated lipase levels and 4 had autopsy findings of pancreatitis. Four patients with pancreatitis or hyperamylasemia had glucose levels ≥ 700 mg/dL.

Risk Factors

The reports did not provide systematic information on risk factors for diabetes. Limited body weight data were available for 146 patients. In 26% ($n = 38$), there was no clear evidence of obesity or substantial weight gain. Information on family history was provided for 63 patients; 44% ($n = 28$) of these had no family history of diabetes.

DISCUSSION

The FDA MedWatch system can provide signals of adverse events associated with marketed drugs. Limitations of the system include lack of control populations, incomplete case descriptions, and substantial under-reporting. Several of our findings suggest a relation between clozapine use and diabetes. These include the number of cases reported, the temporal relation to initiation of clozapine therapy, and the prompt reversibility of the diabetes on withdrawal of the drug in some cases. Furthermore, the mean age of the affected patients (40 ± 12 years) is considerably less than that which is typical of patients with type 2 diabetes. Data from the National Health Interview Surveys indicate that the overwhelming majority of newly diagnosed cases of type 2 diabetes occurs in patients older than 44 years, with the highest frequency in the 65-year to 74-year age cohort (30). In addition to the relative young age of the clozapine-associated cases, the sex imbalance is also atypical of diabetes. The male:female ratio for patients with diabetes is usually 0:8 (30). There are no known sex-related differences for the prevalence of schizophrenia (31), or in clozapine prescribing patterns over time (29).

Among patients who received clozapine during a 10-year period, we identified 197 new cases of diabetes in the United States. During this time interval, approximately 13 million clozapine prescriptions were written (2). Clozapine prescriptions are written weekly (or now biweekly

Table 2. Cases of Severe Hyperglycemia

Diabetes Presentation	Year of Presentation	Age	Sex	Glucose Level (mg/dL.)	Acidosis or Ketosis	Time to Onset	Clozapine Dose (mg)*	Comments
New onset	1995	64	F	1229		3 months	150	
New onset	1999	57	F	720	Yes	20 months	450	Mental status change, hyperamylasemia
New onset	1995	51	M	1700		3 weeks	200	
New onset	2000	51	M	722	Yes	6 months	200	
New onset	1999	50	F	1000	Yes	30 days	400	Improved with dose reduction
New onset	1996	50	M	1100		22 days	250	
New onset	1998	49	F	800-1000 (vitreal)	Yes	6 weeks	100	Death
New onset	1993	49	M	3500		?	?	
New onset	1999	46	M	750		4 months	400	
New onset	1994	46	M	762	Yes	5 weeks	500	
New onset	1998	44	M	800	Yes	9 months	250	Drug stoppage, death
New onset	1991	43	F	700		3-4 weeks	400	Myocardial infarction
New onset	2000	42	M	1350	Yes	8 months	300	
New onset	1997	41	M	1028		5 weeks	200	Mental status change, hyperamylasemia
New onset	1992	41	M	829		2 months	900	Improved after drug stoppage
New onset	1996	41	M	1000		10 days	300	
New onset	1999	40	M	990	Yes	16 days	?	
New onset	2000	40	M	1300	Yes	43 days	300	Mental status change, death
New onset	1996	39	F	1200		1 month	300	Death from cardiopulmonary complications
New onset	1993	38	M	1300-1400		7 weeks	450	Coma
New onset	2000	38	M	776		45 days	300	Improved after drug stoppage
New onset	1997	37	M	1000	Yes	11 weeks	75	Death
New onset	1996	37	M	700		<33 days	300	
New onset	1997	36	F	700		25 months	650	Loss of consciousness
New onset	1993	35	M	1000	Yes	?	300	Death
New onset	1999	35	M	1000	Yes	?	?	Coma
New onset	1993	35	M	900		20 days	175	
New onset	1999	34	M	1100		80 days	400	Coma, sepsis, death
New onset	1992	34	F	1224	Yes	6 weeks	250	Intubated, improved after drug stoppage
New onset	1995	34	M	700	Yes	6 weeks	300	
New onset	1996	33	M	1300		2-6 weeks	150	
New onset	1993	33	M	1300	Yes	16 months	600	Gastrointestinal bleed, improved after drug stoppage
New onset	1996	32	M	1281	Yes	?	600	Pancreatitis
New onset	1996	32	M	930	Yes	8 weeks	425	Mental status change, hypotensive, improved after drug stoppage
New onset	1999	31	M	1200	Yes	6 weeks	800	Mental status change, intubation
New onset	1999	31	M	756	Yes	3 months	200	Improved after drug stoppage
New onset	1997	31	M	757	Yes	7-8 months	100	Improved after drug stoppage
New onset	1999	30	M	755	Yes	35 days	350	Mental status change
New onset	1995	29	M	1060	Yes	6 days	50	Mental status change, death
New onset	1999	27	M	1010		39 days	300	Improved after drug stoppage
New onset	1994	24	F	1360		1 month	250	
New onset	2000	21	M	867	Yes	12 months	325	Improved after drug stoppage
New onset	1995	15	M	1300		34 days	300	Pancreatitis
New onset	1996	15	M	>800		~4 weeks	300	Improved after drug stoppage
New onset	1998	?	M	900		8 days	300	Pneumonia
Exacerbation	2000	49	F	965	Yes	18 months	100	Improved after dose reduction
Exacerbation	1992	39	M	1000		2.3 years	800	
Exacerbation	1991	39	F	800		12 months	150	
Exacerbation	1996	36	M	1175	Yes	?	750	Pneumonia
Unknown	1996	35	F	700		5 months	300	
Unknown	1993	30s	M	1000	Yes	5 months	400	Collapse

* Maximal daily dose.

? = unknown; F = female; M = male.

in stable patients), so the number of patients treated with clozapine during this period ranges from 20,000 to 40,000 per year. Ninety-two percent of clozapine "appearances" (new prescriptions, refills, and samples) were for patients up to 64 years of age, and 73% for patients up to 44 years of age (29). In this population, the expected number of newly diagnosed patients with diabetes would be about 2.3/1000 per year or about 46 cases per year (30). Although the 197 cases we identified are consistent with these estimates, substantial underreporting is characteristic of systems such as MedWatch (32–39). Experience with several drugs has demonstrated that only 1% to 10% of events are captured through this form of surveillance (32–39). Thus, our 197 patients may be a substantial underestimation of the true number of patients with diabetes in this population. On the other hand, surveillance for agranulocytosis may have resulted in better reporting.

There is no obvious mechanism by which clozapine impairs carbohydrate metabolism. Although weight gain can occur, available data do not implicate this factor in the development of hyperglycemia (8,28,40). Furthermore, the prompt (<1 month) onset of diabetes in many patients strongly argues against a primary role for weight gain, although it may contribute to the late-onset hyperglycemia that was observed.

There is no overt chemical similarity between clozapine and known islet cell toxins, such as alloxan, pentamidine, and streptozocin. Although all of these compounds have ring structures, the rings are not uniformly planar, nor are there common side chains. Chlorpromazine, a classic antipsychotic with a similar, triple ring structure but a different side chain, has also been associated with glucose intolerance (41), and fatal, rapid-onset neuroleptic malignant syndrome and diabetic ketoacidosis occurred in a 44-year-old man 21 days after initiating chlorpromazine and 5 days after a test dose of zuclopenthixol decanoate (42). There also have been recent reports of hyperglycemia associated with olanzapine, another atypical antipsychotic agent (26,43–48). Indeed, 2 patients in our series experienced repeat deterioration in glycemic control when switched to risperidone or olanzapine after clozapine discontinuation (17). It is also possible that clozapine metabolites contribute to carbohydrate intolerance or that clozapine metabolism differs in affected persons (8,49–51).

The causes of diabetes identified in these reports might be unrelated to clozapine. Indeed, some have postulated that both type 1 and type 2 diabetes are more common in patients with schizophrenia (52–57). These studies, however, are limited by the changes in diagnostic criteria for schizophrenia, small sample sizes, retrospective designs, absence of contemporaneous controls, or prior use of other antipsychotic agents that may also increase carbohydrate intolerance. Of note, patients with tardive dysk-

nesia appear to have more glucose intolerance than do patients without movement disorders (58,59), and glucose tolerance improves with discontinuation of antipsychotic agents (58). Further studies will be needed to define the background rates of diabetes in patients with schizophrenia and the effect of individual or classes of antipsychotic agents on carbohydrate tolerance.

The results of this survey suggest that there may be a causal relationship between clozapine and the development or worsening of diabetes. The onset of hyperglycemia may be rapid and severe, the association is not dose dependent, and the risk does not end with extended use. The effects of clozapine-induced sedation may delay the diagnosis of hyperglycemia in some patients. Therefore, clinicians should be alert to this potential complication. Spontaneous adverse event reporting can neither establish causality nor determine incidence and prevalence; therefore, additional investigation is warranted.

ACKNOWLEDGMENT

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REFERENCES

1. Umbricht D, Kane JM. Medical complications of new antipsychotic drugs. *Schizophr Bull*. 1996;22:475–483.
2. IMS HEALTH-National Prescription Audit Plus®. 1991–1992 (book data), 1993–2000 (electronic data). Mail order data not included prior to 1993. Plymouth Meeting, PA.
3. Ai D, Roper TA, Riley JA. Diabetic ketoacidosis and clozapine [letter]. *Postgrad Med J*. 1998;74:493–494.
4. Avram A, Patel V, Taylor HC. Clozapine-induced diabetic ketoacidosis: report of a case and critical review of the literature. In: *Abstracts of the American Association of Clinical Endocrinologists Annual Meeting*. 2000;4:5.
5. Bruggman NJ, Cohen D, de Vries RH. Diabetes mellitus after treatment with clozapine [letter] [in Dutch]. *Ned Tijdschr Geneesk*. 2000;144:437–439.
6. Colli A, Cociolo M, Francobandiera G, et al. Diabetic ketoacidosis associated with clozapine treatment [letter]. *Diabetes Care*. 1999;22:175–176.
7. Good MI. Lethal interaction of clozapine and buspirone [letter?]. *Am J Psychiatry*. 1997;154:1472–1473.
8. Hagg S, Joelsson L, Mjorndal T, et al. Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. *J Clin Psychiatry*. 1998;59:294–299.
9. Isakov I, Klesner J, Masand PS. Insulin-resistant hyperglycemia induced by clozapine [letter]. *Psychosomatics*. 2000;41:4.

10. Kamran A, Doraiswamy PM, Jane JL, et al. Severe hyperglycemia associated with high doses of clozapine [letter]. *Am J Psychiatry*. 1994;151:1395.
11. Koller E, Bennett K, Dubitsky G, et al. Clozapine-associated diabetes. In: *Abstracts of The Endocrine Society Annual Meeting*. 1999;214: P1-377.
12. Kostaglu AE, Yazici KM, Erbas T, Guvener N. Ketoacidosis as a side effect of clozapine: a case report [letter]. *Acta Psychiatr Scand*. 1996; 93:217-218.
13. Koren W, Krieris Y, Duchowiczny K. Lactic acidosis and fatal myocardial infarction due to clozapine. *Ann Pharmacother*. 1997;31: 168-170.
14. Koval MS, Raines LJ, Christie S. Diabetic ketoacidosis with clozapine treatment [letter]. *Am J Psychiatry*. 1994;151:1520-1521.
15. Maule S, Giannella R, Lanzio M, Villari V. Diabetic ketoacidosis with clozapine treatment [letter]. *Diabetes Nutr Metab*. 1999;12: 187-188.
16. Melkersson KI, Hulting AL, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose insulin homeostasis in patients with schizophrenia or related psychoses. *J Clin Psychiatry*. 1999;60:783-791.
17. Mohan D. Schizophrenia and diabetes mellitus [letter]. *Br J Psychiatry*. 1999;174:180-181.
18. Peterson GA, Byrd SL. Diabetic ketoacidosis from clozapine and lithium cotreatment [letter]. *Am J Psychiatry*. 1996;153:737-738.
19. Picrides M. Clozapine monotherapy and ketoacidosis [letter]. *Br J Psychiatry*. 1997;171:90-91.
20. Popli AN, Konicki PE, Jurjus GJ, et al. Clozapine and associated diabetes mellitus. *J Clin Psychiatry*. 1997;58:108-111.
21. Ramackers GM, Rambharos R, Matroos G. Diabetes mellitus after treatment with clozapine [letter]. [in Dutch]. *Ned Tijdschr Geneesk*. 2000;144:1463-1464.
22. Rigalleau V, Gatta B, Bonnaud S, et al. Diabetes as the result of anti-psychotic drugs: a report of three cases. *Diabetes Med*. 2000;17: 484-486.
23. Smith H, Kenny-Herbert J, Knowles L. Clozapine-induced diabetic ketoacidosis [letter]. *Aust NZ J Psychiatry*. 1999;33:120-121.
24. Thompson J, Chengappa KNR, Good CB, et al. Hepatitis, hyperglycemia, pleural effusion, eosinophilia, hematuria, and proteinuria occurring early in clozapine treatment. *Int Clin Psychopharmacol*. 1998;13:95-98.
25. Wehner H, Alexander B, Perry PJ. Diabetes mellitus associated with clozapine therapy. *Pharmacotherapy*. 2000;20:844-847.
26. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. *Biol Psychiatry*. 1998;44:779-783.
27. Wu G, Dias P, Wu C, et al. Hyperglycemia, hyperlipidemia, and periodic paralysis: a case report of new side effects of clozapine. *Prog Neuropsychopharmacol Biol Psychiatry*. 2000;24:1395-1400.
28. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five year naturalistic study. *Am J Psychiatry*. 2000;157:975-981.
29. IMS HEALTH-National Disease and Therapeutic Index®. Plymouth Meeting, PA.
30. Kenny SJ, Aubert RE, Geiss LS. Prevalence and incidence of non-insulin dependent diabetes. In: Harris MI, Cowie CC, Stern MP, et al., eds. *Diabetes in America*. 2nd ed. Bethesda: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:47-67. Publication 95-1468.
31. Andreasen NC, Kane JM, Keith S, et al. Schizophrenia and other psychotic disorders. In: First MB, ed. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994:273-316.
32. Bates DW, Cullen DJ, Laird N, et al, for the ADE Prevention Study Group. Incidence of adverse drug events and potential adverse drug events: implications for prevention. *JAMA*. 1995;274:29-34.
33. Bennett BS, Lipman AG. Comparative study of prospective surveillance and voluntary reporting in determining the incidence of adverse events. *Am J Hosp Pharm*. 1977;34:931-936.
34. Eland LA, Belton KJ, van Grootheste AC, et al. Attitudinal survey of voluntary reporting of adverse drug reactions. *Br J Clin Pharmacol*. 1999;48:623-627.
35. Inman WIIW. Investigation of deaths from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age. *BMJ*. 1968;2:193-199.
36. Kimmel SE, Sekeres MA, Berlin JA, et al. Adverse events after protamine administration in patients undergoing cardiopulmonary bypass: risk and predictors of under-reporting. *J Clin Epidemiol*. 1998;51:1-10.
37. McGettigan P, Golden J, Conroy RM, et al. Reporting of adverse drug reactions by hospital doctors and the response to intervention. *Br J Clin Pharmacol*. 1997;44:98-100.
38. Rogers AS, Israel E, Smith CR, et al. Physician knowledge, attitudes, and behavior related to reporting adverse drug events. *Arch Intern Med*. 1988;148:1596-1600.
39. Tyler LS, Nickman NA. Hospital pharmacy compliance with JCAHO standards and ASHP guidelines for reporting adverse drug reactions. *Am J Hosp Pharm*. 1992;49:845-850.
40. Frankenburg FR, Zanarini MC, Kando J, Centorrino F. Clozapine and body mass change. *Biol Psychiatry*. 1998;43:520-524.
41. Annoni HR, Orzi L, Steinle J. Effect of chlorpromazine (CPZ) on insulin release in vivo and in vitro in the rat. *J Pharmacol Exp Ther*. 1973;187:423-429.
42. De Boer C, Gaete HP. Neuroleptic malignancy syndrome and diabetic keto-acidosis. *Br J Psychiatry*. 1992;161:856-858.
43. Fertig MK, Brooks VG, Sheldon PS, English CW. Hyperglycemia associated with olanzapine [letter]. *J Clin Psychiatry*. 1998;59:687-689.
44. Gatta B, Rigalleau V, Gin H. Diabetic ketoacidosis with olanzapine treatment [letter]. *Diabetes Care*. 1999;22:1002-1003.
45. Goldstein LE, Sporn J, Brown S, et al. New-onset diabetes mellitus, and diabetic ketoacidosis associated with olanzapine treatment. *Psychosomatics*. 1999;40:438-443.
46. Ober SK, Hudak R, Rusterholtz A. Hyperglycemia and olanzapine [letter]. *Am J Psychiatry*. 1999;156:970.
47. Lindenmayer JP, Patel R. Olanzapine-induced ketoacidosis with diabetes [letter]. *Am J Psychiatry*. 1999;156:1471.
48. Von Hayek D, Huttel V, Reiss J, et al. Hyperglycemia and ketoacidosis associated with olanzapine [in German]. *Nervenarzt*. 1999;70: 836-837.
49. Lane HY, Change YC, Chang WH, et al. Effects of gender and age on plasma levels of clozapine and its metabolites: analyzed by critical statistics. *J Clin Psychiatry*. 1999;60:36-40.
50. Perry PJ, Bever KA, Arndt S, Combs MD. Relationship between patient variables and plasma clozapine concentrations: a dosing nomogram. *Biol Psychiatry*. 1998;44:733-738.
51. Melkersson KI, Hulting AL, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. *J Clin Psychiatry*. 2000;61:742-749.
52. Brambilla F, Guastalla A, Guerrini A, et al. Glucose-insulin metabolism in chronic schizophrenia. *Dis Nerv Syst*. 1976;37:98-103.
53. Dixon L, Weiden P, Delahanty J, et al. Prevalence and correlates of diabetes in national schizophrenia samples. *Schizophr Bull*. 2000; 26:903-912.

54. Dvirskii AA. The reciprocally modifying effects of schizophrenia and diabetes mellitus on their phenotypic manifestations [in Russian]. *Tsitol Genet.* 1997;31:67-70.
55. McKee HA, D'Arcy PF, Wilson OJ. Diabetes and schizophrenia. *J Clin Hosp Pharm.* 1986;11:297-299.
56. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. *Compr Psychiatry.* 1996;37:68-73.
57. Wright P, Sham PC, Gilvarry CM. Autoimmune diseases in the pedigrees of schizophrenic and control subjects. *Schizophr Res.* 1996;20:261-267.
58. Mukherjee S, Roth SD, Sandyk R, Schnur DB. Persistent tardive dyskinesia and neuroleptic effects on glucose tolerance. *Psychiatry Res.* 1989;29:17-27.
59. Schultz SK, Arndt S, Ho B-C, et al. Impaired glucose tolerance and abnormal movements in patients with schizophrenia. *Am J Psychiatry.* 1999;156:640-642.

REVIEWS OF THERAPEUTICS

Olanzapine-Associated Diabetes Mellitus

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Study Objective: To explore the clinical characteristics of hyperglycemia in patients treated with olanzapine.

Design: Retrospective, epidemiologic survey of spontaneously reported adverse events related to olanzapine therapy.

Setting: Government-affiliated drug evaluation center.

Patients: Two hundred thirty-seven patients with olanzapine-associated diabetes or hyperglycemia.

Intervention: One hundred ninety-six cases from January 1994–May 15, 2001, were identified with the United States Food and Drug Administration's MedWatch Drug Surveillance System, and 41 cases published through May 15, 2001, were identified with MEDLINE or through meeting abstracts.

Measurements and Main Results: Of the 237 cases, 188 were new-onset diabetes, 44 were exacerbations of preexistent disease, and 5 could not be classified. Mean patient age for newly diagnosed cases was 40.7 ± 12.9 years and male:female ratio was 1.8. Seventy-three percent of all cases of hyperglycemia appeared within 6 months of start of olanzapine therapy. Eighty patients had metabolic acidosis or ketosis, 41 had glucose levels of 1000 mg/dl or greater, and 15 patients died. When olanzapine was discontinued or the dosage decreased, 78% of patients had improved glycemic control. Hyperglycemia recurred in 8 of 10 cases with rechallenge.

Conclusions: Number of reports, temporal relationship to start of olanzapine therapy, relatively young age, and improvement on drug withdrawal suggest that olanzapine may precipitate or unmask diabetes in susceptible patients. (Pharmacotherapy 2002;22(7):841–852)

OUTLINE

Methods

Results

Nature of Hyperglycemia Reports

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The contents of this publication represent the views of the authors and do not necessarily constitute an official position of the U.S. Food and Drug Administration or the U.S. Government.

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Demographic Features

Time to Onset

Olanzapine Dosages

Serious Outcomes

Metabolic Acidosis

Mental Status Changes

Setting

Pancreatitis or Hyperamylasemia

Deaths

Additional Risk Factors

Concomitant Drugs

Olanzapine Withdrawal and Rechallenge

Discussion

Conclusion

Olanzapine (Zyprexa; Eli Lilly and Company, Indianapolis, IN), marketed in the United States since 1996, is a psychotropic agent indicated for the management of schizophrenia^{1,2} and short-term treatment of acute manic episodes in bipolar disorder in adults.¹ In addition to approved indications, it has been administered for the treatment of a variety of other conditions including psychosis in dementia and Parkinson's disease, delusional or resistant depression, conduct disorders, aggression, agitation, resistant anxiety disorders, and delirium.³⁻⁶ Known adverse reactions to olanzapine include orthostatic hypotension, weight gain, akathisia, increased salivation, and somnolence.¹ Published reports of hyperglycemia occurring in association with olanzapine began occurring in 1998.⁷⁻⁹ The spectrum of reported illness ranged from mild glucose intolerance to diabetic ketoacidosis and nonketotic hyperosmolar coma. To gain further insight into the clinical characteristics of diabetes reported in association with olanzapine, we attempted to identify all such cases that had been submitted to the Food and Drug Administration's (FDA) MedWatch surveillance program.

Methods

We identified cases by querying the FDA MedWatch Drug Surveillance System (January 1994–May 15, 2001). Published cases were identified by means of MEDLINE (through May 15, 2001). Selected abstracts from national psychiatry meetings also were reviewed. We combined reports occurring in multiple identification systems. Drug utilization data were obtained from the National Prescription Audit Plus (IMS Health, Inc., Plymouth Meeting, PA) and the National Disease and Therapeutic Index (IMS Health, Inc.) databases.

We assessed documentation of diabetes, severity of hyperglycemia, whether the hyperglycemia was newly diagnosed, demographic features, time to onset of hyperglycemia, and effect of drug discontinuation. We defined "documentation" of newly diagnosed diabetes on the basis of a fasting glucose level of 126 mg/dl (7 mmol/L) or greater, a random glucose level of 200 mg/dl (11 mmol/L) or greater, or elevated glycohemoglobin values; and/or presence of metabolic acidosis or ketosis; and/or physician institution of an antidiabetic drug. Patients without definitive documentation were classified separately. Because individual MedWatch reports

and published cases vary in the completeness of the demographic and clinical information provided, we have specified where such data were missing. Hence, this is a descriptive report based primarily on summary statistics.

We used correlation coefficients, χ^2 tests, and unpaired *t* tests (all two-tailed) to assess the relationship between certain variables or groups; *p* values of 0.05 or less were viewed as significant.

Results

We identified 237 distinct cases of olanzapine-associated diabetes or hyperglycemia, including 41 cases in 22 publications.⁷⁻²⁸ Of these reports, 215 originated in the United States and 22 were from international sources.

Nature of Hyperglycemia Reports

Among the 237 reports, there were 188 (79%) cases of newly diagnosed hyperglycemia, 44 (19%) cases of exacerbation of established preexistent diabetes, and 5 (2%) cases that could not be classified. Of the 188 cases of newly diagnosed hyperglycemia, 153 cases fit the serum glucose or glycohemoglobin criteria for the diagnosis of diabetes. Of the patients whose diabetes was determined by fasting blood glucose level, all but two had fasting glucose levels of 140 mg/dl or greater. Of the 35 patients with new-onset hyperglycemia whose reports did not include sufficient glucose data for the diagnosis of diabetes, 19 received antidiabetic drug therapy. Five of the 19 patients were also reported to be acidotic or ketotic. Another three patients were acidotic or ketotic at the time of hyperglycemia, but lacked additional diagnostic data. In addition to these 188 newly diagnosed cases, there were 44 reports of patients with established diabetes in whom metabolic status worsened after starting olanzapine. As stated previously, there were five additional cases in which it was unclear whether the diabetes was newly diagnosed or preexistent.

Demographic Features

At the time of the adverse event, those with newly diagnosed hyperglycemia were younger than those with an exacerbation of preexistent diabetes (Table 1). Among the 153 cases (81 with age data) of newly diagnosed diabetes that were diagnosed by serum glucose or glycohemoglobin levels, the mean $\pm$ SD age was

Table 1. Age Distribution of 226 Patients with Olanzapine-Associated Hyperglycemia

Nature of Hyperglycemia Report	Age (yrs) ^a	Distribution by Age Cohort (yrs), no.						
		11-20	21-30	31-40	41-50	51-60	61-70	≥70
Newly diagnosed hyperglycemia (n=184)	49.7 ± 12.9	12	23	90	55	29	10	4
Glucose or glycohemoglobin level (n=151)	39.8 ± 12.4	9	20	53	45	11	8	3
Drug therapy + acidosis or ketosis (n=20)	47.4 ± 12.4	0	2	3	8	5	1	1
Less well documented (n=13)	41.3 ± 17.0	3	1	2	2	4	1	0
Exacerbation of preexistent diabetes (n=38)	51.7 ± 15.4	2	0	7	11	9	4	5
Unknown if new onset or exacerbation (n=4)	38.8 ± 5.4	0	0	3	1	0	0	0
Total	42.6 ± 13.8	14	23	70	67	28	14	10

^aData are mean ± SD.

Age was unknown for 11 patients. Age range of the 226 patients was 13-75 years. Hyperglycemic events were categorized by type of documentation available and patients' age in years at the time of the event.

39.8 ± 12.4 years (range 13-75 yrs), and 68% of these cases occurred before the age of 45 years. Fifty percent of these cases occurred in the third and fourth decades of life. There were twice as many men as women in this subgroup. Twelve cases of newly diagnosed hyperglycemia occurred in the 11-20-year age group, and six of these cases were pediatric patients younger than 18 years. Of the 44 patients (38 with age data) with exacerbation of preexistent diabetes, mean age was 51.7 ± 15.4 years (range 17-79 years), with a male:female ratio of 1.5.

Information on race was available for 150 patients, and of these, 84 (56%) were Caucasian, 58 (39%) were of African descent, 5 (3%) were Hispanic, and 3 (2%) were Asian.

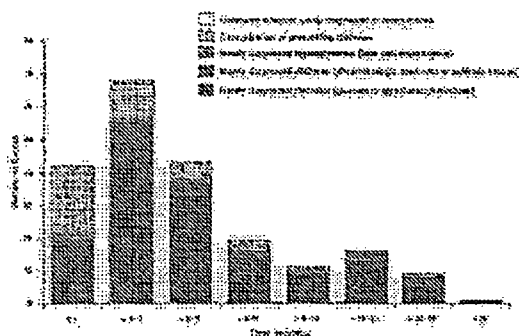


Figure 1. Time to hyperglycemic event. Hyperglycemic events were categorized by the time to occurrence after start of olanzapine therapy. Data were available for 209 (89%) of the 237 patients. Among these, hyperglycemia was identified within the first 6 months of olanzapine therapy in 153 patients (73%). A notable number of cases had delayed onset up to 48 months.

Time to Onset

The time to diagnosis of hyperglycemia for all subjects for whom these data were available (209 patients) ranged from 1 day to 45 months, but for 73% (153 patients), it was 6 months or less from the time olanzapine therapy was started (Figure 1). Among those with newly diagnosed diabetes documented by glucose or glycohemoglobin levels and for whom adequate time-to-onset information was available (142 patients), the onset of diabetes occurred within the first month of olanzapine therapy in 18 patients (13%). Forty-seven percent of such cases occurred within the first 3 months, and 70% of such cases occurred within 6 months of drug exposure. Time-to-onset information was available for 38 of 44 patients with exacerbation of preexistent diabetes. In these patients, the glycemic exacerbation was observed within the first month of olanzapine therapy in 59% of cases, within the first 3 months in 84%, and within the first 6 months in 97%.

Olanzapine Dosages

Dosage information was available for 202 (85%) of the 237 cases. In these patients, the mean ± SD olanzapine dosage was 15.6 ± 7.0 mg/day (range 2.5-49 mg/day). Mean daily doses did not differ by sex (male patients 15.3 ± 6.8 mg, female patients 15.6 ± 7.2 mg). Mean daily doses were lower for patients with preexistent diabetes (13.2 ± 6.2 mg) versus those with new-onset hyperglycemia (16.1 ± 7.0 mg) ($p=0.02$) and tended to be higher in those with ketosis or acidosis (16.6 ± 6.8 mg) than in those without (15.0 ± 7.0 mg) ($p=0.12$). There was no significant correlation between dose and the reported glucose level or between dose and time

to onset. Drug levels, which may be more predictive of clinical effects, typically were not available.

Serious Outcomes

Metabolic abnormalities ranged from mild glucose intolerance to diabetic ketoacidosis and hyperosmolar coma. In 69 cases, the blood glucose level was 700 mg/dl or greater. Of these, at least 65 (94%) had newly diagnosed diabetes and 2 (3%) had exacerbation of preexistent diabetes. Two other cases could not be classified because of incomplete information. (In two additional cases, the patients progressed to hyperosmolar coma with glucose values of 1676 mg/dl and 800 mg/dl, respectively. Eight months earlier, the first patient had a fasting glucose of 131 mg/dl and a hemoglobin A_{1c} of 9.4%. The second patient developed hyperglycemia again with rechallenge.) Of these 69 patients, 41 (59%) had blood glucose levels of 1000 mg/dl or greater. Thirty-eight (93%) of the 41 cases were newly diagnosed diabetes. At least 43 (62%) of the cases with high glucose levels occurred within 6 months of the start of olanzapine therapy. (Hyperglycemia [800 mg/dl] occurred within 3.5 months of rechallenge in an additional patient.) The mean age of these patients was 41.4 ± 12.7 years (if glucose ≥ 700 mg/dl but < 1000 mg/dl) or 41.4 ± 9.4 years (if glucose ≥ 1000 mg/dl). Information on ethnic background was available for 30 of those with high glucose levels (≥ 700 mg/dl). Forty-two percent (13 patients) were African-American, whereas 54% (17 patients) were Caucasian.

Metabolic Acidosis

There were 80 cases of ketosis or metabolic acidosis; 92% (74 patients) of these cases were newly diagnosed diabetes. In three patients, whether the diabetes was newly diagnosed or preexistent was unclear. Although the degree of acidosis was generally mild, the presenting glucose value was 300 mg/dl or greater in 57 patients. In 41 patients, the acidosis or ketosis was accompanied by glucose values of 700 mg/dl or greater.

Mental Status Changes

In 43 patients, mental status changes (obtundation or confusion) occurred in conjunction with the hyperglycemia. Of these, 42 patients had newly diagnosed diabetes and 1 had exacerbation of preexistent diabetes.

Table 2. Characteristics of the 15 Patients Who Died

Characteristic	Data
Age, mean $\pm$ SD (yrs)	43.1 ± 16.3
M/F (no.)	2/7
Ethnic background (no.)	
Caucasian	6
African-American	1
Asian	1
Unknown	7
Hyperglycemia presentation (no.)	
Newly diagnosed	14
Exacerbation	1
Time to onset < 3 mo. (no.)	8
Olanzapine dose, mean $\pm$ SD (mg)	17.9 ± 10.3
Glucose level ≥ 700 mg/dl (no.)	3
Acidosis (no.)	9

Setting

Most cases occurred in the community setting. In four patients, hyperglycemia was identified during incarceration in a prison. In two of these patients, glucose levels were 1622 and 1299 mg/dl, respectively. In a third patient, the glycohemoglobin was 13%, and the patient subsequently died. The fourth patient, with a history of diabetes, had a glucose level of 800 mg/dl and was reported to be "unresponsive to high insulin doses." Whether the mental status changes that can occur with hyperglycemia were the reason for incarceration was not known.

Pancreatitis or Hyperamylasemia

Pancreatitis or hyperamylasemia in association with hyperglycemia was reported in 17 patients. Of the 10 patients with concomitant acidosis or ketosis, 7 had elevated lipase levels, diagnostic computed tomographic findings, and/or treatment with pancreatic enzymes. Six patients with reported pancreatitis or hyperamylasemia had glucose values of 700 mg/dl or greater, and four of these patients had elevated lipase levels or confirmatory imaging studies. One case occurred in a 15-year-old boy who died of necrotizing pancreatitis 1 month after diabetes mellitus was diagnosed.

Deaths

Fifteen patients (8 male and 7 female patients, 6 Caucasian) died, including the 15-year-old boy (Table 2). Fourteen of these deaths occurred in patients with newly diagnosed diabetes. For eight of these patients, the time to onset was less

than 3 months. The mean daily dose of olanzapine was 17.9 ± 10.3 mg. Of the 15 deaths, 13 occurred during or shortly after a hyperglycemic episode, with acidosis or ketosis reported in 9 of the 13 cases. In the other two cases, the patients died a month after the hyperglycemia was identified, one with necrotizing pancreatitis and the other of unknown causes. Often, these patients had many medical problems at the time of death, making it difficult to assign a primary role for the hyperglycemia in their deterioration. One of the patients, a 39-year-old woman with symptoms of polydipsia and blurred vision, died after 2 months of olanzapine therapy. At autopsy, the vitreal glucose level was 867 mg/dl, and the patient was acidotic.

Additional Risk Factors

The reports did not uniformly provide systematic information on risk factors for diabetes. Limited body weight data were available for 169 patients. Approximately 24% of these patients did not appear either to be overweight or to have had sustained weight gain. Of the 80 patients with newly diagnosed hyperglycemia for whom family history information was provided, 49 (61%) had a positive family history (in 2 cases, it was remote), and 37 (46%) had a negative family history for diabetes. Hepatitis, a putative risk factor^{24,25} was reported in six patients (five with hepatitis C and one with hepatitis B). There was also no systematic pattern of concomitant drug therapy, as reported below.

Concomitant Drugs

There was no consistent pattern of concomitant drug therapy that emerged from the data reported for these patients. Only a limited number of patients were receiving drugs known to induce hyperglycemia. One patient received systemic steroids for sinusitis, two others received nonsystemic steroids as a cream or inhaler, one had been taking niacin, and nine had been taking thiazide diuretics. Of note, eight patients had been taking another atypical antipsychotic (risperidone [three patients], clozapine [four], or aripiprazole [one]). Treatment with valproate, a controversial putative risk factor for hyperglycemia,²⁶⁻²⁸ was reported for 59 of the 190 patients with some information on aetiological or concomitant drug therapy. The frequency of known valproate therapy in those

with glucose levels of 700 mg/dl or greater (35%), however, did not differ from that in patients with glucose levels less than 700 mg/dl (33%) ($\chi^2=0.1$, degrees of freedom [df]=1, $p=0.75$). Valproate therapy was reported in seven cases (41%) of pancreatitis or hyperamylasaemia. The other most frequently reported concurrent drugs were lithium, benztropine, conventional antipsychotics, thyroid hormone, antidepressants (fluoxetine, paroxetine, sertraline, venlafaxine), and clonazepam. A trend for a higher frequency of lithium therapy in those with glucose levels of 700 mg/dl or greater (20%) than that in patients with lower glucose levels (9%) failed to reach significance ($\chi^2=3.4$, df=1, $p=0.06$).

Olanzapine Withdrawal and Rechallenge

Complete data on the course of diabetes were lacking in many cases. Olanzapine was discontinued for various reasons in 105 cases, but follow-up data were available only for 76 of these cases. Of the 76 cases, 60 patients (79%) were reported to have improved, and 16 (21%) did not improve. Complete follow-up information was not available to determine how many of the patients who improved had glucose levels that returned to normal or how many of these patients required continuing therapy. Nonetheless, some of the cases with more complete information were compelling. A thin, otherwise healthy, 72-year-old man with a negative family history of diabetes was hospitalized for psychiatric decompensation after self-discontinuation of drug therapy. His glucose levels were normal, and he was started on olanzapine 10 mg/day. Approximately 2 months later, for behavioral changes, his dosage was decreased to 5 mg/day. Shortly thereafter, the patient became polydipsic and somnolent. He was hospitalized with a glucose level of 1600 mg/dl. Olanzapine was discontinued. The patient was treated initially with insulin and later with oral antidiabetic agents. Subsequently, these also were discontinued. The patient remained normoglycemic without antidiabetic agents for 8 months after the hyperglycemic episode—although subsequently a low dosage of an oral antidiabetic was required.

Of the nine patients switched from olanzapine to another identified atypical antipsychotic, glucose control improved in five of seven patients switched to risperidone and in one of two patients switched to quetiapine. Two patients who developed diabetes while taking olanzapine also had a history of hyperglycemia with

clozapine.

The olanzapine dosage was reduced in at least six patients. Follow-up data were available only for five patients because one patient died of complications before a response to the lower dosage could be assessed. Of the five patients, three improved and two had no change. For patients in whom olanzapine was not discontinued, insufficient data were available to determine the course of their diabetes.

Ten patients were rechallenged with olanzapine. Of these, eight (80%) experienced deterioration in glycemic control. This occurred within 3 days of rechallenge for two patients. In two others, deterioration in glycemic control occurred 7 and 8 days after rechallenge. Approximately 5-6 months after reinstitution of olanzapine, another patient developed diabetic ketoacidosis and hyperamylasemia complicated by diffuse clotting and death. Among the 10 patients, outcome was unknown for one patient. The one other patient who did not have a recurrence of hyperglycemia had an interval weight loss of at least 24 pounds. Glycemic control again improved after olanzapine discontinuation in three patients.

Discussion

We identified 237 cases of newly diagnosed hyperglycemia or diabetes mellitus, or diabetic exacerbation, associated with olanzapine. These reports are most notable for the number of patients in whom glucose levels equaled or exceeded 700 mg/dl and for the relatively young age of these patients. In contrast to our findings, the hyperosmolar diabetic state typically is found in elderly patients, often living alone, who decompensate because of a stroke, infection, or drug therapy and who are unable to ingest sufficient fluid.^{21,22} We also identified other significant outcomes, including metabolic acidosis or ketosis in 89 patients, obtundation or confusion in 43, pancreatitis or hyperamylasemia in 17, and death in close temporal proximity to the hyperglycemic episode in 13. The gravity of these outcomes highlights the need to further examine this potential association.

Several of our findings suggest a relationship between olanzapine therapy and diabetes. These include the number of cases reported, the temporal relationship to the start of olanzapine therapy, and the prompt reversibility of hyperglycemia with drug withdrawal in some cases. Furthermore, the mean age in the newly

diagnosed cases in our sample (40.7 yrs) is considerably less than the typical mean age of patients with newly diagnosed type 2 diabetes. Data from the National Health Interview Surveys (NHIS) indicate that the overwhelming majority of newly diagnosed cases of type 2 diabetes occurs in older individuals, with the highest incidence in the 65-74-year age cohort (8.6/1000/yr).²³ In the U.S. population, prevalence also increases with age: 81% of diabetes cases are in people older than 44 years. Indeed, in the 65-74-year and the 75-year and older age groups, 11% and 10%, respectively, have diabetes. In contrast, the incidence of diabetes in people aged 25-44 years is 1.79/1000/year, and only 1% in that age group have the disease.²³ Figure 2 illustrates an indirect comparison of the cumulative relative frequency of new-onset diabetes cases by age in our study with that of the U.S. population. The frequency of newly diagnosed cases in the 0-44-year age group appears to be twice as high among olanzapine-treated patients (66%) than in the U.S. population (33%). When we compared the distribution of olanzapine-associated new-onset cases with that of the NHIS using the same age groups, we determined that the difference was statistically significant ($\chi^2=113.6$, $df=5$, $p<0.0001$). These data suggest that the onset of diabetes mellitus occurs earlier in life among

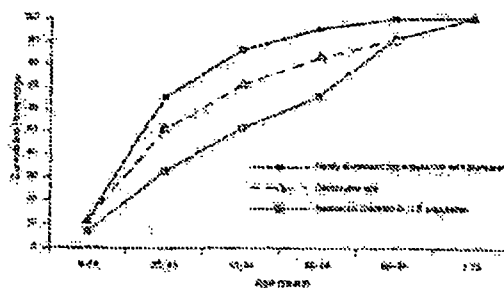


Figure 2. Distribution by age. Age distribution of olanzapine-associated new-onset diabetes was compared with the distribution of new-onset diabetes cases in the U.S. population.²³ The National Disease and Therapeutic Index drug appearance data from office visits for 1996-2000 were used to assess olanzapine treatment by age.²⁴ Drug appearances include new and refill prescriptions, as well as samples provided to patients by physicians. Patient age was unspecified for 18% of drug appearances. There were twice as many cases of diabetes associated with olanzapine in the 0-44-year age range as there were in the U.S. population survey, demonstrating the relatively young age of these cases. The two distributions were different ($p<0.0001$).

those receiving olanzapine than it does in the general population, with the sharpest rise in those younger than 44 years. The age distribution of patients with olanzapine-associated newly diagnosed hyperglycemia is also to the left of the age distribution for all olanzapine prescription recipients (based on utilization data from IMS Health, Inc.³⁶). This suggests that the distribution of cases is unlikely to simply reflect the age distribution of the population that receives the drug. This relatively young age at the time of onset of hyperglycemia also was observed with another atypical antipsychotic, clozapine.³⁸

In addition to the relative youth of the olanzapine-associated cases, the observed imbalance between the sexes is atypical of diabetes. The male:female ratio for all cases of newly diagnosed hyperglycemia in our series was 1.8. Data from NHIS indicate a male:female prevalence ratio of 0.8 and a male:female incidence ratio of 0.7.⁴² There is no known sex disparity for the prevalence of schizophrenia or bipolar disease.⁴³⁻⁴⁵ The National Disease and Therapeutic Index data indicate that the male:female ratio of olanzapine therapy is 0.8 (Figure 3).³⁹ This same sex disparity was

observed with clozapine-associated hyperglycemia.³⁸

No other clear risk factors for olanzapine-associated hyperglycemia emerged from this study other than possibly race and lithium therapy. African-Americans compose about 10% of patients receiving olanzapine (Figure 4) but compose nearly 39% (58 of 150) of cases of diabetes with ethnic heritage information in this report. Although the prevalence of diabetes was higher among African-Americans than among Caucasians for all age groups, the disparity in prevalence increases with age. The prevalence of diabetes is approximately 1.3 times higher in the 25-44-year age group and is only 2-fold higher in older age groups.⁴⁷ We did not find a clear dose effect, although there was a trend for newly diagnosed cases and cases with ketosis or acidosis to have higher mean olanzapine daily doses. There was a weak association between concomitant lithium therapy and very high glucose levels. Lithium can cause diabetes insipidus and weight gain⁴⁸ and, as such, increase the risk for hyperosmolar states.

There is no obvious mechanism by which olanzapine might impair carbohydrate metabolism. Although weight gain can occur during therapy,⁴ the prompt onset of diabetes in many

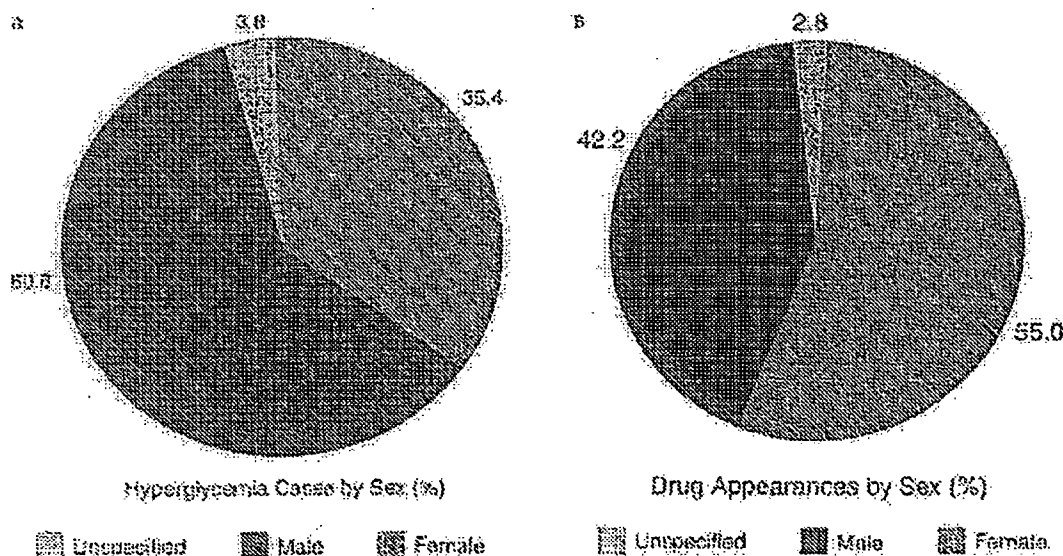


Figure 3. Sex of patients with olanzapine-associated hyperglycemia (A) and sex of patients treated with olanzapine (B). National Disease and Therapeutic Index drug appearance data from office visits for 1996-2003 were used.³⁹ Drug appearances include new and refill prescriptions, as well as samples provided to patients by physicians. The patterns do not explain the sex differences observed in the adverse event reports. Curiously, these data indicate that 38% of the men versus 44% of the women receiving olanzapine were younger than 45 years. Diabetes in this age group is more common in women.⁴⁹

patients (six cases within the first week of treatment) argues against a primary role for weight gain in the development of olanzapine-associated diabetes. Weight gain may contribute to the late-onset hyperglycemia that was observed. The variations in the time to onset of hyperglycemia may reflect several mechanisms of action (e.g., direct islet cell toxin reaction vs interference with non-insulin-mediated glucose utilization vs insulin resistance). There is no overt chemical similarity between olanzapine and other compounds known to be islet cell toxins (Figure 3).^{44,45} Olanzapine also may be unmasking diabetes in genetically vulnerable patients. The metabolism of olanzapine in sensitive individuals may differ from that in unaffected individuals as well.

There are limitations to this report. The MedWatch database relies on spontaneous adverse event reporting. Substantial under-reporting is characteristic of systems such as MedWatch.^{46,47} Indeed, olanzapine does not require specific routine laboratory monitoring, and the symptoms of diabetes may be missed in low-functioning patients. Distortions in reporting may occur over time as prescribers

become aware of a particular adverse event from experience, literature, and/or changes to product labels. Also, clinicians possibly were more attuned to hyperglycemia because weight gain is a known adverse effect⁴ and glucose monitoring may have been more common in such patients. Although we know the total number of prescriptions, approximately 15 million between 1995 and 2000 inclusive, we cannot determine patient-year-exposure (i.e., we have no precise estimates on patient carryover from year to year or the numbers of patients who received olanzapine in the populations who contributed to these reports).⁴⁸ Furthermore, control populations were absent, and case descriptions may be incomplete. Even indirect comparisons of age distribution of our cases with population patterns derived from another study can be biased by several factors. Hence, we cannot determine causality or incidence. The possibility that other factors (e.g., detection bias, preexistent risk factors, prior drug therapy, or concomitant drugs) contributed to the hyperglycemia cannot be excluded. Nonetheless, the MedWatch surveillance system can provide signals for adverse events, including those that might not be

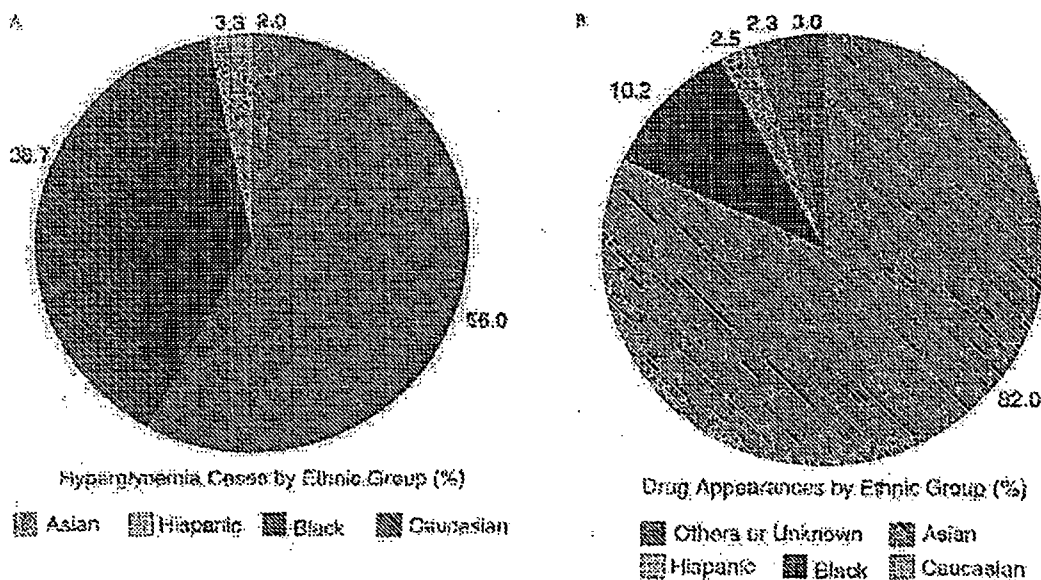


Figure 4. Ethnic background of patients with olanzapine-associated hyperglycemia for whom such information was available (A) and ethnic background of patients treated with olanzapine (B). National Disease and Therapeutic Index drug appearance data from office visits for 1995-2000 were used.⁴⁹ Drug appearances include new and refill prescriptions, as well as samples provided to patients by physicians. The patterns do not explain the racial differences observed in the adverse event reports.

identified during relatively short efficacy trials.

Indeed, preliminary findings from a retrospective analysis of a large prescription claims database suggest that the risk for incident diabetes (defined as starting antidiabetic pharmacotherapy) was comparably higher (about 3-fold) in patients receiving a number of antipsychotic agents, including olanzapine, than in those who did not.²⁹ These findings, in turn, are supported by results of smaller studies suggesting that antipsychotic agents, including some conventional neuroleptics, are associated with altered glucose tolerance and insulin response, especially in the setting of tardive dyskinesia,^{30,31} and that glucose tolerance improves with the discontinuation of antipsychotic agents.³² Finally, hyperglycemia associated with many of the newer antipsychotics has been reported,³³⁻³⁵ although the majority of published cases implicate clozapine or olanzapine.

A drug that potentially precipitates diabetes in patients with chronic mental illness has implications for the patients and their families and clinicians.^{33,36} Low-functioning patients may lack sufficient insight to recognize the symptoms of diabetes or may lack access to medical care. Because olanzapine is known to cause weight gain, dry mouth, and sedation,¹ laboratory

evaluation of patients with weight loss or polydipsia could be delayed. Mental status changes associated with hyperglycemia or hypoglycemia may be mistaken for psychotic or antisocial behavior and result in improper management or incarceration. The availability of insulin can magnify the lethality of suicide attempts.³⁷ Further, switching to another antipsychotic agent or noncompliance with the offending agent while a patient is taking antidiabetic pharmacotherapy may result in hypoglycemia.³⁸

In patients with olanzapine-associated diabetes, the decision to switch to another antipsychotic versus continuing olanzapine is a difficult one. In the absence of prospective, direct-comparison studies, whether substantive differences exist in the hyperglycemic risk for the various atypical antipsychotic agents is not known. Moreover, changing to another drug carries the risk of a psychotic flare.

Conclusion

These results suggest a causal relationship between olanzapine and development or worsening of diabetes. The onset of hyperglycemia may be rapid and severe, the association is not dose dependent, and the risk does not

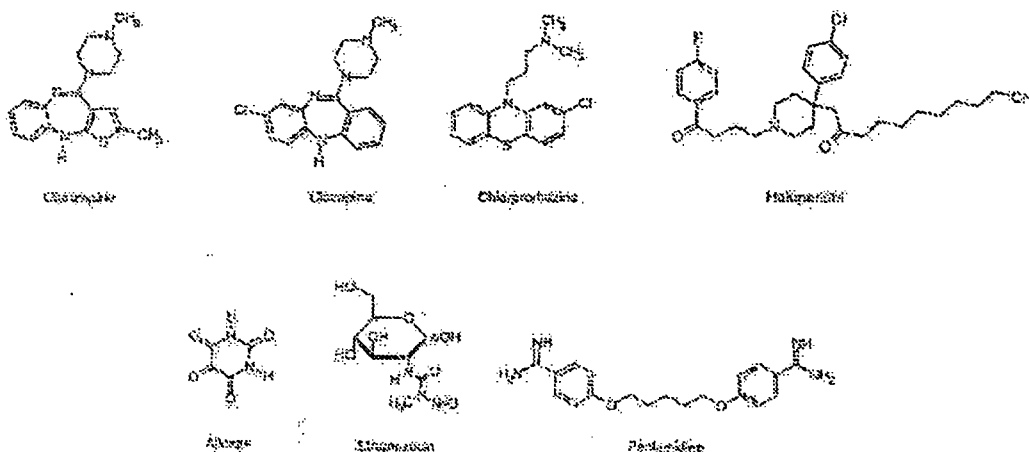


Figure 3. Chemical structures. The physical chemical properties of olanzapine that could contribute to β cell toxic reaction are unknown. Aripiprazole, risperidone, and perphenazine are structural compounds known to induce glucose intolerance through β cell damage. Chlorpromazine, a classic antipsychotic agent, also has been associated with diabetes,³⁹ and haloperidol alters the insulin response to a carbohydrate load.⁴⁰ Although these compounds all have ring structures, the rings are not uniformly planar nor are any of the side chains common to all.

vanish with extended therapy. Awareness of the potential safety issues will help guide drug selection and direct adverse event monitoring so that patients may more fully benefit from the substantial therapeutic efficacy offered by the atypical antipsychotic agents. Because spontaneous adverse event surveillance can neither establish causality nor determine true incidence and prevalence, further research is indicated.

Addendum

Subsequent to acceptance of our manuscript for publication, we extended our FDA MedWatch inquiry through February 2002, and the findings support our original observations.³²⁻³⁴ We identified an additional 32 cases of hyperglycemia (42 domestic, 10 foreign). Of these, 37 were newly diagnosed hyperglycemia, 13 were exacerbation of preexistent diabetes, and 2 could not be categorized. Among the cases with age information, the mean $\pm$ SD age at the time of diagnosis was 45.1 $\pm$ 14.4 years overall (48 patients), 43.4 $\pm$ 13.2 years for those with newly diagnosed hyperglycemia (35 patients), and 50.0 $\pm$ 17.6 years for those with exacerbation of preexistent disease (12 patients). Two cases occurred in children aged 14 and 16 years, respectively. The male:female ratio was 1.8:1 (51 patients).

Of the 34 patients with ethnic background information, 19 (56%) were Caucasian, 10 (29%) were African-American, 3 (9%) were Asian, and 2 (6%) were Hispanic. Among 38 cases with time-to-onset data, hyperglycemia occurred within 6 months of starting olanzapine in 23 patients (60%). Ketosis and/or acidosis in the setting of hyperglycemia was reported in 29 cases. Of five reports of pancreatitis, four cases were documented by lipase levels or computed tomographic findings; two cases were complicated by death. Eight additional deaths occurred; one of these deaths occurred in a 33-year-old man within 1 month of diagnosis and after olanzapine had been discontinued.

Glucose levels of 700 mg/dl or greater were reported in 14 cases, four of which had levels of 1000 mg/dl or greater. Twelve of these cases occurred in patients with newly diagnosed hyperglycemia, and the other two occurred in patients with exacerbation of preexistent diabetes. Ten of the cases with glucose levels of 700 mg/dl or greater were accompanied by varying degrees of ketosis and/or acidosis. Three of the patients with high glucose levels had

pancreatitis documented by lipase levels and/or computed tomography. Five patients with glucose levels of 700 mg/dl or greater died. One patient had an abnormal fasting glucose level in his record (137 mg/dl) prior to starting olanzapine, but the physicians were unaware of its existence or its significance before the patient progressed to a hyperosmolar state and died.

Mean olanzapine dosage in 43 cases was 14.1 $\pm$ 7.3 mg/day (using the maximum known therapeutic dose and excluding an overdose of 1500 mg). No correlation was noted between time to onset and dosage ($r=0.37$, 36 patients). Some information for concomitant drug therapy was available for 41 cases (79%). Four patients received no concomitant drugs, three were taking a thiazide diuretic, four received nonsystemic corticosteroids (nasal or inhaled), and two were taking systemic corticosteroids (cloprednol 5 mg or prednisone 10 mg). One patient was taking quetiapine; another may have been taking risperidone concurrently. Seven patients received valproate, and six were taking lithium. Olanzapine was discontinued in 27 patients. Although follow-up was incomplete, insulin dosages were decreased successfully in two patients, and antidiabetic drug therapy was discontinued in another two patients. For the latter two patients, oral antidiabetic agents needed to be instituted 8 and 13 months later, respectively.

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References

1. Eli Lilly and Company. Zyprexa home page. Available from <http://www.zyprexa.com>. Accessed June 8, 2001.
2. Marder SR, Brunen CE, Marder TR. Atypical antipsychotics. 1. Pharmacology, pharmacokinetics, and efficacy. *Ann Pharmacother*. 1999;33:73-85.
3. Archuleta JR, Topkoff JL, Held K, Frey L. Psychosis due to neurological conditions. *Curr Treatment Options Neurol*. 2001;3:343-55.
4. Goodnick PJ, Bartus CA. Use of olanzapine in non-psychotic psychiatric disorders. *Expert Opin Pharmacother*. 2001;2:607-60.
5. Spahimian A, Masand PS. Olanzapine in the treatment of delirium. *Psychosomatics*. 1998;39:422-30.
6. Finkling RL, McNamara SR, Gracious RL. Pediatric uses of atypical antipsychotics. *Expert Opin Pharmacother*. 2000;1:223-43.
7. Reitterer TL, Mendelson SC, Dursen PG, Ojimon ML. Olanzapine-induced glucose dysregulation. *Ann Pharmacother*. 2000;34:833-7.
8. Banerjee DG, Davydov L, Bous SR. Olanzapine-induced

- diabetes mellitus. *Ann Pharmacother* 2001;35:363-3.
8. Ter Braak GL. Het hyperglykemisch dehydratationsyndroom (comatose). *Ned Tijdschr Geneesk* 1998;142:2262.
9. Dancette DE, Granger JP, Robertson PS. Olanzapine-induced acute pancreatitis. *Ann Pharmacother* 2000;34:1128-31.
10. Fazzig AR, Kraska VG, Shilton PS, Baglioni CW. Hyperglycemia associated with olanzapine. *J Clin Psychiatry* 1998;59:667-9.
11. Goldstein LE, Sporn J, Brown S, et al. New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. *Psychosomatics* 1999;44:778-83.
12. Costa R, Rigalieu V, Gin H. Diabetic ketoacidosis with olanzapine treatment [letter]. *Diabetes Care* 1999;22:1602-3.
13. Isral N, Oldan RL, Batist G, et al. Atypical antipsychotic-induced diabetes mellitus. Poster presentation at the annual meeting of the American Psychiatric Association, Chicago, May 13-16, 2000.
14. Johnson RJ, Al-Tajer MT, Hadlock LV, Guo M, Nasdabli CL. Increasing insulin dose for olanzapine-related diabetes. *Am J Psychiatry* 2001;158:130-1.
15. Koller E, Maliszewski S, Doraiswamy PM. Atypical antipsychotic drugs and hyperglycemia in adolescents [letter]. *JAMA* 2001;286:1547-8.
16. Lindenmeyer JR, Patel R. Olanzapine-induced ketoacidosis with diabetes mellitus [letter]. *Am J Psychiatry* 1999;156:9.
17. Munch J, Carey M. Diabetes mellitus associated with atypical antipsychotic medications: new case report and review of the literature. *J Am Board Fam Pract* 2001;14:778-82.
18. Ober SK, Hudak R, Buxtehuth A. Hyperglycemia and olanzapine [letter]. *Am J Psychiatry* 1999;156:970.
19. Rigalieu V, Costa R, Bonnard M, et al. Diabetes as a result of atypical antipsychotic drugs: a report of three cases. *Diabetes Med* 2000;17:854-6.
20. Buchner J, Mukerjee SM. Olanzapine-induced hyperglycemic, nonketotic coma. *Ann Pharmacother* 2001;35:300-2.
21. Seaburg HL, McLendon BM, Doraiswamy PM. Olanzapine-associated severe hyperglycemia, ketonuria, and acidosis: case report and review of literature. *Pharmacotherapy* 2001;21:1449-54.
22. Selva KA, Scott SM. Diabetic ketoacidosis associated with olanzapine in an adolescent patient. *J Pediatr* 2001;138:938-9.
23. Smith T. Hyperglycemia in patients treated with olanzapine. Poster presentation at the American Psychiatric Association Institute on Psychiatric Services meeting, New Orleans, October 26-November 2, 1999.
24. Van Meter S, Seaburg H, McLendon B, Doraiswamy PM. Olanzapine, new-onset diabetes and suicidal ideation [letter]. *J Clin Psychiatry* 2001;62:993-4.
25. Van Haeck D, Huif V, Kess J, Fusch HS. Hyperglycemic and ketonuric coma under olanzapine. *Neurologie* 1999;19:636-7.
26. Wilson ER, D'Souza L, Sarkar M, Newton M. New-onset diabetes and ketoacidosis with atypical antipsychotics. Presented at the annual meeting of the American College of Neuropsychopharmacology, Acapulco, Mexico, December 12, 1999.
27. Worsching DA, Spellberg GJ, Erhart SM, Marder SR, Worsching WC. Novel antipsychotics and new-onset diabetes. *Biol Psychiatry* 1998;44:778-83.
28. Garcidue Serrano A, Guerrero Igea EJ, Lopez Jimenez JA, Paloma Gil S, Gila Reina A. Hypothalamic lesions in chronic patients infected with hepatitis C virus. *Gastroenterol Hepatol* 2001;24:127-31.
29. Figueira S, Hernandez C, Enriquez J, et al. Metabolic and thyroid antibody prevalence in patients with hepatitis C virus infection: effect of treatment with interferon. *J Lab Clin Med* 2001;137:48-52.
30. Ollersen H, Geun L, Andersen T, Durr M. Weight gain during treatment with valproate. *Acta Neurol Scand* 1988;77:63-8.
31. Hojary A, Tabbal E, Fekris A, et al. Olanzapine and cardiovascular risk factors in valproate-treated women. *Am J Med* 2001;111:96-9.
32. Jallon R, Picard F. Bodyweight gain and anticonvulsants: a comparative review. *Drug Saf* 2001;24:667-76.
33. Turnbull DM, Bone AJ, Tames FJ, Wilson L, Baird JD, Sherratt HS. The effect of valproate on blood metabolite concentrations in spontaneously diabetic, ketoacidotic, BB/E Wistar rats. *Diabetes Res* 1983;1:43-8.
34. Arieff AA, Carroll HJ. Non-ketotic hyperosmolar coma with hyperglycemia: clinical features, pathophysiology, renal function, acid-base balance, plasma-cerebrospinal fluid equilibria, and the effects of therapy in 37 cases. *Medicine (Baltimore)* 1972;51:73-94.
35. Gerich JE, Martin MM, Recant L. Clinical and metabolic characteristics of hyperosmolar non-ketotic coma. *Diabetes* 1977;26:226-38.
36. Kenny SJ, Aubert RE, Geiss LS. Prevalence and incidence of non-insulin-dependent diabetes. In: Harris MI, Cowie CC, Stern MP, Boyko VJ, Reiber GE, Bennett PH, eds. *Diabetes in America*, 2nd ed. Publication no. 93-1468. Bethesda, MD: National Institutes of Health—National Institute of Diabetes and Digestive and Kidney Diseases, 1993:47-67.
37. IMS Health. IMS Health—National Disease and Therapeutic Index. Plymouth Meeting, PA.
38. Koller E, Schneider R, Bennett K, Dubinsky G. Olanzapine-associated diabetes. *Am J Med* 2001;111:718-23.
39. Andreasen NC, Kane JM, Keefe S, Marder SR, McGlashan T. Schizophrenia and other psychotic disorders. In: First MB, ed. *Diagnostic and statistical manual of mental disorders*, 4th ed. Washington, DC: American Psychiatric Association, 1994:273-316.
40. Hendrich V, Alshuler LL, Gitlin MJ, Delahanty S, Hammen C. Gender and bipolar illness. *J Clin Psychiatry* 2000;61:393-8.
41. Uysal T, Rodie J. Gender differences in mood disorders: a literature review. *Arch Psychiatr* 2001;29:269-74.
42. Kaplan HL, Sadock BJ. *Kaplan and Sadock's synopsis of psychiatry*, 5th ed. Media, PA: Williams and Wilkins, 1997:1049-50.
43. Ammon HE, Giel L, Steinle J. Effect of chlorpromazine (CPZ) on insulin release *in vivo* and *in vitro* in the rat. *J Pharmacol Exp Ther* 1973;187:473-9.
44. Brumblis R, Gervasi A, Guastalla A. Neuroendocrine effects during haloperidol therapy in chronic schizophrenics. *Psychopharmacologia* 1983;44:17-22.
45. Bates DW, Cullen DJ, Laird N, for the ADE Prevention Study Group. Incidence of adverse drug events and potential adverse drug events: implications for prevention. *JAMA* 1993;274:29-34.
46. Bennett BS, Lipman AG. Comparative study of prospective surveillance and voluntary reporting in determining the incidence of adverse events. *Am J Hosp Pharm* 1977;34:631-6.
47. Eland LA, Nelson RJ, van Groenou AG, Meesters AP, Bawin MH, Stricker BH. Antinatal survey of voluntary reporting of adverse drug reactions. *Br J Clin Pharmacol* 1992;34:513-7.
48. Juman WHW. Investigation of deaths from pulmonary, coronary and cerebral thrombosis and embolism in women of child-bearing age. *Br Med J* 1968;2:193-9.
49. Kimmel SE, Scherer MA, Berlin JA, Goldberg LR, Strom BL. Adverse events after promazine administration in patients undergoing cardiopulmonary bypass: risk and predictors of under-reporting. *J Clin Epidemiol* 1995;48:11-18.
50. McGettigan P, Golden J, Conroy RM, Arthur N, Feely J. Reporting of adverse drug reactions by hospital doctors and the response to intervention. *Br J Clin Pharmacol* 1997;44:93-100.
51. Smith Rogers A, Israel E, Smith CL, Levine D, McBean AM. Physician knowledge, attitudes, and behavior related to reporting adverse drug events. *Arch Intern Med* 1986;146:600-609.
52. Tyler LS, Dickinson NA. Hospital pharmacy compliance with JCAHO standards and ASHP guidelines for reporting adverse drug reactions. *Am J Hosp Pharm* 1992;49:885-90.
53. IMS Health. IMS Health—National Prescription Audit Plus. Plymouth Meeting, PA.
54. Kwong K, Cavazzani R, Hornbuckle K, et al. Higher incidences of diabetes mellitus during exposure to antipsychotics: findings from a retrospective cohort study in the U.S. Poster presentation at the 41st annual meeting of the New Clinical

- Drug Evaluation Unit, Phoenix, May 22-31, 2001.
36. Mukherjee S, Roth SH, Sandyle R, Schmitz DB. Persistent metabolic hyponatremia and neuroleptic effects on glucose tolerance. *Psychiatry Res* 1989;29:17-27.
 37. Schatz EC, Arnold S, Ho BC, Olfert SE, Andreassen NC. Impaired glucose tolerance and abnormal movements in patients with schizophrenia. *Am J Psychiatry* 1994;151:640-2.
 38. Kauran A, Dursawansy PM, Jane JL, Roseman EB, Duan L. Severe hypoglycemia associated with high doses of clozapine [letter]. *Am J Psychiatry* 1994;151:1373.
 39. Henderson DC, Caglieri E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a two-year naturalistic study. *Am J Psychiatry* 2000;157:975-81.
 40. Sobel M, Jorgens ED, Evans MA. New-onset diabetes mellitus associated with the initiation of quetiapine treatment. *J Clin Psychiatry* 1999;60:336-7.
 41. Cevikler PE, Jacobs RM, Bain RK. Diabetic ketoacidosis associated with risperidone treatment? *Psychosomatics* 2000;41:568-70.
 42. Kropp S, Enrich RM, Bleich S, Dagner D. Clozapine-related hyperglycemia in a nondiabetic woman [letter]. *Can J Psychiatry* 2001;46:437.
 43. Ragucci KR, Well RJ. Olanzapine-induced diabetic ketoacidosis. *Ann Pharmacother* 2001;35:1555-8.
 44. Tatar CJ, Early JJ, Fruchling RJ. Olanzapine-induced neutropenia in patients with history of clozapine treatment: two case reports from a state psychiatric institution. *J Clin Psychiatry* 2000;61:672-3.

Risperidone-Associated Diabetes Mellitus: A Pharmacovigilance Study

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Abstract and Introduction

Abstract

Study Objective: To explore the clinical characteristics of hyperglycemia in patients treated with risperidone.
Design: Pharmacovigilance survey of spontaneously reported adverse events in risperidone-treated patients, with reports of haloperidol-associated hyperglycemia used as a control.
Setting: Government-affiliated drug evaluation center.
Intervention: The Food and Drug Administration MedWatch surveillance program was queried (risperidone, 1993-February 2002; haloperidol, late 1970s-February 2002) and results pooled with published cases.
Measurements and Main Results: We identified 131 reports of risperidone-associated hyperglycemia in addition to seven reports of patients with hyperglycemia who received combined risperidone-haloperidol therapy and six reports of acidosis that occurred in the absence of hyperglycemia. We found 13 reports of haloperidol-associated hyperglycemia and 11 reports of acidosis without hyperglycemia. Of the reports of risperidone-associated hyperglycemia (monotherapy), 78 patients had newly diagnosed hyperglycemia, 46 had exacerbated preexisting diabetes, and 7 could not be classified. Mean $\pm$ SD age was 39.8 ± 17.4 years (range 8-96 yrs). Patients with new-onset diabetes (mean $\pm$ SD age 34.8 ± 15.7 yrs) were younger than those with preexisting diabetes (mean $\pm$ SD age 48.8 ± 17.5 yrs). The overall male:female ratio was 1.5. In most patients, hyperglycemia appeared within 3 months of the start of risperidone therapy. Severity of disease ranged from mild glucose intolerance to diabetic ketoacidosis or hyperosmolar coma. Twenty-six patients with acidosis or ketosis were reported. Four patients died.
Conclusion: Atypical antipsychotic treatment may unmask or precipitate hyperglycemia. Although such cases attributed to clozapine or olanzapine are more numerous than those associated with risperidone, the number for risperidone-associated hyperglycemia is relatively higher than that observed with the conventional neuroleptic haloperidol.

Introduction

Risperidone is a psychotropic agent that was approved in the United States in 1993 for treatment of schizophrenia.^[1] Its efficacy in reducing psychotic features was demonstrated in 4-, 6-, and 8-week placebo-controlled trials.^[1] In addition to the approved indication, risperidone has been administered for treatment of a variety of other conditions, such as dementia-related behavioral disorders, delusional disorder, bipolar disorder, and posttraumatic stress syndrome.^[2-6] Risperidone is a benzisoxazole with antiserotonergic (5-HT₂ receptor) and antidopaminergic (D₂ receptor) activity.^[1,6] As such, it is chemically distinct from the atypical antipsychotic agents, clozapine and olanzapine, which are dibenzodiazepines.^[7] Metabolism involves hydroxylation by the polymorphic cytochrome P450 isozyme, 2D6, to an active metabolite, 9-hydroxy-risperidone.^[7,8] Drug levels are increased or clearance is decreased by significant hepatic or renal impairment or coadministration of clozapine, paroxetine, or fluoxetine.^[1,9,10] Clearance is accelerated by carbamazepine.^[11,12] Its administration is accompanied by less weight gain than observed with the atypical anti-psychotics clozapine and olanzapine, but more than observed with many conventional antipsychotics.^[1,12,13]

Reports of diabetes have been sporadic in the last 5 years, but the risk and characteristics of risperidone-associated hyperglycemia remain unclear.^[14,15] To gain further insight into this potential problem, we attempted to identify all such cases that had been reported to the MedWatch Drug Surveillance System of the Food and Drug Administration (FDA). We compared these with reports of hyperglycemia associated with the conventional neuroleptic haloperidol. Haloperidol has been marketed in the United States since 1967 for psychotic disorders and was subsequently approved for administration in Tourette's syndrome (facial and vocal tics) and severe pediatric behavior disorders. Haloperidol historically has not been associated with hyperglycemia and weight gain.

Methods

We identified cases by querying the FDA MedWatch Drug Surveillance System (risperidone, 1993-February 2002; haloperidol, late 1970s-February 2002). Published cases were identified by means of MEDLINE (through February 2002). Selected abstracts from national psychiatry meetings also were reviewed. We combined reports occurring in several identification systems. Drug utilization data were obtained from the National Prescription Audit Plus™

(IMS Health, Inc., Plymouth Meeting, PA) and the National Disease and Therapeutic Index Audit™ (IMS Health, Inc.) databases. Patients whose reports suggested treatment with only risperidone or haloperidol were considered to be receiving monotherapy. Patients treated with both risperidone and haloperidol were considered to be receiving combination therapy. Other psychiatric drugs could be administered to patients in either treatment classification. Our calculations are for patients receiving monotherapy unless otherwise specified. We assessed documentation of diabetes, severity of hyperglycemia, whether the hyperglycemia was newly diagnosed, demographics, time to onset of hyperglycemia, dosages, and effect of drug discontinuation. We defined newly diagnosed diabetes on the basis of a fasting glucose level of 126 mg/dl (7 mmol/L) or greater, a random glucose level of 200 mg/dl (11 mmol/L) or greater, elevated glycohemoglobin values, presence of frank ketoacidosis or ketosis, and/or physician institution of an antidiabetic drug. Patients whose acidosis was not related to or did not occur in the setting of hyperglycemia were excluded, and patients without definitive documentation were classified separately. In patients whose dosage was changed, the maximum daily dose was used. Because individual MedWatch reports and published cases vary in completeness of demographics and clinical information provided, we have specified where such data were missing. Hence, this is a descriptive report based primarily on summary statistics. We used correlation coefficients, Kruskal-Wallis tests, χ^2 tests, and unpaired *t* tests to assess the relationship between certain variables or groups; *p* values of 0.05 or less were considered nominally significant for the purpose of identifying possible associations between variables or groups. Reporting rates were determined from United States reports and estimates of patient exposure. Patient exposure was estimated by multiplying the number of prescriptions by the duration of a prescription. Data from the IMS Health National Prescription Audit Plus™ were used to estimate the number of prescriptions. (Sources included chain, independent, food store, and mail-order pharmacies; mail-order data were not available before 1993.) Such data were available from 1981 on. Data from the IMS Health National Disease and Therapeutic Index Audit™ were used to estimate the mean duration of a prescription. (Drug appearances in the IMS sampling system can result from writing a prescription or refill, a hospital order, dispensing a sample, and/or administration of the drug in the office setting, but sampling does not occur in every medical setting.) Data from 1996 on were used because they were more complete for this parameter. To estimate relative risk, the ratio of reporting rates for risperidone agents and haloperidol was determined. Data from the IMS Health National Disease and Therapeutic Index Audit™ were also used to identify demographic use patterns. Data from 1994 on were used.

Results

We identified 131 distinct cases of risperidone-associated diabetes or hyperglycemia; seven cases appeared in three publications ([Table 1](#)).⁽¹⁴⁻¹⁶⁾

Nature of Hyperglycemia Reports

Patients in these reports experience a variety of disorders, such as aggression, agitation, anxiety, autism, conduct disorder, bipolar disorder, dementia, depression, psychosis, and Tourette's syndrome. Of the 131 reports, 124 originated in the United States and 7 from international sources. Seven additional reports of hyperglycemia with combined risperidone-haloperidol therapy and six additional reports of acidosis were not associated with hyperglycemia.⁽¹⁷⁾ All of the combination therapy cases and three of the acidosis cases occurred in the United States. There were 13 reports of haloperidol-associated hyperglycemia^(18,21) and 11 reports of acidosis in the apparent absence of hyperglycemia.^(22,26) One patient with haloperidol-associated hyperglycemia was treated with olanzapine. Ten of the haloperidol-associated hyperglycemia cases and seven of the acidosis cases occurred in the United States. One other case of acidosis that did not occur in association with hyperglycemia was reported in a patient from outside the United States who was treated with both risperidone and haloperidol. Of the patients with risperidone-associated hyperglycemia (monotherapy), 78 had newly diagnosed hyperglycemia, 46 had exacerbation of preexisting disease, and 7 could not be classified ([Table 2](#)). Of the cases of haloperidol-associated hyperglycemia (monotherapy), 10 had newly diagnosed hyperglycemia, 2 had exacerbation of preexisting disease, and 1 could not be classified. Of the patients with hyperglycemia diagnosed after treatment with both risperidone and haloperidol, four had newly diagnosed hyperglycemia, two patients had exacerbation of preexisting disease, and one could not be classified. For both risperidone and haloperidol, bowel disease (obstruction, necrosis, perforation) and neuroleptic malignancy syndrome appeared to underlie most of the cases in which acidosis occurred in the absence of hyperglycemia.

Reporting Rates for Hyperglycemic Adverse Events

The reporting rate for risperidone mono-therapy was 21 times higher than that for haloperidol monotherapy if prescription sales data from 1981 on are used. This may be an underestimate because it excludes the first decade of haloperidol marketing. The reporting rate ratio of risperidone:haloperidol monotherapy is 8.5 if prescription sales data from 1994 are used. (There were no significant sales of risperidone in 1993.)

Demographics

The mean $\pm$ SD age of patients with risperidone-associated hyperglycemia (Table 3) was 39.8 ± 17.4 years (range 8-96 yrs). Patients with new-onset hyperglycemia (mean $\pm$ SD age 34.8 ± 15.7 yrs) were younger than those with exacerbated diabetes mellitus (48.8 ± 17.5 yrs, $p < 0.001$) and tended to be younger than those with new-onset, haloperidol-associated hyperglycemia (mean $\pm$ SD age 50.2 ± 21.7 yrs, $p = 0.055$). When the cumulative distribution of new-onset diabetes cases by age in our series was compared with that of the U.S. population (National Health Interview Survey data),^[27] the relative frequency of diabetes appeared to be higher for risperidone-treated patients in the younger age cohorts whether or not patients receiving combination therapy were included (Kruskal-Wallis test with χ^2 statistic, $\chi^2 = 90.8$ and 93.7 , respectively, degrees of freedom [df]=5, $p < 0.001$). In addition, when the cumulative distribution of new-onset diabetes cases by age in our series was compared with that of the population of patients receiving risperidone, those who developed diabetes appeared to be younger than the general population receiving risperidone whether or not patients receiving combination therapy were included (Kruskal-Wallis test with χ^2 statistic, $\chi^2 = 45.6$ and 48.3 , respectively, df=5, $p < 0.001$) (Figure 1). The IMS Health National Disease and Therapeutic Index Audit™ data suggest that since 1994, patients who receive risperidone (mean age 46.8 yrs) are younger than those who receive haloperidol (mean age 57.6 yrs).

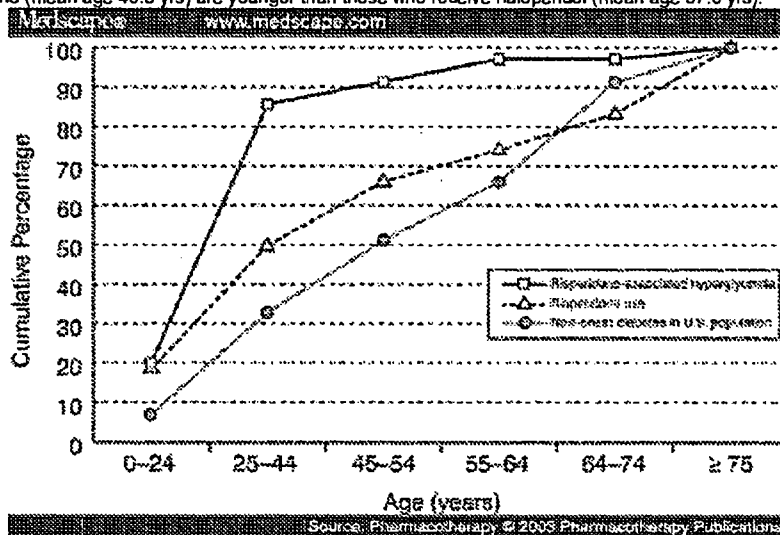


Figure 1. Distribution by age. Age distribution of risperidone-associated diabetes was compared with the distribution of new-onset diabetes cases in the U.S. population.^[27] The IMS Health National Disease and Therapeutic Index Audit™ data were used to assess risperidone treatment by age. Drug appearances include new and refill prescriptions as well as samples provided to patients by physicians. Patient age was unspecified for 3.7% of drug appearances. Proportionately, there were more than twice as many cases of risperidone-associated diabetes in the 0-44-year age range as there were in the U.S. population survey.

The overall male:female ratio for patients with hyperglycemia while receiving risperidone was 1.5, which could be attributed to the sex disparity in new-onset patients (male:female ratio 2.0). By contrast, the male:female ratio for new-onset patients receiving haloperidol was 0.7, but the sample size was small (10 patients). Actual administration data from the IMS Health National Disease and Therapeutic Index Audit™ suggest a male:female ratio of 0.8 for patients treated with either risperidone or haloperidol.

Time to Onset

The time to diagnosis of hyperglycemia in 96 patients for whom these data were available ranged from 1 day-48 months, but for 65 (68%) patients, it was 6 months or less from the time risperidone therapy was started (Figure 2). Time-to-diagnosis data were available for six of the seven patients receiving risperidone and haloperidol. Sixty-seven percent of patients with hyperglycemia were diagnosed within 6 months. The time to diagnosis was shorter in those with preexisting diabetes; these patients frequently observed changes in glucose control within days or

weeks. Deterioration in glycemic control was noted within the first 3 months for 25 (71%) of 35 such patients receiving monotherapy and both of two such patients receiving combination therapy. In comparison, hyperglycemia was identified within the first 3 months for 29 (48%) of 60 patients with new-onset disease receiving monotherapy and one (33%) of three patients with new-onset patients receiving combination therapy.

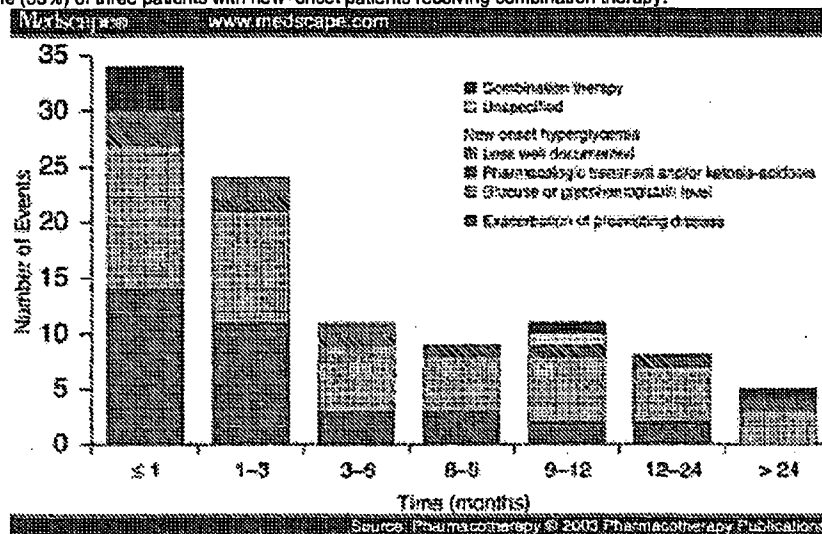


Figure 2. Time to hyperglycemic event. Hyperglycemic events were categorized by the time to occurrence after the start of risperidone therapy. Data were available for 102 (74%) of 138 patients. Among these, hyperglycemia was identified within the first 6 months of therapy in 69 (68%) patients. A notable number had delayed onset of disease.

Drug Dosages

Drug dosage data were available for 103 monotherapy patients except for one patient in whom hyperglycemia was identified after a 180-mg risperidone overdose. Dosages ranged from 0.5-12 mg/day. The mean $\pm$ SD dosage of 4.7 ± 2.5 mg/day was the same for new-onset patients and those with preexisting diabetes. For the six additional patients who were receiving combination therapy, the mean $\pm$ SD dosage was 6.3 ± 3.4 mg/day, which was not statistically different from the mean dosage for those receiving monotherapy ($p=0.3$). Dosage and time-to-onset data were available for 92 patients, six of whom were receiving combination therapy. There was no correlation between dosage and time to onset ($r=0.18$). Drug levels were not typically available.

Serious Outcomes

Four of the patients receiving risperidone monotherapy died; all were relatively young (40, 50, 51, and 55 yrs); three had new-onset hyperglycemia. Time to onset of hyperglycemia was 2 days-14 months; cause of death was unclear or unknown. Three of the patients had acidosis or ketosis. In addition, a 33-year-old woman receiving combination therapy died 2 weeks after risperidone therapy was started. Among the patients receiving risperidone, four had pancreatitis or hyperamylasemia in association with hyperglycemia. In the patient with known confounding concomitant acidosis, pancreatitis was diagnosed by computed tomography. Three of the patients who died were not receiving valproate; concomitant drugs were unknown for the fourth patient.

An additional report of pancreatitis was confirmed by lipase levels. Severity of reported cases ranged from mild glucose intolerance to diabetic ketoacidosis or hyperosmolar coma. Twenty-six of the patients receiving risperidone and two of those receiving combination therapy had acidosis or ketosis. Twelve patients had symptoms consistent with neuroleptic malignancy syndrome (elevated creatine kinase, rhabdomyolysis, elevated temperature); eight of these patients had new-onset hyperglycemia, four had preexisting diabetes (Table 4). The severity of reported cases ranged from mild glucose intolerance to diabetic ketoacidosis or hyperosmolar coma. Twenty-six of the patients treated with risperidone and two of those treated with combination risperidone-haloperidol therapy had acidosis or ketosis. In 31 patients receiving risperidone therapy and three receiving combination therapy, glucose levels equaled or exceeded 500 mg/dl (Table 5). Reports of acidosis-ketosis,

rhabdomyolysis, neuroleptic malignancy syndrome, and death were concentrated in the patients with more profound hyperglycemia.

Drug Withdrawal and Rechallenge

For various reasons, risperidone was reduced in 5 and discontinued in 47 patients receiving monotherapy; it was discontinued in 4 patients receiving combination therapy. Glycemic control improved in 12 patients receiving monotherapy and 1 patient receiving combination therapy. Hyperglycemia recurred in one patient within 1 week of rechallenge. Information on outcomes in other patients was lacking or confounded by treatment with antidiabetic therapy or conversion to another atypical antipsychotic agent.

Concomitant Drugs

No consistent pattern of concomitant drug therapy emerged from the data reported for these patients. Two were receiving no concomitant drugs, and only a limited number were receiving drugs known to induce hyperglycemia. One patient received a systemic corticosteroid (prednisone 5 mg) for chronic obstructive pulmonary disease, two received inhaled steroids, one had been taking niacin, and four had been taking thiazide diuretics. One patient had been taking unspecified drugs for human immunodeficiency virus infection. Of note, two patients -- one receiving monotherapy and one receiving combination therapy with haloperidol -- were taking another atypical antipsychotic, quetiapine. Three were being treated with chlorpromazine, which has been postulated to have effects on insulin release.^[28]

Treatment with valproate, a controversial putative risk factor for diabetes,^[29-32] was reported for 23 of 89 patients receiving monotherapy for whom some information was available regarding serial or concomitant drug therapy. Valproate administration was reported in three of seven combination therapy patients. The frequency of valproate administration in patients with glucose levels of 500 mg/dl or greater did not differ from that in patients with lower levels. Concomitant drug data were available for three of four patients with pancreatitis or hyperamylasemia; none of these patients received valproate. The other most frequently reported concurrent drugs were lithium, benzotropine, antidepressants (fluoxetine, paroxetine, sertraline, and trazodone), lorazepam, conventional antipsychotics, propranolol, and clonidine. The frequency of lithium administration in patients with glucose levels of 500 mg/dl or greater did not differ from that in patients with lower levels.

Risk Factors

The reports did not uniformly provide systematic information on risk factors for diabetes. Of the 34 patients with newly diagnosed hyperglycemia for whom family history was provided, 21 (62%) had a positive family history and 13 (38%) had a negative family history for diabetes. One patient whose hyperglycemia could not be classified as new or an exacerbation of preexisting diabetes had a negative family history. Limited body weight data were available for 37 monotherapy patients. Approximately 20% of these patients did not appear to be significantly overweight to have sustained a significant weight gain.

Discussion

Voluntary pharmacovigilance systems such as MedWatch, although limited by a lack of contemporaneous randomized control populations, incomplete case descriptions, and substantial underreporting, can signal adverse events that are not identified in the relatively short clinical trials with small and select populations used for registration of drugs.^[33-35] New-onset hyperglycemia and the exacerbation of previously diagnosed diabetes mellitus have been reported with three atypical antipsychotics -- clozapine and olanzapine (dibenzodiazepines) and quetiapine (a dibenzothiazepine) -- after they were approved.^[36-40] The data presented here similarly suggest that treatment with risperidone, a benzisoxazole, is associated with development of hyperglycemia. The time to onset of hyperglycemia was 3 months or less for most of the patients, and improvement of hyperglycemia followed withdrawal of the drug in some cases. Furthermore, the mean age of newly diagnosed patients in our series (34.8 years) was considerably younger than the typical mean age of patients with type 2 diabetes and newly diagnosed patients receiving haloperidol (50.2 years). Most notable were the higher reporting rates for risperidone compared with those for haloperidol.

The underlying cause of risperidone-associated hyperglycemia remains elusive. Any mechanism must explain the relatively rapid onset of hyperglycemia observed in most patients and presumably would be independent of weight gain. Of course, any significant weight gain could be expected to increase insulin resistance and contribute to later onset of hyperglycemia. Although weight gain has been reported with clozapine and olanzapine, the temporal relationship between the start of drug treatment and onset of hyperglycemia strongly suggests that weight gain is not the sole cause of deterioration in glucose tolerance.

Direct toxic effects of antipsychotic agents on islet cell function or on glucose transport into the cell would be consistent with rapid onset of action. Alternatively, members of this class of drug could interfere with the action of

Insulin in target tissues.^[41-43] Whatever the mechanism, genetic and environmental factors could predispose a subset of patients to adverse effects on glucose homeostasis.

One study assessed the effect of seven antipsychotic agents on basal and glucose-stimulated insulin release from rat β -cells.^[44] Drugs were added acutely at only one concentration (10^{-6} M), with a 30-minute preincubation in buffer alone. The incubation media were assayed for insulin after exposure to glucose alone or glucose plus drug for 1 and 4 hours. None of the drugs affected basal or glucose-stimulated insulin release at 1 hour. Clozapine increased insulin release after 4 hours of incubation under basal (3.3 mmol glucose) but not stimulated (16.7 mmol glucose) conditions. Haloperidol inhibited glucose-stimulated insulin release after 4 hours.

The magnitude of the changes induced by these drugs was small and overlapped considerably with results from the other drugs. The p values for comparisons with control were 0.03 (Mann-Whitney rank sum test), and the apparent effects of these two drugs conceivably were the result of several comparisons of drug groups with controls. None of the other drugs, such as risperidone and olanzapine, had a statistically significant effect on insulin release at 4 hours. Drug metabolites were not tested in this system. The investigators did not study the effects of preincubation with drugs. Within the limits of the experiment, the data suggest that none of the tested atypical antipsychotics adversely affect rat β -cell function in vitro when given acutely at a concentration of 10^{-6} M. Clozapine may augment basal insulin release, but further data are needed before this finding can be accepted.

Alternatively, some atypical antipsychotics and/or their metabolites may inhibit glucose transport into the central nervous system or peripheral tissues.^[45, 46] One study^[45] showed that risperidone and clozapine inhibited the uptake of ^3H -2-deoxyglucose in a dose-dependent fashion in rat pheochromocytoma (PC12) cells (dose range 2-100 μM for both drugs, IC_{50} 35 μM for risperidone and 20 μM for clozapine; the clozapine metabolite desmethylclozapine was even more potent, with an IC_{50} of 15 μM). This inhibition occurred rapidly (within 15 minutes) and was antagonized by addition of increasing doses of nonradioactive 2-deoxyglucose. Schild analysis of the concentration-response curves demonstrated linear regression lines with slopes that were significantly different from 1, indicating noncompetitive antagonism of the drugs' inhibitory effects by 2-deoxyglucose.

These data suggest that some antipsychotic drugs (or their metabolites; unfortunately, risperidone metabolites were not tested) may be capable of inhibiting glucose transport into central nervous system neurons. Given the relatively low concentrations of glucose in brain extracellular fluids and the high concentrations of antipsychotic drugs, these effects may be significant. The authors speculate that effects on neurons that regulate energy metabolism may account for hyperglycemia, weight gain, and other adverse events.^[46]

These in vitro data suggest that there may be differences in the hyperglycemic risk for the various atypical antipsychotic agents, that the differences are not based on the weight gain alone, and that chemical structure of the parent drug or metabolite is functionally significant. These data are supported indirectly by the relative number of reports of hyperglycemia for the atypical antipsychotic agents. A total of 384 (238 domestic) cases of hyperglycemia were reported for clozapine (1990-March 2001), 289 (257 domestic) for olanzapine (1994-February 2002), 138 (134 domestic) for risperidone (1993-February 2002), and 20 (17 domestic) for haloperidol (late 1970s-February 2002).^[37, 38] Estimated years of patient exposure based on the numbers of U.S. prescriptions and mean duration of therapy through February 2002 were (in thousands) 678.7 for clozapine, 2104.6 for olanzapine, 3111.3 for risperidone, and 6497.4 for haloperidol.^[47]

Reporting rate ratios [(domestic cases drug 1/patient exposure drug 1) divided by (domestic cases drug 2/patient exposure drug 2)] cannot be determined precisely because the time interval for collection of the adverse events and prescription data differ, reporting patterns may have changed over time, and reporting may be higher for a registry drug (clozapine). However, the data suggest that there may be differences in the diabetogenic potential of the various drugs: clozapine > olanzapine > risperidone > haloperidol.

Selection of the specific antipsychotic agent for a particular patient will be driven more by a drug's capacity to reduce psychiatric symptoms than by its diabetic potential alone. In the absence of definitive studies about causality and risk, it is probably prudent to screen patients for diabetes (fasting serum glucose ≥ 126 mg/dl, random serum glucose ≥ 200 mg/dl) at the start of antipsychotic therapy and monitor intermittently thereafter. Clinicians should be alert to the sedation and confusion that may result from glucose hyperosmolarity as well as directly from the drug itself because low-functioning patients may lack the insight to recognize the symptoms of diabetes. Although conversion to another antipsychotic has been empirically useful for some patients, there are no definitive data on relative diabetic potential of the various agents and the patient characteristics that contribute to reversibility. Conversion also introduces the risk of a psychotic flare.

Conclusion

These data, along with similar reports of hyperglycemia with olanzapine, clozapine, and quetiapine, suggest that atypical antipsychotic administration may unmask or precipitate hyperglycemia. The onset of hyperglycemia may be rapid and severe. Although most cases occurred within 3 months, risk is not eliminated with extended therapy. The most severe hyperglycemia was observed in patients without previously diagnosed diabetes and who, as such, were not monitoring glucose levels. The association was not dose dependent. Definitive conclusions about causality and relative risk cannot be made until controlled prospective studies are conducted that include serum levels of parent drug and metabolites.

Tables

Table 1. Comparative Numbers of Cases and Demographics

Treatment	No. of Patients with Hyperglycemia	Age Range (yrs)	Mean $\pm$ SD Age (yrs)	Male:Female Ratio
Risperidone	131 ^a (124 from U.S.)	8-96 (12 pls < 19 yrs)	39.8 $\pm$ 17.4 (n=112)	1.5 (n=121)
Haloperidol	13 ^{a, b} (10 from U.S.)	16-82 (2 pls < 19 yrs)	48.1 $\pm$ 20.0 (n=13)	0.9 (n=13)
Risperidone + haloperidol	7 (7 from U.S.)	30-50	35.6 $\pm$ 7.3 (n=7)	0.8 (n=7)
All risperidone	138 ^a	8-96	39.5 $\pm$ 17.0 (n=119)	1.5 (n=128)
All haloperidol	20 ^{a, b}	16-82	43.7 $\pm$ 17.5 (n=20)	0.8 (n=20)
Treatment	No. of Patients with Other Acidosis	Age Range (yrs)	Mean $\pm$ SD Age (yrs)	Male:Female Ratio
Risperidone	6 (3 from U.S.)	12-69 (1 pt < 19 yrs)	45.8 $\pm$ 21.2 (n=5)	0.2 (n=5)
Haloperidol	11 ^a (7 from U.S.)	21-76	48.7 $\pm$ 19.5 (n=11)	1.6 (n=11)
Risperidone + haloperidol	1 (not from U.S.)	43	43 (n=1)	1 male

^a35-yr-old man with preexisting diabetes experienced hyperglycemia first with haloperidol, then with risperidone.

^b51-yr-old woman with new-onset hyperglycemia was receiving olanzapine as well.

^c29-yr-old man was receiving olanzapine as well.

Table 2. Number of Cases by Type of Hyperglycemia

Type of Hyperglycemia	Risperidone	Risperidone + Haloperidol	Total	Haloperidol
Newly diagnosed	78	4	82	10
Glucose or glycohemoglobin level	55	3	58	6
Required treatment	9	0	9	2
Ketosis-acidosis	1	0	1	1
Less well documented	13	1	14	1
Exacerbation of preexisting disease	48	2	48	2
Unknown	7	1	8	1
Totals	131	7	138	13

Table 3. Demographics by Type of Hyperglycemia

Type of Hyperglycemia	Risperidone		Risperidone ± Haloperidol		Haloperidol	
	Mean ± SD Age (yrs)	Male:Female Ratio	Mean ± SD Age (yrs)	Male:Female Ratio	Mean ± SD Age (yrs)	Male:Female Ratio
New-onset	34.8 ± 15.7 (n=70)	2.0 (n=76)	37.0 ± 9.4 (n=4)	0.3 (n=4)	50.2 ± 21.7 (n=10)	1.5 (n=10)
Exacerbation of preexisting disease	48.8 ± 17.5 (n=39)	1.0 (n=41)	35.5 ± 8.7 (n=2)	1.0 (n=2)	45.5 ± 14.8 (n=2)	1.0 (n=2)
Unknown	38.0 ± 2.6 (n=3)	1.0 (n=4)	30.0 ± 0.0 (n=1)	1 male	32.0 ± 0.0 (n=1)	1 male

Table 4. Numbers of Patients Who Experienced Serious Adverse Events

Type of Hyperglycemia	Acidosis-Ketosis	NMS-Like Symptoms	Pancreatitis	Death
New-onset	22 ^a (1)	8	3 ^b (1)	3
Exacerbation of preexisting disease	3 (1)	4 ^c	1	1 (1) ^d
Unspecified	1	0	0	0
Totals	26 (2)	12	4 (1)	4 (1)

Numbers in parentheses indicate patients receiving combination treatment.

NMS = neuroleptic malignancy syndrome.

^aOne of the 22 patients had lactic acidosis-ischemic bowel.

^bPlus one patient with "pancreatic failure."

^cIn one of these patients, NMS was possible; another patient had an unexplained increase in creatine kinase level with fever.

^dOccurred after the start of treatment with an oral hypoglycemic agent.

Table 5. Number of Cases of Severe Hyperglycemia and Associated Adverse Events

Glucose Level (mg/dl)	Type of Hyperglycemia			Acidosis-Ketosis		NMS-Like Symptoms		Pancreatitis		Death	
	New Onset	Exacerbation	Unspecified	New Onset	Exacerbation	New Onset	Exacerbation	New Onset	Exacerbation	New Onset	Exacerbation
≥ 500-699	13	5 (1)	1	5	2 (1)	0	1	0	1	1	0
≥ 700-999	2 (1)	1	0	1 (1)	0	0	0	0 (1)	0	0	0
≥ 1000	9 ^a (1)	0	0	7	0	4	0	0 ^b	0	1	0
Totals	24 (2)	6 (1)	1	13 (1)	2 (1)	4	1	0 (1)	1	2	0

Numbers in parentheses indicate patients receiving combination treatment.

NMS = neuroleptic malignancy syndrome.

^aPlus one case in which glucose level reached 1023 mg/dl despite initial treatment with an oral antidiabetic agent.

^bPlus one case of pancreatic failure.

References

1. Anonymous. Risperidone. Physicians' desk reference. Montvale, NJ: Medical Economics, 2003:1786-90.
2. Kiraly SJ, Gibson RE, Ancill RJ, Holliday SG. Risperidone: treatment response in adult and geriatric patients. *Int J Psychiatry Med* 1998;28:255-63.
3. Krashin D, Oates EW. Risperidone as adjunct therapy for post-traumatic stress disorder. *Mil Med* 1999;164:605-6.
4. Zarate CA Jr, Baldessarini RJ, Siegel AJ, et al. Risperidone in the elderly: a pharmacoeconomic study. *J Clin Psychiatry* 1997;58:311-17.
5. Yatham LN. The role of novel antipsychotics in bipolar disorders. *J Clin Psychol* 2002;63:10-4.
6. He H, Richardson JS. A pharmacological, pharmacokinetic and clinical overview of risperidone, a new antipsychotic that blocks 5-HT₂ and dopamine D₂ receptors. *Int Clin Psychopharmacol* 1995;10:19-30.
7. Baldessarini RJ. Drugs and the treatment of psychiatric disorders: psychosis and anxiety. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Goodman Gilman A, eds. *Goodman and Gilman's: the pharmacological basis of therapeutics*, 9th ed. New York: McGraw-Hill, 1996:399-430.
8. Mannens G, Huang ML, Mauldermans W, Hendricks J, Woestenberghs R, Heykants J. Absorption, metabolism, and excretion of risperidone in humans. *Drug Metab Dispos* 1993;21:1134-41.
9. Eap CB, Bondolfi G, Zullino D, et al. Pharmacokinetic drug interaction potential of risperidone with cytochrome p450 isozymes as assessed by the dextromethorphan, the caffeine, and the mephenytoin test. *Ther Drug Monit* 2001;23:228-31.
10. Sproule BA, Naranjo CA, Brenner KE, Hassan PC. Selective serotonin reuptake inhibitors and CNS drug interactions: a critical review of the evidence. *Clin Pharmacokinet* 1997;33:454-71.
11. Ono S, Mihara K, Suzuki A, et al. Significant pharmacokinetic interaction between risperidone and carbamazepine: its relationship to CYP2D6 genotypes. *Psychopharmacology (Berl)* 2002;162:50-54.
12. Lindenmayer J-P, Nathan A-M, Smith RC. Hyperglycemia associated with the use of atypical antipsychotics. *J Clin Psychiatry* 2001;62 (suppl 23):30-8.
13. Kelly DL, Conley RR, Love RC, Horn DS, Ushchak CM. Weight gain in adolescents treated with risperidone and conventional antipsychotics over six months. *J Child Adolesc Psychopharmacol* 1998;8:151-9.
14. Croarkin PE, Jacobs KM, Bain BK. Diabetic ketoacidosis associated with risperidone treatment? *Psychosomatics* 2000;41:369-70.
15. Wirshing DA, Pierre JM, Eyeler J, Weinbach J, Wirshing WC. Risperidone: associated new-onset diabetes. *Biol Psychiatry* 2001;50:148-9.
16. Brescan DW. Risperidone and glucose intolerance [abstr]. Presented at the 150th annual meeting of the American Psychiatric Association, San Diego, CA., May 17-22, 1997.
17. Hidaka S. Two cases of perforation of the colon in long-term hospitalized schizophrenic patients during psychotropic drug administration. *Clin Psychiatry* 1999;41:425-8.
18. Litovitz T. 1988 annual report of the American Association of Poison Control Centers national data collection system. *Am J Emerg Med* 1989;7:495-545.
19. Litovitz T. 1990 annual report of the American Association of Poison Control Centers national data collection system. *Am J Emerg Med* 1991;9:461-509.
20. Litovitz T. 1994 annual report of the American Association of Poison Control Centers national data collection system. *Am J Emerg Med* 1995;13:551-97.
21. Miyahira Y. A case report of death from neuroleptic malignancy syndrome due to long-acting haloperidol. *Kyushu Neuropsychiatry* 1998;44:322-3.
22. Capron M, Lafitte B, Benedit M, et al. Necrotizing colitis in a 29-year-old man under high-dose neuroleptics (French). *Reanim Urgences* 1999;8:701-4.
23. Dharmarajan TS, Bullecer MF, Gorich G. Drug-related hyperthermia. *J Am Med Dir Assoc* 2001;2:160-5.
24. Dohin-Caplanne S. Severe hepatitis complicating exercise-induced heatstroke favored by treatment with neuroleptic and anticholinergic drugs (French). *Gastroenterol Clin Biol* 1995;19:637-8.
25. Litovitz T. 1987 annual report of the American Association of Poison Control Centers national data collection system. *Am J Emerg Med* 1988;6:479-515.
26. Litovitz T. 1998 annual report of the American Association of Poison Control Centers national data collection system. *Am J Emerg Med* 1999;17:435-87.

27. Kenny SJ, Aubert RE, Geiss LS. Prevalence and incidence of non-insulin dependent diabetes. In: Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, eds. Diabetes in America, 2nd ed. Publication no. 95-1468. Bethesda, MD: National Institutes of Health-National Institute of Diabetes, Digestive, and Kidney Diseases, 1995:47-67.
28. Ammon HR, Orzi L, Steinle J. Effect of chlorpromazine (CPZ) on insulin release in vivo and in vitro in the rat. *J Pharmacol Exp Ther* 1973;187:423-9.
29. Isojarvi JI, Tauboll E, Pakarinen AJ, et al. Altered ovarian function and cardiovascular risk factors in valproate-treated women. *Am J Med* 2001;111:290-6.
30. Jallon P, Picard F. Body weight gain and anticonvulsants: a comparative review. *Drug Saf* 2001;24:969-78.
31. Odinesen H, Gram L, Andersen T, Dam M. Weight gain during treatment with valproate. *Acta Neurol Scand* 1984;70:65-9.
32. Turnbull DM, Bone AJ, Tames FJ, Wilson L, Baird JD, Sherratt HS. The effect of valproate on blood metabolite concentrations in spontaneously diabetic, ketoacidotic, BB/E Wistar rats. *Diabetes Res* 1985;2:45-8.
33. Brewer T, Colditz G. Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. *JAMA* 1999;281:824-9.
34. Lasser KE, Allen PD, Woolhandler SF, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA* 2002;287: 2215-20.
35. Wood AJ. Thrombotic thrombocytopenic purpura and clopidogrel: a need for new approaches to drug safety. *N Engl J Med* 2000;342:1824-6.
36. Domon SE, Cargile CS. Quetiapine-associated hyperglycemia and hypertriglyceridemia. *J Am Acad Child Adolesc Psychiatry* 2002;41:495-6.
37. Koller EA, Schneider B, Bennett K, Dubitsky G. Clozapine-associated diabetes mellitus. *Am J Med* 2001;111:716-23.
38. Koller EA, Doraiswamy PM. Olanzapine-associated diabetes mellitus. *Pharmacotherapy* 2002;22:841-52.
39. Procyshyn RM, Pande S, Tse G. New-onset diabetes associated with quetiapine. *Can J Psychiatry* 2000;45:668-9.
40. Sobel M, Jagers ED, Franz MA. New-onset diabetes associated with the initiation of quetiapine treatment. *J Clin Psychol* 1999;60:556-7.
41. Lacruz A, Baptista T, Mendoza S, Mendoza-Guillen JM, Hernandez L. Antipsychotic drug-induced obesity in rats: correlation between leptin, insulin, and body weight during sulpride treatment. *Mol Psychiatry* 2000;5:70-6.
42. Melkersson K, Hulting A-L, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. *J Clin Psychiatry* 1999;60:783-91.
43. Melkersson K, Hulting A-L, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. *J Clin Psychiatry* 2000;61:742-9.
44. Melkersson K, Khan A, Hilding A, Hulting A-L. Different effects of antipsychotic drugs on insulin release in vitro. *Eur Neuropsychopharmacol* 2001;11:327-32.
45. Ardizzone TD, Bradley RJ, Freeman III AM, Dwyer DS. Inhibition of glucose transport in PC12 cells by the atypical antipsychotic drugs risperidone and clozapine, and structural analogues of clozapine. *Brain Res* 2001;923:82-90.
46. Dwyer DS, Liu Ye, Bradley RJ. Dopamine receptor antagonists modulate glucose uptake in rat pheochromocytoma (PC12) cells. *Neurosci Lett* 1999;274:151-4.
47. Koller, EA, Cross JT, Doraiswamy PM, Malozowski SN. Pancreatitis associated with atypical antipsychotics: from the FDA MedWatch surveillance system. *Pharmacotherapy*, in press.

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Glucose Intolerance with Atypical Antipsychotics

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Abstract

Background: Previous studies have suggested that the atypical antipsychotics clozapine and olanzapine may be associated with an increased risk of glucose intolerance and diabetes mellitus. Early studies have also suggested an association between use of conventional antipsychotics and the development of glucose intolerance.

Objective: To examine quantitatively the association between glucose intolerance including diabetes mellitus and the use of the atypical antipsychotics clozapine, olanzapine or risperidone, and to identify possible risk factors for the development of glucose intolerance during treatment with these drugs.

Methods: All reports suggestive of glucose intolerance for clozapine, olanzapine and risperidone were identified in the WHO database for adverse drug reactions. In the analyses of possible risk factors for glucose intolerance all other reports of adverse drug reactions for clozapine, olanzapine and risperidone were used as reference. Using the Bayesian Confidence Propagation Neural Network method, the strengths of the associations over time between glucose intolerance and the use of these drugs were analysed. For comparison, the strengths of the associations between glucose intolerance and the use of the conventional antipsychotics haloperidol and chlorpromazine were also analysed.

Results: Clozapine, olanzapine and risperidone were significantly associated with glucose intolerance. In contrast, chlorpromazine and haloperidol were not associated with glucose intolerance. For clozapine, olanzapine and risperidone grouped together, the following potential risk factors for glucose intolerance were identified: an underlying diabetic condition (odds ratio [OR] 10.22, 95% CI 8.20–12.73), an increase in weight (OR 2.36, 95% CI 1.76–3.17), male gender (OR 1.27, 95% CI 1.11–1.47), and concomitant use of valproic acid (OR 1.97, 95% CI 1.61–2.40), selective serotonin reuptake inhibitors (OR 1.63, 95% CI 1.33–1.99) or buspirone (OR 2.24, 95% CI 1.33–3.77).

Conclusion: Treatment with clozapine, olanzapine or risperidone appears to be associated with an increased risk of glucose intolerance.

Background

Compared with conventional antipsychotics, the new generation antipsychotic agents, often referred to as atypical antipsychotics, are characterised by a reduced liability to induce extrapyramidal symptoms.^[1,2] Also other properties, such as an increased efficacy towards the negative symptoms of schizophrenia, lack of or small increases in prolactin levels, and effectiveness in some patients previously regarded as treatment-refractory, have been attributed to these second-generation antipsychotic drugs.^[1,2]

It has been increasingly recognised that the atypical agents clozapine and olanzapine may cause glucose intolerance and hyperglycaemia.^[3-8] Early studies have also suggested an association between conventional antipsychotics and altered glucose-insulin homeostasis.^[9-12] Moreover, schizophrenia itself has been linked to an increased risk for developing hyperglycaemia or diabetes mellitus.^[13-17] The possible mechanisms behind these effects are still largely unknown. Since it was shown that clozapine plasma concentrations were positively correlated to insulin levels in 13 clozapine-treated patients,^[6] it may be anticipated that clozapine induces insulin resistance, which is associated with a compensatory increase in insulin secretion. Subjects who are unable to achieve this compensation develop diabetes mellitus. Antipsychotic agents, and particularly atypical antipsychotics such as clozapine and olanzapine, may also promote other metabolic effects such as excessive weight gain,^[18,19] hypertriglyceridaemia,^[20-23] and hyperleptinaemia.^[24,25] All these effects may be part of a drug-induced metabolic syndrome.

Recently, it has been proposed that clozapine, and possibly also olanzapine, may be more likely to cause glucose intolerance compared with conventional antipsychotics.^[5,20] No similar suspicion seems to have been put forward for risperidone, which has been suggested to be the drug of choice when an atypical agent is needed in a patient with diabetes mellitus.^[26] Important risk factors for glucose intolerance in general are obesity, lack of physical activity, and a personal or family history of diabetes mellitus. Specific risk factors for glu-

cose intolerance with atypical antipsychotics have not yet been characterised.

The aim of the present study was to identify the role of the atypical antipsychotics clozapine, olanzapine and risperidone in the development of glucose intolerance. Moreover, a further aim of the study was to identify possible risk factors for the development of glucose intolerance during treatment with these drugs.

Methods

The WHO Collaborating Centre for International Drug Monitoring receives summary clinical reports of individual adverse drug reactions from the national centres in 63 countries around the world. This information is stored in a large international database containing more than 2.5 million adverse drug reaction reports.

Reports were identified for clozapine, olanzapine and risperidone in the WHO database, which included the following diagnoses: glucose tolerance abnormal, hyperglycaemia, diabetes mellitus, diabetes mellitus aggravated, ketosis, diabetic coma and glycosuria. For convenience, all these diagnoses were designated glucose intolerance in this study. Duplicated reports were deleted from the database prior to the analysis. From each report, the following information can be obtained: country of origin, age and gender of the patient, suspected reactions, suspected as well as concomitant drug treatment, dosage, route of administration and duration of treatment of the suspected drug, date of onset of the adverse drug reaction, information on dechallenge and rechallenge, and outcome. Most reports, however, contain incomplete information.

Additional adverse drug reactions in the reported cases were also reviewed because the same adverse reaction can be coded in more than one way. For example, the adverse reaction term diabetes mellitus aggravated can be coded as hyperglycaemia and condition aggravated, and the term diabetic coma can be coded as coma and hyperglycaemia and acidosis. Moreover, additional adverse reaction diagnoses may indicate associated events,

such as increased serum lipid levels, increased or decreased weight, liver events, or pancreatitis.

To quantify the possible adverse effect of glucose intolerance, the strengths of the associations over time between glucose intolerance and the atypical antipsychotics clozapine, olanzapine and risperidone were analysed using the Bayesian Confidence Propagation Neural Network (BCPNN) technique on the data in the WHO database. The strengths of the associations between glucose intolerance and the conventional antipsychotics haloperidol and chlorpromazine were analysed for comparison. The BCPNN technique has been described in detail previously^[27,28] and is now used routinely in signal detection analysis. In short, in the WHO database, all adverse reaction reports contain at least one drug and one adverse reaction. The BCPNN method is based on Bayes theorem and uses neural network architecture to search for unexpectedly strong dependencies between drugs and adverse reactions within the dataset. The dependencies are selected using a measure of disproportionality called the information component (IC). For each specific drug-adverse reaction combination an IC and its standard deviation (SD) can be calculated, and changes in its value can be examined over time. A drug-adverse reaction combination, which is reported more often than would be expected from the rest of the reports of the database, has a positive IC value. The IC value is based on the following information: the number of case reports with a particular drug, the number of case reports with a particular adverse reaction, the number of reports with the specific drug-adverse reaction combination, and the total number of reports. New data may cause the IC to either increase or decrease. When the IC value is calculated from large numbers, a new report is less likely to cause a fluctuation in the IC value. The SD for each IC provides a measure of the robustness of the value. An IC -2 SD value above zero demonstrates a significant positive quantitative association between the drug and the adverse reaction. The likelihood of a true association is higher when a significant quantitative association increases over time.

In the analyses of risk factors for glucose intolerance, χ^2 -tests, Student's t-tests, Fisher's exact tests and Wilcoxon rank sum tests were used for statistical comparisons between groups. Statistical significance was defined as $p = 0.05$ or below.

Results

From its start in 1968 until December 2000, the WHO Collaborating Centre received 868 reports of glucose intolerance with clozapine ($n = 480$), olanzapine ($n = 253$), and risperidone ($n = 138$). The distribution of the reports over the searched reactions is presented in figure 1. In three cases, the patient received two atypical antipsychotics concomitantly. Therefore, the total number of reports is less than the sum of reports for the individual drugs.

The strengths of the associations over time between the atypical agents clozapine, olanzapine or risperidone and glucose intolerance are presented in figure 2. As the IC -2SD values were above zero for all the three compounds, they were significantly associated with glucose intolerance. For clozapine, first introduced in the early 1970s, the number of reports of glucose intolerance was very small until 1991 as reflected in the low and fluctuating IC values. For risperidone, introduced in 1993, and for olanzapine, introduced in 1996, reporting of glucose intolerance had already taken place in the first years after marketing as indicated by increasing and stabilising IC values. The strengths of the associations over time between chlorpromazine or haloperidol and glucose intolerance are presented in figure 3. In contrast to the atypical agents, chlorpromazine and haloperidol were not associated with glucose intolerance. The number of reports of glucose intolerance has remained small for both chlorpromazine and haloperidol, introduced in the early and late 1950s, respectively.

In 74% of the cases where the outcome after discontinuation of the drug was known ($n = 114$), the glucose intolerance had improved. A rechallenge with the drug was carried out in 24 cases (18 for clozapine, five for olanzapine, one for risperidone), and resulted in a reoccurrence of

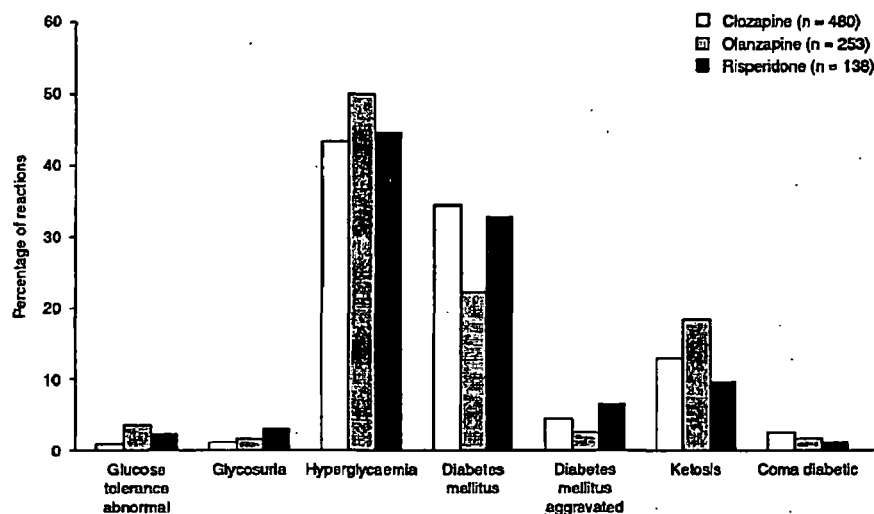


Fig. 1. Distribution of glucose intolerance reactions among atypical antipsychotics.

glucose intolerance in 17 cases (71%; 12 for clozapine, four for olanzapine, one for risperidone).

Of the reports of glucose intolerance with clozapine, olanzapine and risperidone, 505 (61.4%) concerned men and 318 (38.6%) concerned women. For all other adverse drug reactions with clozapine, olanzapine and risperidone, the corresponding proportions were 21 419 (55.5%) and 17 178 (44.5%),

respectively. Using females as reference the odds ratio (OR) for males and glucose intolerance was 1.27 (95% CI 1.11–1.47). The mean ages of men and women with glucose intolerance were 40.0 and 42.5 years, respectively, and of those with other adverse reactions 39.1 and 43.9 years, respectively (difference not significant). Forty-nine cases (5.6%) of glucose intolerance reported an increase in

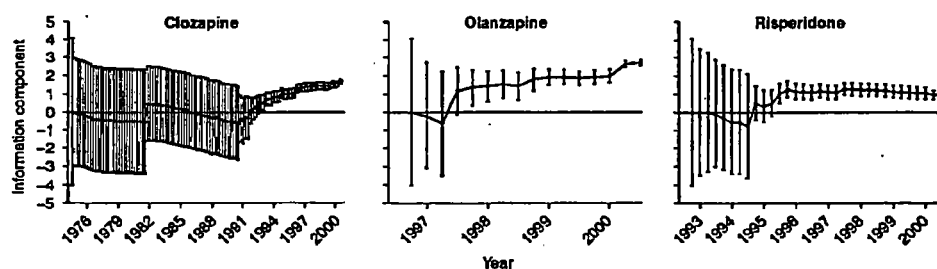


Fig. 2. The strengths of the associations over time between glucose intolerance and clozapine, olanzapine and risperidone. An information component (IC) value increasing with time, with an IC -2SD value above zero demonstrates a significant positive quantitative association between the drug and the adverse reaction.

weight (20 for clozapine, 24 for olanzapine, six for risperidone) compared with 1 022 (2.5%) of those with other adverse reactions (OR 2.36, 95% CI 1.76–3.17). Thirteen cases (1.5%) of glucose intolerance reported a decrease in weight (ten for clozapine, two for olanzapine, one for risperidone) compared with 176 (0.4%) of those with other adverse reactions (OR 3.55, 95% CI 2.02–6.27). Weight increase was twice as frequent with olanzapine compared with the other two agents.

The treatment durations until the onset of glucose intolerance were known in 47 cases. The median treatment duration was 13 (interquartile range 8–75) days for risperidone ($n = 13$), 52 (interquartile range 36–216) days for clozapine ($n = 19$) and 115 (interquartile range 50–181) days for olanzapine ($n = 23$). Most cases (87%; 41 of 47) occurred within the first year of treatment. The prescribed doses were known in 346 cases of glucose intolerance, and were not significantly different from those in cases with other adverse reactions (table I).

The use of concomitant drugs is presented in table II for clozapine, olanzapine and risperidone grouped together. The concomitant use of insulin or oral antidiabetic agents, which indicates the presence of an underlying diabetic condition, was associated with the highest OR for glucose intolerance (OR 10.22, 95% CI 8.20–12.73 for use of any antidiabetic drug). Use of valproic acid (OR 1.97, 95% CI 1.61–2.40), buspirone (OR 2.24, 95% CI 1.33–3.77), or selective serotonin reuptake inhibitors (OR 1.63, 95% CI 1.33–1.99) was also associated with significantly elevated ORs for glucose intolerance for all three agents combined, whereas the elevated ORs for β -blockers and thiazide diuretics did not reach statistical significance. Concomitant treatment with non-selective reuptake inhibitors, lithium, glucocorticoids, or conventional antipsychotics was not associated with an elevated OR for glucose intolerance for any of the three atypical agents studied. For the cytochrome P450 (CYP) 1A2 substrates clozapine and olanzapine, concomitant use of drugs known to inhibit this enzyme, such as fluvoxamine, cimetidine, and several fluoroquinolones, was not associated with an elevated OR for glucose intolerance

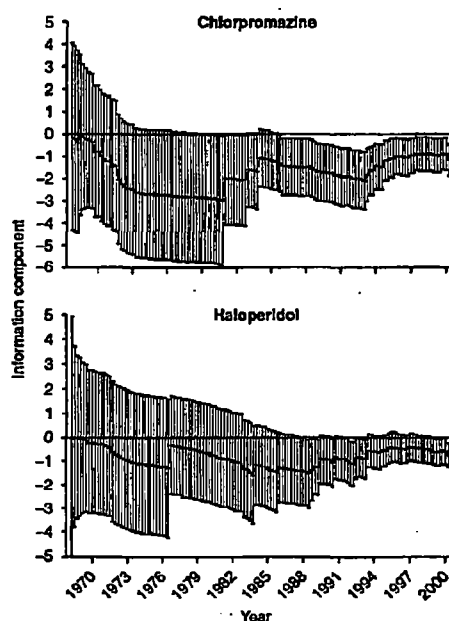


Fig. 3. The strengths of the associations over time between glucose intolerance and chlorpromazine and haloperidol. In contrast to the atypical agents, no associations were found.

(OR 0.51, 95% CI 0.16–1.60 for clozapine; OR 0.72, 95% CI 0.26–1.96 for olanzapine). Similarly, for the CYP2D6 substrate risperidone, concomitant use of drugs known to inhibit this enzyme, such as fluoxetine, paroxetine, and quinidine, was not associated with an elevated OR for glucose intolerance (OR 1.07, 95% CI 0.70–1.62).

All reports of glucose intolerance were scrutinised for the presence of pancreatitis, liver events, increased serum lipid levels, increased or decreased weight, aggravated pre-existing condition, acidosis or ketosis, coma and death. The distribution of these selected events is presented in figure 4. Within the reports of glucose intolerance for all atypical antipsychotics together, use of valproic acid was significantly associated with pancreatitis

Table I. Prescribed daily doses in adverse drug reaction reports of impaired glucose tolerance during treatment with clozapine, olanzapine and risperidone, compared with doses in cases of other adverse drug reactions

Suspected drug		Glucose intolerance	All other adverse drug reactions
Clozapine	No. of reports	252	17 079
	Mean dose $\pm$ SD (mg)	337 $\pm$ 182	353 $\pm$ 232
	Median dose, interquartile range	300, 200–450	300, 200–500
Olanzapine	No. of reports	30	1 977
	Mean dose $\pm$ SD (mg)	31 $\pm$ 89	19 $\pm$ 54
	Median dose, interquartile range	10, 10–15	10, 10–15
Risperidone	No. of reports	64	5 438
	Mean dose $\pm$ SD (mg)	7 $\pm$ 22	5 $\pm$ 12
	Median dose, interquartile range	4, 2–6	3, 2–6

SD = standard deviation.

(OR 2.44, 95% CI 1.22–4.86) and acidosis/ketosis (OR 2.17, 95% CI 1.40–3.37), selective serotonin reuptake inhibitors were significantly associated with coma (OR 2.40, 95% CI 1.25–4.61), buspirone was significantly associated with pancreatitis (OR 7.02, 95% CI 2.15–2.98) and liver events (OR 4.83, 95% CI 1.31–17.76), and insulin, and oral antidiabetic agents were significantly associated with aggravated pre-existing condition (OR 13.50, 95% CI 7.48–24.35 for insulin; OR 2.32, 95% CI 1.04–5.20 for sulfonylureas; OR 4.31, 95% CI 1.30–14.30 for biguanides).

Discussion

In contrast to the conventional agents chlorpromazine and haloperidol all three atypical antipsychotics investigated in the study were associated with glucose intolerance. The results support the existence of a higher risk of glucose intolerance with atypical antipsychotics including risperidone as has already been suggested by others.^[29]

A number of factors limit the generalisations that can be made from this material. Spontaneous reports of adverse drug reactions represent a suspicion that a drug caused the event, but the causal role is often not established. The reporting of adverse drug reactions may be influenced by several factors such as the extent of use of the drug, the year of introduction to the market, general knowledge of the effects and adverse effects of the drug, public attention to specific problems, and health professionals' attitudes to reporting of adverse

drug reactions. It can generally be assumed that adverse drug reactions are both underreported and subject to biased reporting. Comparisons between individual drugs of the magnitudes of risk for an adverse drug reaction can therefore not be made. Despite these limitations, spontaneous adverse drug reaction reporting has become an established tool in drug monitoring.^[30] The BCPNN method further increases the value of spontaneous reporting by facilitating early detection of adverse drug reactions and by providing a statistical measure of the likelihood and size of an association.^[27]

Men were over-represented among reports of glucose intolerance in our study. This result is in agreement with a recent review of the published literature, which concluded that male gender might be a risk factor for glucose intolerance with atypical antipsychotics.^[31] We did not find any relation between age and glucose intolerance, which was unexpected since glucose intolerance is known to be more common among the elderly. However, because we used all other adverse drug reactions to the studied drugs for comparison, our results do not exclude age as a possible risk factor for glucose intolerance. It is possible that the risk of developing an adverse drug reaction in general increases with increasing age.

An increase in weight was more common among reports of glucose intolerance compared with other adverse reactions. Because the risk of glucose intolerance is known to increase with increasing weight it might be assumed that the increased risk associated with the three atypical an-

Table II. Use of concomitant drugs in adverse drug reaction reports of impaired glucose tolerance during treatment with clozapine, olanzapine and risperidone

Concomitant drugs	Glucose intolerance (%) [n = 868]	All other adverse reactions (%) [n = 41 316]	Odds ratio (95% CI)
Any concomitant drug	61.1	53.9	1.34 (1.17–1.54) ^a
Insulin	6.5	0.5	14.93 (10.89–20.27) ^b
Sulfonylurea	4.8	0.8	6.53 (4.70–9.08) ^b
Biguanides	1.5	0.2	8.04 (4.45–14.52) ^b
SSRI ^c	12.9	8.3	1.63 (1.33–1.99) ^d
NSRI ^e	4.0	4.3	0.94 (0.67–1.33)
Valproic acid	13.4	7.3	1.97 (1.61–2.40) ^f
Buspirone	1.7	0.8	2.24 (1.33–3.77) ^g
Beta-blockers	3.6	2.5	1.43 (0.99–2.05) ^h
Thiazides	0.6	0.3	1.82 (0.74–4.46)
Lithium	7.0	6.8	1.07 (0.82–1.38)
Glucocorticoids	0.7	0.7	1.01 (0.45–2.26)
Antipsychotics ⁱ	11.6	12.9	0.89 (0.72–1.09)

a In the evaluation of the individual drugs, the OR was significantly elevated for risperidone (OR 1.76, 95% CI 1.21–2.56), but not for olanzapine (OR 1.31, 95% CI 0.99–1.73), or clozapine (OR 1.16, 95% CI 0.87–1.59).

b In the evaluation of the individual drugs, the ORs were significantly elevated for clozapine (OR 11.34, 95% CI 7.10–18.13 for insulin; OR 7.24, 95% CI 4.86–10.79 for sulfonylureas; OR 9.27, 95% CI 4.35–19.78 for biguanides), risperidone (OR 36.21, 95% CI 21.16–61.97 for insulin; OR 10.86, 95% CI 5.66–20.85 for sulfonylureas; OR 14.02, 95% CI 4.06–48.42 for biguanides), and olanzapine with the exception of biguanides (OR 9.96, 95% CI 5.18–19.17 for insulin; OR 3.67, 95% CI 1.64–8.20 for sulfonylureas; OR 3.03, 95% CI 0.69–13.25 for biguanides).

c The following drugs were included: citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.

d In the evaluation of the individual drugs, the OR was significantly elevated for clozapine (OR 1.98, 95% CI 1.45–2.70) and for olanzapine (OR 1.46, 95% CI 1.06–2.00), but not for risperidone (OR 0.99, 95% CI 0.59–1.65).

e The following drugs were included: amineptine, amitriptyline, domipramine, desipramine, dibenzepine, dosulepine, doxepine, imipramine, lofepramine, maprotiline, nortriptyline, opipramole, protriptyline, venlafaxine.

f In the evaluation of the individual drugs, the OR was significantly elevated for olanzapine (OR 2.79, 95% CI 2.06–3.79) and for risperidone (OR 2.38, 95% CI 1.47–3.85), but not for clozapine (OR 1.15, 95% CI 0.83–1.61).

g In the evaluation of the individual drugs, the OR was significantly elevated for olanzapine (OR 3.65, 95% CI 1.79–7.44), but not for clozapine (OR 1.39, 95% CI 0.51–3.77) or risperidone (OR 1.38, 95% CI 0.34–5.66).

h In the evaluation of the individual drugs, the OR was significantly elevated for olanzapine (OR 2.39, 95% CI 1.34–4.29), but not for clozapine (OR 0.98, 95% CI 0.56–1.72) or risperidone (OR 1.67, 95% CI 0.68–4.11).

i The following drug groups were included: phenothiazines, butyrophenones, thioxanthenes, and diphenylbutylpiperidines.

NSRI = non-selective reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors.

tipsychotics is due to their effect on weight only. The average increase in weight associated with 10 weeks of treatment was 2.58kg for chlorpromazine, 1.08kg for haloperidol, 2.10kg for risperidone, 4.15kg for olanzapine and 4.45kg for clozapine in a meta-analysis.^[32] These findings might support a relation between the average increase in weight and the risk of glucose intolerance. In a recent study,^[29] however, even non-obese patients treated with clozapine and olanzapine exhibited abnormal glucose balance with decreased insulin sensitivity index. The de-

crease in weight seen more commonly among reports of glucose intolerance compared with other adverse reactions was considered to be secondary to the diabetic condition.

The prescribed doses in the cases of glucose intolerance did not differ significantly from those in all other adverse reactions. Furthermore, there was no overrepresentation among the cases of glucose intolerance of concomitant treatment with drugs known to inhibit the metabolism of clozapine and olanzapine via CYP1A2 or of risperidone via CYP2D6. These data may support the notion

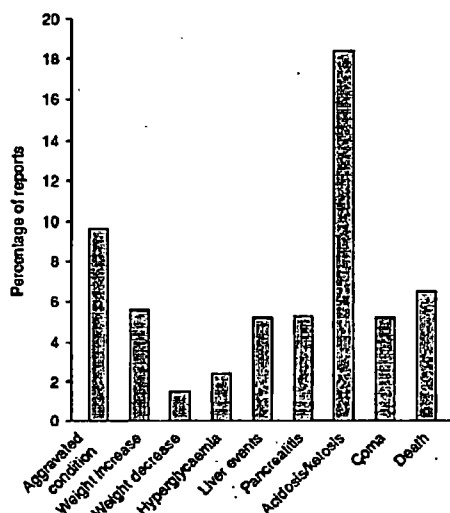


Fig. 4. Selected adverse reaction diagnoses in cases of glucose intolerance ($n = 868$). The aggravated condition includes the diagnoses diabetes mellitus aggravated and condition aggravated. Hyperlipidaemia includes the diagnoses hypercholesterolaemia and hypertriglyceridaemia. Liver events include the diagnoses increased liver enzymes or other liver parameters, abnormal liver function, fatty liver, and hepatomegaly. Pancreatitis includes the diagnoses increased serum amylase, lipase and pancreatitis.

that the dose is not an important risk factor for glucose intolerance. On the other hand, we compared with the doses used when all other adverse drug reactions, which mostly are dose-dependent, occurred. Therefore, it remains an open question whether the dose is a risk factor for glucose intolerance or not.

In most cases, where information regarding the treatment duration was available, glucose intolerance occurred within the first year of treatment. However, it should be taken into account that in the majority of the reports, the treatment duration was unknown. Therefore, the generalisability of the result is uncertain. Moreover, any association between a drug and an adverse drug reaction is more obvious, and thus more likely to be reported shortly

after institution of treatment. Indeed, in a 5-year follow up study of patients treated with clozapine, patients continued to be diagnosed with diabetes mellitus throughout the study period.^[20]

An underlying diabetic condition as reflected by concomitant use of insulin or oral antidiabetic agents was the strongest risk factor identified in the study. As expected, concomitant use of insulin or oral antidiabetic agents was found to associate significantly with aggravation of pre-existing diabetic disorder. Also, concomitant treatment with valproic acid, selective serotonin reuptake inhibitors or buspirone was found to be a significant risk factor for glucose intolerance. Interestingly, valproic acid is known to induce a metabolic syndrome with centripetal obesity, hyperinsulinaemia, lipid abnormalities and polycystic ovaries in women with epilepsy.^[33]

The identification of selective serotonin reuptake inhibitors as significant risk factors for glucose intolerance with clozapine, olanzapine and risperidone was unexpected, since these drugs have been associated with a risk of hypoglycaemia in patients with diabetes.^[34] However, one case report has been published, where paroxetine was associated with hyperglycaemia in a patient with no previous history of diabetes.^[35] Studies in mice have shown inconsistent findings.^[36,37] In one study,^[36] fluoxetine and sertraline induced hypoglycaemia, but in another study,^[37] fluoxetine and fluvoxamine induced hyperglycaemia. The discrepancy may at least in part be explained by differences in the experimental conditions, such as the timing of the blood sampling, as the hyperglycaemic effect was of short duration. The insulin levels were unchanged during hyperglycaemia, indicating suppression of insulin release. Patients who experience insulin resistance during treatment with, for example clozapine or olanzapine, may experience a decompensation with overt diabetes if the insulin secretion is inhibited. The findings in our study therefore support previous findings suggesting a relative inhibition of the insulin release by serotonin reuptake inhibitors.

Some further data exist to support an increased risk of glucose intolerance from concomitant treat-

ment with buspirone as found in the present study. In a published case report of severe hyperglycaemia with clozapine,^[38] the event occurred soon after buspirone was added to the treatment. Buspirone is a serotonin 5-HT_{1A} receptor agonist. In a study in rats,^[39] treatment with buspirone was associated with increased glucose levels with no change in the insulin secretion. A more selective 5-HT_{1A} receptor agonist 8-hydroxy-2(di-n-propylamino) tetralin (8-OH-DPAT), was associated with both increased glucose levels and decreased insulin secretion. The effects were abolished in the presence of a 5-HT_{1A} receptor antagonist, (-)-pindolol. Experimental data, therefore, indicate that buspirone may have similar effects on the glucose metabolism as the serotonin reuptake inhibitors.

In conclusion, we found that clozapine, olanzapine and risperidone were associated with glucose intolerance. We identified the following risk factors for glucose intolerance: an underlying diabetic condition, an increase in weight, male gender, and concomitant use of valproic acid, selective serotonin reuptake inhibitors, or buspirone. We suggest that patients treated with clozapine, olanzapine or risperidone should undergo regular monitoring of weight and blood glucose and plasma lipid levels, particularly in the presence of additional risk factors for diabetes mellitus. Although it cannot be excluded that the association seen in this study may be due to the underlying condition treated rather than the drugs themselves, more frequent monitoring of blood glucose should be considered if valproic acid, a selective serotonin reuptake inhibitor or buspirone is instituted in a patient already taking clozapine, olanzapine or risperidone.

Acknowledgements

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The authors are indebted to the national centres mentioned in this study, who contributed data. The opinions and conclusions, however, are not necessarily those of the various centres nor of the WHO.

References

1. Waddington JL, O'Callaghan E. What makes an antipsychotic agent 'atypical'? conserving the definition. *CNS Drugs* 1997; 7: 341-6
2. Stanniland C, Taylor D. Tolerability of atypical antipsychotics. *Drug Saf* 2000; 22 (3): 195-214
3. Popli AP, Konicki PE, Jurjus GI, et al. Clozapine and associated diabetes mellitus. *J Clin Psychiatry* 1997; 58: 108-11
4. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. *Biol Psychiatry* 1998; 44: 778-83
5. Hägg S, Joelsson L, Mjörndal T, et al. Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. *J Clin Psychiatry* 1998; 59: 294-9
6. Melkersson KI, Hulting A-L, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. *J Clin Psychiatry* 1999; 60: 783-91
7. Goldstein LE, Sporn J, Brown S, et al. New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. *Psychosomatics* 1999; 40: 438-43
8. Bettinger TL, Mendelson SC, Dorson FG, et al. Olanzapine-induced glucose dysregulation. *Ann Pharmacother* 2000; 34: 865-7
9. Amesson GA. Phenothiazine derivatives and glucose metabolism. *J Neuropsychiat* 1964; 5: 181-98
10. Thomard-Neumann E. Phenothiazines and diabetes in hospitalised women. *Am J Psychiatry* 1968; 124: 978-82
11. Proakis AG, Mennear JH, Miya TS, et al. Phenothiazines-induced hyperglycemia: relation to CNS and adrenal effects. *Proc Soc Exp Biol Med* 1971; 137: 1385-8
12. Schwarz L, Munoz R. Blood sugar levels in patients treated with chlorpromazine. *Am J Psychiatry* 1968; 125: 253-5
13. Ward JL. Glucose tolerance in schizophrenia. *Orthomol Psychiatry* 1972; 44: 137-40
14. Dykes JB. Diabetes in schizophrenia and diabetes in non-psychotic medical patients. *Dis Nerv Syst* 1969; 30: 341-4
15. McKee HA, D'Arcy PF, Wilson P. Diabetes and schizophrenia: a preliminary study. *J Clin Hosp Pharm* 1986; 11: 297-9
16. Brambilla F, Guastalla A, Guerrini A, et al. Glucose-insulin metabolism in chronic schizophrenia. *Dis Nerv Syst* 1976; 37: 98-103
17. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. *Compr Psychiatry* 1996; 37: 68-73
18. Stanton JM. Weight gain associated with neuroleptic medication: a review. *Schizophr Bull* 1995; 21: 463-72
19. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. *J Clin Psychiatry* 1999; 60: 358-63
20. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *Am J Psychiatry* 2000; 157: 975-81
21. Ghaeli P, Dufresne RL. Serum triglyceride levels in patients treated with clozapine. *Am J Health Syst Pharm* 1996; 33: 2079-81
22. Spivak B, Lamschein C, Talmon Y, et al. The impact of clozapine treatment on serum lipids in chronic schizophrenic patients. *Clin Neuropharmacol* 1999; 22: 98-101
23. Gaulin BD, Markowitz JS, Caley CF, et al. Clozapine-associated elevation in serum triglycerides. *Am J Psychiatry* 1999; 156: 1270-2

24. Brönnel T, Blum WF, Ziegler A, et al. Serum leptin levels increase rapidly after initiation of clozapine therapy. *Mol Psychiatry* 1998; 3: 76-80
25. Kraus T, Haack M, Schuld A, et al. Body weight and leptin plasma levels during treatment with antipsychotic drugs. *Am J Psychiatry* 1999; 156: 312-4
26. Melamed Y, Mazeh D, Elizur A. Risperidone treatment for a patient suffering from schizophrenia and IDDM [letter]. *Can J Psychiatry* 1998; 43: 956
27. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol* 1998; 54: 315-21
28. Orre R, Lansner A, Bate A, et al. Bayesian neural networks with confidence estimations applied to data mining. *Comput Stat Data Anal* 2000; 34: 473-93
29. Henderson DC. Atypical antipsychotic-induced diabetes mellitus: how strong is the evidence? *CNS Drugs* 2002; 16: 77-89
30. Edwards IR, Wiholm B-E, Martinez C. Concepts in risk-benefit assessment. *Drug Saf* 1996; 15: 1-7
31. Mir S, Taylor D. Atypical antipsychotics and hyperglycemia. *Int Clin Psychopharmacol* 2001; 16: 63-73
32. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; 156: 1686-96
33. Isojärvi JT, Rättyä J, Myllylä VV, et al. Valproate, lamotrigine, and insulin-mediated risks in women with epilepsy. *Ann Neurol* 1998; 43: 446-51
34. Goodnick PJ, Henry JH, Buki VM. Treatment of depression in diabetes mellitus. *J Clin Psychiatry* 1995; 56: 128-36
35. Petty KJ. Hyperglycemia associated with paroxetine [letter]. *Ann Intern Med* 1996; 125: 782
36. Erenmemisoglu A, Ozdogan UK, Saraymen R, et al. Effect of some antidepressants on glycaemia and insulin levels of normoglycaemic and alloxan-induced hyperglycemic mice. *J Pharm Pharmacol* 1999; 51: 741-3
37. Yamada J, Sugimoto Y, Inoue K. Selective serotonin reuptake inhibitors fluoxetine and fluvoxamine induce hyperglycemia by different mechanisms. *Eur J Pharmacol* 1999; 382: 211-5
38. Good MI. Lethal interaction of clozapine and buspirone? *Am J Psychiatry* 1997; 154: 1472-3
39. Uvnäs-Moberg K, Ahlenius S, Alster P, et al. Effects of selective serotonin and dopamine agonists on plasma levels of glucose, insulin and glucagon in the rat. *Neuroendocrinology* 1996; 63: 269-74

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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.

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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

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D3097.2

24 SEP 2003

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
Office of Drug Evaluation I.
U.S. Food and Drug Administration
Attn: Document Control Room
1451 Rockville Pike
Rockville, MD 20857

Re: NDA 20-272
RISPERDAL® (risperidone) Tablets
Cross-reference NDAs 20-588, 21-444
Response to Request for Label Revision

Dear Dr. Katz,

Please refer to your letter of September 16, 2003 with a request for a change in RISPERDAL labeling to include a Warning for "Hyperglycemia and Diabetes Mellitus".

Unfortunately, prior to receipt of your letter, we did not have the opportunity to provide you the new data we have been gathering on this subject since agreement with you on diabetes-related labeling in your letter of November 19, 2002, nor did we have an opportunity to review the data on which your request was based.

The proposed class labeling is not consistent with our interpretation of the data regarding RISPERDAL. We would like the opportunity to share our data and interpretations to ensure accurate labeling. We would appreciate your review of the summary contained in this letter, and would like to request a teleconference with you on Friday, September 26, 2003. The objective of the teleconference will be to reach consensus that updated data on RISPERDAL should be reviewed before a final decision is reached on the appropriate labeling for RISPERDAL.

The proposed class Warning titled "Hyperglycemia and Diabetes" refers to both hyperglycemia/diabetes and to more serious and life-threatening adverse events (diabetic ketoacidosis, hyperosmolar coma, and death). Two key points make the proposed class warning not applicable to RISPERDAL.

- 1) A substantial body of epidemiologic evidence argues against an association between RISPERDAL and a risk of diabetes that is greater than can be attributed to conventional antipsychotics, or even in some studies to untreated patients. Additionally, there is little evidence that serious and life-threatening events (diabetic ketoacidosis, hyperosmolar coma, and death) occur with a greater

incidence among patients treated with RISPERDAL than in a comparable background population. These data suggest that it may not be appropriate to group RISPERDAL with other atypical antipsychotics (e.g., olanzapine, clozapine) for which such risks have been consistently documented.

- 2) There are clinically significant differences in diabetes risk among the atypical antipsychotics. RISPERDAL is associated with a lower epidemiologic risk than some other atypical antipsychotics. This difference among drugs is further supported by evidence from mechanistic studies, and argues against grouping all atypical antipsychotic agents.

In support of these points, we would like to discuss the following evidence with the Division:

- Epidemiology studies - including new data from our studies, and an overview of all 8 published studies on this topic,
- Mechanistic studies - including new data concerning glucoregulatory physiology and differential mechanism of action, and
- Clinical studies - including our risperidone clinical trials database, which includes over 12,000 RISPERDAL-treated patients, an increase of approximately 50% since submission of clinical data on August 10, 2000 in response to FDA's request for information on the effect of risperidone on glucose metabolism.

Epidemiology.

Epidemiologic Evidence Regarding Serious and Life-threatening Events;

In a recent Medicaid claims database analysis of >100,000 persons, olanzapine was associated with a 60% increased risk (OR=1.6) of diabetic ketoacidosis (DKA) as compared to risperidone. The study found duration of exposure was correlated with difference in risk (higher risk of DKA with increasing duration of exposure to olanzapine compared to risperidone). Further, in 38,552 patients exposed to risperidone or olanzapine for at least 180 days, olanzapine demonstrated a 250% increased risk (OR=3.5) of DKA as compared to risperidone¹.

An analysis of MedWatch data through first quarter 2002 utilizing an empirical Bayesian geometric mean (ratio of the observed count to the expected count for a given drug event combination) examined the relationship of six antipsychotics (risperidone, olanzapine, quetiapine, clozapine, ziprasidone, haloperidol) to specific diabetes-related MedDRA terms. Very little data were available for quetiapine and ziprasidone due to the significantly lower usage of these drugs during this time period. Of the remaining four agents, when examining 'diabetes mellitus, insulin dependent' or 'diabetes mellitus, non-insulin dependent' as terms, the largest effect was seen with clozapine, second largest with olanzapine and the least with risperidone. When examining 'diabetic ketoacidosis' as a term, the largest effect was again seen with olanzapine, second largest with clozapine and the least effect with risperidone. In both of these comparisons, risperidone did not score worse than haloperidol. (Lincoln Technologies, Inc., Wellesley Hills, MA,

Epidemiology Summary

We are aware of 19 different epidemiological studies in the public domain evaluating the association between antipsychotics and development of diabetes. Of these studies, 8 have been published in peer-reviewed journals (all 8 are reviewed in Table 1).

The weight of evidence from the available epidemiology research suggests that RISPERDAL is not associated with increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. This evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other atypical antipsychotics (e.g., olanzapine, clozapine).

Studies of Glucoregulatory Physiology / Mechanism of Action

Evidence from controlled studies specifically aimed at evaluation of glucose metabolism suggests some atypical antipsychotics (e.g., olanzapine, clozapine) have significantly more risk in impairing glucose regulation than risperidone. A modified oral glucose tolerance test (OGTT) performed in a cross-sectional sample of 48 schizophrenic patients demonstrated greater risk of significant glucose elevations in olanzapine- and clozapine-treated patients than in risperidone-treated patients.¹⁰ Three 'clamp' studies (hyperglycemic and hyperinsulinemic clamps in humans and a comprehensive metabolic study in an animal model) have also been conducted. These studies are summarized below:

- a. Two clamp studies in healthy volunteers treated with olanzapine, risperidone or placebo were not highly informative; each study measured either insulin secretion or insulin sensitivity, but not both.^{11,12} Both glucose and insulin exert similar actions to increase glucose uptake into tissues (e.g., muscle and fat) and to suppress glucose production by liver. It is therefore necessary to measure both insulin secretion and insulin sensitivity in the same subject in order to properly assess potential drug effects.
- b. A dog model was intensively studied by Ader et al., including both a euglycemic clamp to assess insulin sensitivity and a full stepwise hyperglycemic clamp for insulin secretion.¹³ Adiposity was assessed by MRI. Olanzapine was found to cause significant increases in adiposity, hepatic insulin resistance, and beta-cell dysfunction (a potential mechanism for drug-induced DKA)¹⁴. Risperidone-treated dogs were comparable to placebo in all these parameters. This study elucidates at least one plausible mechanism for olanzapine-induced glucose metabolism dysregulation which is not shared by risperidone.

The weight of evidence from the available physiological data supports differences in the risk of glucose dysregulation among atypical antipsychotics, particularly between risperidone, a benzisoxazole, and the chemically distinct dibenzodiazepines (e.g., olanzapine, clozapine). There is little evidence to support a common glucoregulatory effect among these structurally diverse chemical classes.

RISPERDAL Clinical Trials

Completed clinical trials of RISPERDAL through December 1, 2002 were examined for incidence of glucose related adverse events and random glucose levels when available (see Table 2).

Data from clinical trials indicate that the risk for glucose related adverse events with RISPERDAL is comparable to placebo or the conventional antipsychotic haloperidol.

Weight of Evidence

In view of the data summarized above, the proposed class labeling concerning hyperglycemia and diabetes does not accurately reflect the current evidence related to RISPERDAL. There is limited evidence for increased risk associated with RISPERDAL compared to conventional antipsychotics or untreated patients, and there is a particular lack of evidence suggesting an increased risk of serious and life-threatening events, such as diabetic ketoacidosis. Furthermore, a substantial body of epidemiologic evidence supports a differential effect among atypical antipsychotics. Data concerning physiologic mechanisms of action also suggest that risk for both diabetes and ketoacidosis is not a class effect.

We request that other submissions concerning RISPERDAL be concluded without being linked to the review that is needed to address the proposed diabetes class warning.

I will contact Mr. Steve Hardeman to confirm an appropriate time to contact you on September 26, 2003, or as soon thereafter as possible.

Thank you for your review of this brief summary. If you have any questions, please contact me at 609-730-3486.

Sincerely yours,



Edward G. Brann
Director, Regulatory Affairs

Cc: S. Hardeman

Table 1. All Published Epidemiological Studies of Antipsychotics and Diabetes

Reference	Conclusions	Primary Results	Risk* (95%CI)	Population
American Journal of Psychiatry – April 2002, Sernyak et al. ²	"... the prevalence of diabetes was significantly increased for patients who received clozapine, olanzapine, and quetiapine, but not risperidone."	RIS = CONV OLZ > CONV QUE > CONV CLZ > CONV	1.1 (0.98-1.1) 1.1 (1.04-1.2)* 1.3 (1.1-1.6)* 1.3 (1.1-1.5)*	38,632 schizophrenia patients from the VA (1999)
British Medical Journal – August 2002, Koro et al. ³	"The risk [for diabetes] was significantly increased with the newer antipsychotic olanzapine but not with the other newer antipsychotic, risperidone."	RIS = Untreated OLZ > Untreated RIS = CONV OLZ > CONV	2.2 (0.9-5.2) 5.8 (2.0-16.7)* 1.6 (0.7-3.8) 4.2 (1.5-12.2)*	19,637 schizophrenia patients from the U.K. GPRD (1987-2000)
The Journal of Clinical Psychiatry – October 2002, Gianfrancesco et al. ⁴	"In contrast to these agents [olanzapine and clozapine], risperidone was not associated with an increased risk of type 2 diabetes."	RIS = Untreated OLZ > Untreated CLZ > Untreated OLZ > RIS CONV = RIS	0.9 (0.4-2.1) 3.1 (1.6-5.9)* 7.4 (1.6-34.8)* 3.5* 2.4	7,395 psychosis patients from 2 insurance claims databases (1/1996-12/1997)
The Journal of Clinical Psychiatry – December 2002, Caro et al. ⁵	"Compared with risperidone, olanzapine was associated with an increased risk of developing diabetes."	OLZ > RIS	1.2 (1.00-1.4)*	33,946 patients from a Quebec health claims database (1/1997-12/1999)
Journal of Clinical Epidemiology – 2003, Buse et al. ⁶	"An increased risk of developing diabetes compared with the AdvancePCS general patient population was observed during treatment with conventional or atypical antipsychotics."	RIS > Untreated OLZ > Untreated QUE > Untreated CLZ > Untreated RIS > HAL OLZ = HAL QUE < HAL CLZ = HAL	3.4 (3.1-3.8)* 3.0 (2.6-3.5)* 1.7 (1.2-2.4)* 3.3 (1.4-8.0)* 1.2 (1.01-1.5)* 1.1 (0.9-1.4) 0.7 (0.5-0.97)* 1.3 (0.6-2.9)	58,751 patients from the Advance PCS prescription claims database (12/1998-2/2000)
Clinical Therapeutics – April 2003, Gianfrancesco et al. ⁷	"In contrast to olanzapine, ..., risperidone... was not associated with an increased risk for development of type 2 diabetes..."	RIS = Untreated OLZ > Untreated OLZ > RIS CONV = RIS	1.0 (0.4-3.0) 4.3 (2.1-8.8)* 4.2* 1.9	5,236 patients with mood disorders from 2 insurance claims databases (1/1996-12/1997)
Journal of Clinical Psychopharm. – August 2003, Gianfrancesco et al. ⁸	"...quetiapine and risperidone patients had estimated odds of ... diabetes that were lower than those of patients untreated with antipsychotics (not statistically significant) ...olanzapine had odds that were significantly greater than those of patients untreated..."	RIS = Untreated OLZ > Untreated QUE = Untreated CONV = Untreated	0.7 (0.3-1.4) 1.4 (1.0-2.0)* 1.0 (0.4-2.3) 1.0 (0.7-1.6)	16,878 patients with psychosis from 2 insurance claims databases (4/1997-10/2000)
Pharmacother – August 2003, Fuller et al. ⁹	"Olanzapine was associated with a ... increased risk of development of diabetes compared with risperidone in a VA population..."	OLZ > RIS FLU = RIS HAL = RIS	1.4 (1.1-1.8)* 1.1 (0.7-1.8) 0.9 (0.7-1.2)	5,837 patients from a Veterans Affairs (VA) database (1/1997-12/2000)

* Comparative risk was evaluated utilizing odds ratio, relative risk and hazard ratio assessments in different studies.

* Indicates results are statistically significant (p<0.05). Legend: RIS = risperidone, OLZ = olanzapine, QUE = quetiapine, CLZ = clozapine, HAL = haloperidol, FLU = fluphenazine, CONV = conventional antipsychotics

Table 2. Glucose Related Adverse Events and Random Glucose Levels

	Placebo	Risperidone	Haloperidol	Olanzapine	Other Neuroleptics
Any Glucose Related Adverse Events^a					
	N=1439	N=7326	N=712	N=536	N=293
Short-Term Trials ^b	12 (0.83%)	55 (0.75%)	2 (0.28%)	5 (0.93%)	1 (0.34%)
	—	N=4741	N=579	—	N=234
Long-Term Trials ^c	—	46 (0.97%)	9 (1.55%)	—	0
Elevated Glucose Levels (Short term)					
	N=803	N=3042	—	—	N=606
Suggestive of 'diabetes' ^d	9 (1.12%)	26 (0.85%)	—	—	4 (0.66%)
Suggestive of 'impaired glucose tolerance' ^e	68 (8.47%)	174 (5.72%)	—	—	25 (4.13%)

a = List of glucose-related adverse events: 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, hyperglycemia, hypoglycemia, hypoglycemic reaction, ketoacidosis, and ketonuria

b = short-term trials – duration <3 months

c = long-term trials – duration up to 2 years

d = random glucose levels of ≥ 11.1 mmol/L

e = random glucose levels of ≥ 7.8 and < 11.1 mmol/L

References:

1. Ramaswamy K, Nasrallah, H, and Kozma C. The relationship between duration of exposure and development of DKA in patients in treated with risperidone or olanzapine. [Poster] 42nd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 2003
2. Sernyak M, Leslie D, Alarcon R et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry* 2002;159:561-566
3. Koro C, Fedder D, L'Italien G et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 2002;325:243-248.
4. Gianfrancesco F, Grogg A, Mahmoud R et al. Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan database. *J Clin Psychiatry* 2002;63:920-930
5. Caro J, Ward A, Levinton C et al. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry* 2002;63:1135-1139
6. Buse J, Cavazonni P, Hornbuckle K et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiology* 2003;56:164-170
7. Gianfrancesco F, Grogg A, Mahmoud R et al. Differential effects of antipsychotic agents on the risk of development of type 2 diabetes mellitus in patients with mood disorders. *Clin Therapeutics* 2003;25(4):1150-1171
8. Gianfrancesco F, White R, Wang R et al. Antipsychotic-induced type 2 diabetes: evidence from a large health plan database. *J Clin Psychopharmacol* 2003;23(4):328-335
9. Fuller M, Shermock M, Secic M et al. Comparative study of the development of diabetes mellitus in patients taking risperidone and olanzapine. *Pharmacotherapy* 2003;23(8):1037-1043
10. Newcomer, J et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry*. 2002 (Apr.); 59 (4): 337-45.
11. Sowell, M. et al. Hyperglycemic clamp assessment of insulin secretory responses in normal subjects treated with olanzapine, risperidone and placebo. *J Clin Endo and Met.* 2002; 87 (6); 2918-2923.
12. Beasley, C. et al. Prospective evaluation of insulin sensitivity by the hyperinsulinemic, euglycemic clamp in healthy volunteers treated with olanzapine, risperidone or placebo. Poster presented at the 41st American College of Neuropsychopharmacology annual meeting, December 8-12, 2002; San Juan, Puerto Rico.
13. Ader, M. et. al. Differential metabolic effects between atypical anti-psychotics in normal dogs, Poster presented at American Diabetic Association annual meeting, June 13-17, 2003; New Orleans.
14. Ader, M. et al. Marked increase in adiposity during olanzapine vs risperidone treatment: results of a placebo-controlled study in normal dogs. Poster presented at ECNP annual meeting, September 20-24, 2003; Prague, Czech Republic.

Proposed J&J Participants

Primary Participants

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Garry Neil, MD

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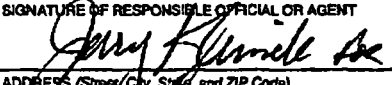
Scott Reines, MD, PhD

Sr. Vice President Drug Development

**Sr. Vice President Drug Development, CNS
Therapeutic Area**

**Vice President Drug Development, Pain and
Pediatric Therapeutic Area**

This application contains the following items: (Check all that apply)		
☐	1. Index	
☐	2. Labeling (check one)	☐ Draft Labeling ☐ Final Printed Labeling
☐	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)	
☐	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))	
☐	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)(v)(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 report 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 (i)(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 314.50 (j)(3))	
☐	18. User Fee Cover Sheet (Form FDA 3397)	
☐	19. Financial Information (21 CFR Part 54)	
☒	20. OTHER (Specify) Request for teleconference	

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 Parts 210, 211 or applicable regulations, Parts 606, and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR Parts 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 Part 202. 5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 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	TYPED NAME AND TITLE	DATE:
	Edward G. Brann Director, Regulatory Affairs	24 SEP 2003
ADDRESS (Street, City, State, and ZIP Code)		Telephone Number
1115 Trenton-Harbourton Road Titusville, New Jersey 08560-0200		(609)-730-3486
Public reporting burden for this collection of information is estimated to average 24 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: Department of Health and Human Services Food and Drug Administration CDER, HFD-99 1401 Rockville Pike Rockville, MD 20852-1448 Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852 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.		



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857NDA 20-272
NDA 20-588
NDA 21-444Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Claude McGowan, Ph.D.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Dr. McGowan:

Please refer to your new drug application (NDA) for Risperdal (risperidone) Tablets and Oral Solution and Risperdal MTAB (risperidone) Orally Disintegrating Tablets.

After reviewing the available data pertaining to the use of atypical antipsychotic medications and diabetes mellitus adverse events, we have concluded that the product labeling for all atypical antipsychotics should be updated to include information about these events.

While we acknowledge that the relationship between atypical antipsychotic use and diabetes mellitus adverse events has not been completely described, we believe the safe use of Risperdal can be enhanced by informing prescribers and patients about these events. Increased attention to the signs and symptoms of diabetes mellitus may lead to earlier detection and appropriate treatment, and thus reduce the risk for the most serious outcomes.

We request that the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of the drug:

WARNINGS**Hyperglycemia and Diabetes Mellitus**

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including Risperdal. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics studied. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. The available data are insufficient to provide reliable estimates of differences in hyperglycemia-related adverse event risk among the marketed atypical antipsychotics.

JJRP 00560077

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D3175.1

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at baseline and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Although we believe that the labeling changes accurately reflect the currently available information about antipsychotic use and diabetes mellitus, we acknowledge that additional labeling changes may be required as new information becomes available. Areas that require additional research include, but are not limited to, identification of subpopulations at greatest risk for diabetes mellitus adverse events, exploration of the relative risk for diabetes mellitus adverse events among the different antipsychotics, and evaluation of potential mechanisms of action.

Please submit twenty copies of final printed labeling, ten of which are individually mounted on heavyweight paper or similar material, exactly as specified above as a "Supplement - Changes Being Effectuated." Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

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

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz

9/11/03 03:14:51 PM

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D3175.3

Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

1125 Trenton-Harbourton Road
P.O. Box 200, Titusville, NJ 08560

26 NOV 2003

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
Office of Drug Evaluation I
U.S. Food and Drug Administration
Attn: Document Control Room
1451 Rockville Pike
Rockville, MD 20857

Re: NDA 20-272/S-035
RISPERDAL® (risperidone) Tablets
Cross-reference NDAs 20-588, 21-444, 21-346
Response to Approval Letter

Dear Dr. Katz,

Please refer to your letter of November 21, 2003 which approved our "Changes Being Effected" supplemental new drug application (S-035) submitted November 6, 2003 to incorporate the hyperglycemia text from the RISPERDAL CONSTA labeling (NDA 21-346) into the oral RISPERDAL labeling under WARNINGS. Your letter requested that we issue a "Dear Healthcare Professional" letter to communicate that new information.

We recognize and agree with your desire to communicate this safety information to physicians. Therefore, Janssen has already voluntarily mailed a medical communication concerning the new "Hyperglycemia and Diabetes Mellitus" labeling to more than 600,000 physicians and healthcare providers. Enclosed please find a copy of the letter. In addition, through their sales representatives, Janssen has individually informed over 70,000 physicians of this label change for RISPERDAL. A complete copy of the package insert, including the new Warning, was provided as part of both communications to physicians. The letter has also been posted on Janssen's website.

Feedback from physicians during this communication process is that the medical community already knows of the reports of hyperglycemia and diabetes with the atypical antipsychotics. Substantial press coverage of the issue has occurred in major media. We are also aware of efforts by Eli Lilly & Co. to communicate this new safety information concerning the atypical antipsychotic class of drugs to physicians.

We request that you review the proactive efforts already undertaken by Janssen to inform and educate the medical community, consider the overall level of information already provided to the public and physicians concerning the issue, and concur that no additional communication on this topic is necessary.

If you have any questions, please contact me at 609-730-2712.

Sincerely yours,


Susan Merchant
Manager, Regulatory Affairs

Enclosure: Janssen Medical Communication, Nov. 2003

JANSSEN



PHARMACEUTICA INC.

P.O. BOX 6387
HILLSBOROUGH, NJ 09044

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D-3179.3

R. 7068

JANSSEN**PHARMACEUTICA INC.**

November 10, 2003

Dear Healthcare Provider,

The Food and Drug Administration (FDA) has requested all manufacturers of atypical antipsychotics to include a warning regarding hyperglycemia and diabetes mellitus in their product labeling. In addition to Janssen, the FDA made this request to the following manufacturers:

AstraZeneca – Seroquel® (quetiapine)
Bristol-Myers Squibb – Abilify™ (aripiprazole)
Eli Lilly and Company – Zyprexa® (olanzapine)
Novartis – Clozaril® (clozapine)
Pfizer – Geodon® (ziprasidone)

In an effort to keep you updated with the most current product information available for the management of your patients, enclosed please find updated prescribing information for RISPERDAL® (risperidone).

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

For additional information about RISPERDAL or any other Janssen product, please call 1-800-JANSSEN (526-7736) from 9AM to 5PM EST, Monday through Friday.

Sincerely,

Ramy Mahmoud, MD
Vice President CNS Medical Affairs
Janssen Pharmaceutica, Inc.

1125 TRENTON-HARBOURTON ROAD
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JJRIS 01263863

D-3179.4

References:

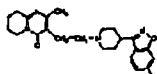
1. Buse JB, Cavazonni P, Hornbuckle K et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiology* 2003;56:164-170.
2. Caro JJ, Ward A, Levinton C and Robinson K. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry* 2002;63:1135-1139.
3. Fuller MA, Shermock KM, Secic M and Grogg AL. Comparative study of the development of diabetes mellitus in patients taking risperidone and olanzapine. *Pharmacotherapy* 2003;23(8):1037-1043.
4. Gianfrancesco F, White R, Wang RH and Nasrallah HA. Antipsychotic-Induced type 2 diabetes: evidence from a large health plan database. *J Clin Psychopharmacol* 2003;23(4):328-335.
5. Gianfrancesco F, Grogg A, Mahmoud R et al. Differential effects of antipsychotic agents on the risk of development of type 2 diabetes mellitus in patients with mood disorders. *Clin Therapeutics* 2003;25(4):1150-1171.
6. Gianfrancesco FD, Grogg AL, Mahmoud RA et al. Differential effects of risperidone, olanzapine, clozapine and conventional antipsychotics on type II diabetes: Findings from a large health plan database. *J Clin Psychiatry* 2002;63:920-930.
7. Koro CE, Fedder DO, L'Italien GJ et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 2002;325:243-245.
8. Sernyak MJ, Leslie DL, Alarcon RD et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry* 2002;159:561-566.

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D-3179.5

RISPERDAL® (risperidone) is a psychotropic drug. The chemical designation is 1-(4-piperidinyl)-4-(4-ethyl-1-piperidinyl)-1,4-dihydro-2-methyl-1H-benzodiazepine-3-one. The molecular weight is 410.49. The structural formula is

agent belonging to the chemical class of benzofuro-1,2-benzoxazol-9-yl-1-phenylhydrazones. Its molecular formula is $C_{21}H_{15}FN_2O$, and



Hepatic Impairment
While the pharmacokinetics of fexofenadine in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of fexofenadine in plasma was increased by about 33% because of the diminished concentration of both albumin and α_1 -acid glycoprotein. **AUSPERRAL[®]** doses should be reduced to patients with liver disease from PRECAUTIONS AND USAGE AND ADMINISTRATION.

Hypertension and Diabetes Mellitus
Hypertension, in some cases extreme and associated with korooidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of

an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polyuria, polydipsia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the atypical drug.

PRECAUTIONS

General

Orthostatic Hypotension
Risperidone may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-escalation period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of Risperidone-treated patients in Phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by titrating the initial dose to 2 mg twice daily (QID) or 1 mg BID in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. Risperidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions that would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of Risperidone and antihypertensive medications.

Sedation

During premarketing testing, sedation occurred in 0.3% (8/2607) of Risperidone-treated patients, two in association with hypotension. Risperidone should be used cautiously in patients with a history of sedation.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Risperidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia

As with other drugs that antagonize dopamine D₂ receptors, risperidone elevates prolactin levels and its elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prolactin of these drugs is contemplated in a patient with previously detected breast cancer. Although discontinuation of these drugs is associated with a decrease in prolactin levels, and improvement has been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tamoxifen in breast; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with Risperidone treatment, especially when associated with direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (Risperidone 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of Risperidone 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since Risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Risperidone therapy does not affect them adversely.

Precautions

Rare cases of oropharyngeal candidiasis have been reported. While the relationship of the events to Risperidone use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce pharyngitis, and it is possible that Risperidone may share this capacity. Severe pharyngitis may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28-year-old female patient receiving Risperidone 16 mg/day. In a large, open premarketing experience (approximately 1300 patients), she experienced jaundice, fever, and leukopenia, but eventually recovered after receiving plasma therapy. The relationship to Risperidone therapy is unknown.

Antiemetic Effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Raye's syndrome, and brain tumor.

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hypothermia and hyperthermia have been reported in association with oral Risperidone use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for Risperidone should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients With Concomitant Illnesses

Clinical experience with Risperidone in patients with certain concomitant systemic illnesses is limited. Caution is advised in using Risperidone in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Risperidone has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product premarketing testing.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²), and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Risperidone.

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance

Since Risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Risperidone therapy does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised not to breast-feed an infant if they are taking Risperidone.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Patients should be advised to avoid alcohol while taking Risperidone.

Phenylalanine

Phenylalanine is a component of aspartame. Each 2 mg Risperidone M-TAB™ Orally Disintegrating Tablet contains 0.58 mg phenylalanine; each 1 mg Risperidone M-TAB™ Orally Disintegrating Tablet contains

0.29 mg phenylalanine; and each 0.5 mg Risperidone M-TAB™ Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of Risperidone and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when Risperidone is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, Risperidone may enhance the hypotensive effects of other therapeutic agents with this potential.

Risperidone may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Carbamazepine and Other Enzyme Inducers

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, nifedipine, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment.

Fluoxetine

Fluoxetine (20 mg QID) has been shown to increase the plasma concentration of risperidone 2.5-3 fold, while the plasma concentration of 9-hydroxyrisperidone was not affected. When concomitant fluoxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperidone. The effects of discontinuation of concomitant fluoxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Lithium

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (p=0.15).

Valproate

Repeated oral doses of risperidone (4 mg QID) did not affect the pre-dose or average plasma concentrations (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (p=0.21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concurrent administration of risperidone.

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (mPM) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made. In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A2, 1A2C, 2C8, 2C9, and 3A4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, Risperidone is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Reproductive Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis or 0.2, 0.76, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m² basis. A non-tumorigenic dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² basis at which these tumors occurred.

Tumor Type	Species	Sex	Multiples of Maximum Human Dose (in mg/m ²)	
			Lowest Effect Level	Highest Effect Level
Pituitary adenomas	mouse	female	0.76 (0.4)	0.2 (0.4)
Endocrine pancreas adenomas	rat	male	1.5 (0.4)	0.4 (0.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (0.4)	none
	rat	female	0.4 (0.4)	none
Mammary gland neoplasms, Total	rat	female	0.8 (0.4)	1.5 (0.4)
	rat	male	1.5 (0.4)	0.4 (0.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis

No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatoma DNA repair assay, in vitro micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility

Risperidone (0.16 to 5 mg/kg) was shown to impair fertility, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.4 to 3 times the maximum recommended human dose (MRHD) on a mg/m² basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were tested. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 3 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the MRHD on a mg/m² basis. Dose-related decreases were also noted in serum testosterone in the same dogs. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C

The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose (MRHD) on a mg/m² basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m² basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m² basis. In three reproductive studies in rats (two Segment II and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-6 mg/kg or 0.4 to 3 times the MRHD on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one Segment II study, there was an increase in stillborn rat pups at doses of 2.5 mg/kg or 1.5 times the MRHD on a mg/m² basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams.

regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior for at least pup body weight gain and survival from Day 1 to 4 of lactation were reduced in pups born to control but nursed by drug-exposed dams. These effects were all noted at the one dose of risperidone tested, i.e., 8 mg/kg or 3 times the MHD on a mg/kg basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of emphysema of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPREDAL® therapy is unknown.

RISPREDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPREDAL® on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPREDAL® did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated With Discontinuation of Treatment

Approximately 9% (34/2507) of RISPREDAL® (risperidone)-treated patients in Phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The most common event (0.5%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPREDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hypotension	0.5%	0%
Somnolence	0.5%	0%
Nausea	0.5%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPREDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPREDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPREDAL®-related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients, but 3.5% in active-control patients in the Phase 2-3 trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials
In two 6 to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPREDAL® groups and at least twice that of placebo were anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia. Adverse events were also observed in one of these two trials (i.e., in the fixed-dose trial comparing RISPREDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events occurred at an incidence of at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbance, reduced salivation, micturition disturbance, diarrhea, weight gain, memory loss, disturbed sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgasmic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPREDAL®-Treated Patients

The table that follows summarizes adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPREDAL®-treated patients treated at doses of 5 to 10 mg/day than among placebo-treated patients in two pooled results of two 6 to 8-week controlled trials. Patients received RISPREDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial or up to a maximum dose of 10 mg/day in the duration study. This table shows the percentage of patients in each dose group (5 to 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Table 1 Incidence of Treatment-Emergent Adverse Events in 6 to 8-Week Controlled Clinical Trials*

Body System/ Preferred Term	RISPREDAL®		
	5 to 10 mg/day (N=224)	16 mg/day (N=77)	Placebo (N=142)
Psychiatric			
Anxiety	20%	25%	19%
Agitation	22%	35%	20%
Depression	12%	20%	9%
Somnolence	3%	8%	7%
Aggressive reaction	1%	3%	1%
Central & peripheral nervous system			
Extrapyramidal symptoms†	17%	24%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal			
Constipation	7%	18%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Salivary increased	2%	0%	1%
Tachycardia	2%	0%	0%
Respiratory system			
Rhinitis	10%	6%	4%
Coughing	3%	3%	1%
Stridor	2%	1%	1%
Pharyngitis	2%	2%	0%
Dyspnea	1%	0%	0%
Body as a whole - general			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Serumoma	1%	0%	0%

Table 1 (continued) Incidence of Treatment-Emergent Adverse Events in 6 to 8-Week Controlled Clinical Trials*

Body System/ Preferred Term	RISPREDAL®		
	5 to 10 mg/day (N=224)	16 mg/day (N=77)	Placebo (N=142)
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-skeletal			
Arthritis	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

* Events reported by at least 1% of patients treated with RISPREDAL® 5 to 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPREDAL® 16 mg/day and placebo are provided as well. Events for which the RISPREDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: Nervousness, injury, and fungal infection.

† Includes tremor, dystonia, hypokinesia, hyperkinesia, hypotonia, hyperkinesia, oculogyric crisis, gait, abnormal gait, involuntary muscle contractions, hypotonia, ataxia, and extrapyramidal symptoms. Although the incidence of extrapyramidal symptoms does not appear to differ for the 10 mg/day group and placebo, the data for individual dose groups in fixed dose trials suggest a dose-response relationship (see DOSE DEPENDENCY OF ADVERSE EVENTS).

Dose Dependency of Adverse Events

Extrapyramidal Symptoms

Data from two fixed-dose trials provided evidence of dose-dependency for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS incidence	7%	12%	18%	18%	21%

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPREDAL® (1, 4, 8, 12, and 16 mg/day) was explored for dose-dependency of adverse events. A Cochran-Mantel-Haenszel test for trend in these data revealed a positive trend ($p < 0.05$) for the following adverse events: drooling, increased duration of sleep, accommodation disturbance, orthostatic dizziness, palpitations, weight gain, muscle dysfunction, ejaculatory dysfunction, orgasmic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

Weight Changes

RISPREDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Changes

The proportions of RISPREDAL® and placebo-treated patients meeting a weight gain criterion of 2.7% of body weight were compared in a pool of 6 to 8-week, placebo-controlled trials, revealing a statistically significant greater incidence of weight gain for RISPREDAL® (18%) compared to placebo (9%).

Laboratory Changes

A between-group comparison for 6 to 8-week placebo-controlled trials revealed no statistically significant RISPREDAL®-placebo differences in the proportions of patients experiencing potentially important changes in routine clinical chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPREDAL®-placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPREDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Changes

Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPREDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term arrhythmia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute).

Other Events Observed During the Premarketing Evaluation of RISPREDAL®

During its premarketing assessment, multiple doses of RISPREDAL® (risperidone) were administered to 2007 patients in Phase 2 and 3 studies. The conditions and duration of exposure to RISPREDAL® varied greatly, and included (in overlapping categories) open-label and double-blind studies, acute and chronic studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or long-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (disorder questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listing that follows.)

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2007 patients exposed to multiple doses of RISPREDAL® who experienced an event of the type cited on at least one occasion while receiving RISPREDAL®. All reported events are included, except those already listed in Table 1. In this table, events for which a drug cause was remote, and those event terms which were so general as to be uninformative, it is important to emphasize that, although the events reported occurred during treatment with RISPREDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in Table 1 are tabulated); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders

Frequent: increased dream activity*, diminished sexual desire*, nervousness, Anxious: impaired concentration, depression, apathy, delirious reaction, euphoria, increased libido, anorexia, Rare: orofacial numbness, delirium, delusional syndrome, yawning.

Central and Peripheral Nervous System Disorders

Frequent: increased sleep duration*. Infrequent: dysarthria, vertigo, stupor, paresthesia, convulsion, Rare: aphasia, cholinergic syndrome, hypoaesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyporeflexia, choreoathetosis.

Gastrointestinal Disorders

Frequent: oropharyngeal reduced sensation*. Infrequent: flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hematemesis, gastritis, Rare: fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, disordered taste, GI hemorrhage, hematemesis.

Body as a Whole-General Disorders

Frequent: fatigue. Infrequent: edema, edema*, malaise, influenza-like symptoms, Rare: pallor, enlarged abdomen, allergic reaction, ascites, serositis, flushing.

Respiratory System Disorders

Infrequent: hyperventilation, bronchospasm, pneumonia, stridor, Rare: asthma, increased sputum, aspiration.

Skin and Appendage Disorders

Frequent: increased pigmentation, photosensitivity. Infrequent: increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. Rare: bullous eruption, skin ulceration, aggravated psoriasis, lichenoid eruptions, urticaria, dermatitis herpetiformis, hyperhidrosis, genital pruritus, urticaria.

Cardiovascular Disorders

Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. Rare: ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders

Infrequent: abnormal accommodation, xerophthalmia. Rare: diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders

Infrequent: hypotension, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. Rare: decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hypophosphatemia, hypomagnesemia, hypocalcemia, hypoglycemia.

Urinary System Disorders

Frequent: polyuria/polydipsia. Infrequent: urinary incontinence, hematuria, dysuria. Rare: urinary retention, cystitis, renal insufficiency.

Musculo-Skeletal System Disorders

Infrequent: myalgia. Rare: arthralgia, synovitis, bursitis, tendinitis, skeletal pain.

Reproductive Disorders, Female

Frequent: menorrhagia, oligomenorrhea, dry vagina. Infrequent: nonpurulent lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders

Infrequent: increased SGOT, increased SGPT. Rare: hepatic failure, cholestatic hepatitis, cholestasis, cholelithiasis, hepatitis, hepatocellular damage.

Pneumal, Bleeding, and Clotting Disorders

Infrequent: epistaxis, purpura. Rare: hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders

Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders

Infrequent: anemia, hypochromic anemia. Rare: normocytic anemia.

Reproductive Disorders, Male

Frequent: erectile dysfunction. Infrequent: ejaculation failure.

White Cell and Resistance Disorders

Rare: leukopenia, lymphadenopathy, neutropenia, Peltz-Huett anomaly.

Endocrine Disorders

Rare: gynecomastia, male breast pain, and/or female hormone disorder.

Special Senses

Rare: bitter taste.

* Incidence based on elicited reports.

Postmarketing Reports

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL[®] therapy, include the following: anaphylactic reaction, angioedema, aphasia, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, hyperglycemia, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, meningitis, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL[®]. A causal relationship with RISPERDAL[®] has not been established. It is important to note that sudden and unexpected death may occur in psychiatric patients whether they remain unmedicated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

RISPERDAL[®] (risperidone) is not a controlled substance.

Physical and Psychological Dependence

RISPERDAL[®] has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL[®] abuse or misuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Postmarketing experience included eight reports of acute RISPERDAL[®] (risperidone) overdose with estimated doses ranging from 20 to 320 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 840 mg, was associated with hypotension, tachycardia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Postmarketing experience includes reports of acute RISPERDAL[®] overdose, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse effects reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL[®] overdose, include female de potentia, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage

In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Consider lavage (or induction, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Because of the rapid distribution of risperidone orally disintegrating tablets, pill fragments may not appear in gastric contents obtained with lavage.

The possibility of arrhythmia, seizure, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in profound hypotension.

There is no specific antidote to RISPERDAL[®]. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose

RISPERDAL[®] (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL[®] was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 8 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended. Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL[®]; however, no clear effect was generally seen in a range of 4 to 8 mg/day. Doses above 8 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Psychotic Use

Safety and effectiveness of RISPERDAL[®] in psychotic patients have not been established.

Dosage to Special Populations

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

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL[®] than normal adults. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk (e.g., those who are elderly or debilitated) should be closely monitored (see PRECAUTIONS). If a once-a-day dosing regimen is to be initiated in a debilitated patient, it is recommended that the patient be started on a twice-a-day regimen for 2-3 days of the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

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

RISPERDAL[®] M-TAB[®] Orally Disintegrating Tablets are supplied in blister packs of 4 tablet units each.

Tablet Accessing

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

Tablet Administration

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

Maintenance Therapy

While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL[®] should remain on it, the effectiveness of RISPERDAL[®] 2 mg/day to 8 mg/day at discharging time was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL[®] was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day, and to a target dose of 4 mg QD on the third day (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL[®], the initial dosing schedule should be followed.

Switching From Other Antipsychotics

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

HOW SUPPLIED

RISPERDAL[®] (risperidone) tablets are imprinted "JANSSEN" and either "Rip" and the strength "0.25", "0.5", or "1" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50.

0.5 mg red-brown tablet bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50.

1 mg white tablet bottles of 60 NDC 50458-303-06, blister pack of 100 NDC 50458-303-01, bottles of 500 NDC 50458-303-50.

2 mg orange tablet bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL[®] (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL[®] (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

RISPERDAL[®] M-TAB[®] (risperidone) Orally Disintegrating Tablets are packed on one side with R03, R1, and R2, respectively, and are packaged in blister packs of 4 (2 X 2) tablets.

0.5 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-305-28, hinge card of 30 tablets NDC 50458-305-30.

1 mg light coral, square, biconvex tablets: 7 blister packages per box, NDC 50458-315-28, hinge card of 30 tablets NDC 50458-315-30.

2 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-325-28, hinge card of 30 tablets NDC 50458-325-30.

3 mg yellow tablet bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

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4 mg green tablet bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

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JANSSEN



PHARMACEUTICA INC.

November 10, 2003

Dear Healthcare Provider,

The Food and Drug Administration (FDA) has requested all manufacturers of atypical antipsychotics to include a warning regarding hyperglycemia and diabetes mellitus in their product labeling. In addition to Janssen, the FDA made this request to the following manufacturers:

AstraZeneca – Seroquel® (quetiapine)
Bristol-Myers Squibb – Abilify™ (aripiprazole)
Eli Lilly and Company – Zyprexa® (olanzapine)
Novartis – Clozaril® (clozapine)
Pfizer – Geodon® (ziprasidone)

In an effort to keep you updated with the most current product information available for the management of your patients, enclosed please find updated prescribing information for RISPERDAL® (risperidone).

Hyperglycemia-related adverse events have infrequently been reported in patients receiving RISPERDAL. Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research¹⁻⁶ suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

For additional information about RISPERDAL or any other Janssen product, please call 1-800-JANSSEN (526-7736) from 9AM to 5PM EST, Monday through Friday.

Sincerely,

Ramy Mahmoud, MD
Vice President CNS Medical Affairs
Janssen Pharmaceutica, Inc.

1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200
(609) 730-2000
US.JANSSEN.COM

JJRI5 00966172

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References:

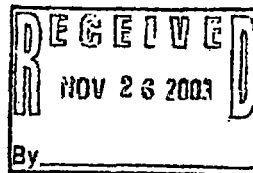
1. Buse JB, Cavazonni P, Hornbuckle K et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiology* 2003;56:164-170.
2. Caro JJ, Ward A, Levinton C and Robinson K. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry* 2002;63:1135-1139.
3. Fuller MA, Shermock KM, Secic M and Grogg AL. Comparative study of the development of diabetes mellitus in patients taking risperidone and olanzapine. *Pharmacotherapy* 2003;23(8):1037-1043.
4. Gianfrancesco F, White R, Wang RH and Nasrallah HA. Antipsychotic-induced type 2 diabetes: evidence from a large health plan database. *J Clin Psychopharmacol* 2003;23(4):328-335.
5. Gianfrancesco F, Grogg A, Mahmoud R et al. Differential effects of antipsychotic agents on the risk of development of type 2 diabetes mellitus in patients with mood disorders. *Clin Therapeutics* 2003;25(4):1150-1171.
6. Gianfrancesco FD, Grogg AL, Mahmoud RA et al. Differential effects of risperidone, olanzapine, clozapine and conventional antipsychotics on type II diabetes: Findings from a large health plan database. *J Clin Psychiatry* 2002;63:920-930.
7. Koro CE, Fedder DO, L'Italien GJ et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 2002;325:243-245.
8. Sernyak MJ, Leslie DL, Alarcon RD et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry* 2002;159:561-566.

11/21



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857NDA 20-272 / SLR-035
NDA 20-588 / SLR-023
NDA 21-444 / SLR-007Janssen Pharmaceutica Products, L.P.
Attention: Susan Merchant
Manager, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-020

Dear Ms. Merchant:

Please refer to your supplemental new drug applications dated November 6, 2003 received November 7, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal (risperidone) Tablets and Oral Solution, and Risperdal M-TAB (risperidone) Orally Disintegrating Tablets.

These "Changes Being Effectuated" supplemental new drug applications incorporate the hyperglycemia text from the Risperdal Consta labeling (NDA 21-346 - approved October 29, 2003) into the Oral Risperdal labeling under WARNINGS. Under DESCRIPTION, hydroxypropyl methylcellulose has been changed to hypromellose.

The changes approved on October 29, 2003, with the deletion of labeling relative to proarrhythmic effects in WARNINGS and PRECAUTIONS; the revision of the ECG Changes subsection under ADVERSE REACTIONS; and the revision of OVERDOSAGE to separate the pre-marketing and post-marketing information and add the terms "extrapyramidal symptoms" and "torsades de pointes" to the post-marketing information have been incorporated into this label.

We have completed our review of these applications and they are approved, effective on the date of this letter, for use as recommended in the submitted labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling (text for the package insert - submitted November 6, 2003).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-272 / SLR-035, NDA 20-588 / SLR-023, and NDA 21-444 / SLR-007." Approval of these submissions by FDA is not required before the labeling is used.

JJRP 00565075

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NDA 20-272 / SLR-035
NDA 20-588 / SLR-023
NDA 21-444 / SLR-007
Page 2

We believe the safe use of the Risperdal drug products can be enhanced by informing prescribers and patients of the addition of "Hyperglycemia and Diabetes Mellitus" labeling information under WARNINGS and request that you issue a letter communicating this important information (i.e., a "Dear Health Care Professional" letter). Please submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

(See appended electronic signature page)

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

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D3180.2

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz
11/21/03 10:17:19 AM

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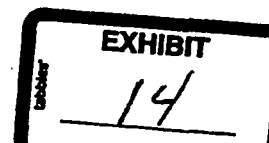
Chapter 4 ADVISORY ACTIONS

This chapter defines and establishes uniform guidance and procedures for Warning Letters and untitled letters.

This chapter includes the following sections:

Section	Topic	Page
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4-1



D4337.1

4-1 WARNING LETTERS

4-1-1 Warning Letter Procedures

When it is consistent with the public protection responsibilities of the Agency and depending on the nature of the violation, it is the Food and Drug Administration's (FDA's) practice to give individuals and firms an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. Warning Letters are issued to achieve voluntary compliance and to establish prior notice. (Prior notice is discussed in Chapter 10.) The use of Warning Letters and the prior notice policy are based on the expectation that most individuals and firms will voluntarily comply with the law.

The Agency position is that Warning Letters are issued only for violations of regulatory significance. Significant violations are those violations that may lead to enforcement action if not promptly and adequately corrected. A Warning Letter is the Agency's principal means of achieving prompt voluntary compliance with the Federal Food, Drug, and Cosmetic Act (the Act).

The Warning Letter was developed to correct violations of the statutes or regulations. Also available to the Agency are enforcement strategies which are based on the particular set of circumstances at hand and may include sequential or concurrent FDA enforcement actions such as recall, seizure, injunction, administrative detention, civil money penalties and/or prosecution to achieve correction. Despite the significance of the violations, there are some circumstances that may preclude the Agency from taking any further enforcement action following the issuance of a Warning Letter. For example, the violation may be serious enough to warrant a Warning Letter and subsequent seizure; however, if the seizable quantity fails to meet the Agency's threshold value for seizures, the Agency may choose not to pursue a seizure. In this instance, the Warning Letter would document prior warning if adequate corrections are not made and enforcement action is warranted at a later time.

Responsible officials in positions of authority in regulated firms have a legal duty to implement whatever measures are necessary to ensure that their products, practices, processes, or other activities comply with the law. Under the law such individuals are presumed to be fully aware of their responsibilities. Consequently, responsible individuals should not assume that they would receive a Warning Letter, or other prior notice, before FDA initiates enforcement action.

FDA is under no legal obligation to warn individuals or firms that they or their products are in violation of the law before taking enforcement action, except in a few specifically defined areas. When acting under the authority of Subchapter C - Electronic Product Radiation Control (formerly the Radiation Control for Health and Safety Act of 1968) of Chapter V of the Act, FDA is required by law to provide a written notification to manufacturers when the Agency discovers products that fail to comply with a performance standard or that contain a radiation safety defect. Because of the legal requirements of Subchapter C, minor variations in the procedures may occur.

A Warning Letter is informal and advisory. It communicates the Agency's position on a matter, but it does not commit FDA to taking enforcement action. For these reasons, FDA does not consider Warning Letters to be final Agency action on which it can be sued.

There are instances when issuing a Warning Letter is not appropriate, and, as previously stated, a Warning Letter is not a prerequisite to taking enforcement action. Examples of situations where the Agency will take enforcement action without necessarily issuing a Warning Letter include:

1. The violation reflects a history of repeated or continual conduct of a similar or substantially similar nature during which time the individual and/or firm has been notified of a similar or substantially similar violation.
2. The violation is intentional or flagrant.
3. The violation presents a reasonable possibility of injury or death.
4. The violations, under Title 18 U.S.C. 1001, are intentional and willful acts that once having occurred cannot be retracted. Also, such a felony violation does not require prior notice. Therefore, Title 18 U.S.C. 1001 violations are not suitable for inclusion in Warning Letters.
5. When adequate notice has been given by other means and the violations have not been corrected, or are continuing. See Chapter 10, Prior Notice, for other methods of establishing prior notice.

In certain situations, the Agency may also take other actions as an alternative to, or concurrently with, the issuance of a Warning Letter. For example:

1. The product violates 402(a)(3) or 402(a)(4); or
2. There is a violation of CGMPs; or
3. The product contains illegal pesticide residues; or
4. The product shows short contents, subpotency, or superpotency.

Additional instructions for Warning Letters in specific product areas are found in compliance program guidance and in compliance policy guides.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

4-1-2 Warning Letters To Government Agencies

Government agencies include federal, state and local agencies. Government establishments should be held to the same standards as nongovernmental establishments. The public health standards are identical, however the method used to ensure compliance with these standards may vary. FDA believes that government establishments will achieve and maintain a higher rate of voluntary compliance with FDA regulations compared with nongovernmental

establishments. Efforts to obtain voluntary compliance should be made and documented before recommending the issuance of a Warning Letter. These efforts may include discussing the violations with the responsible government officials by phone or in a meeting, recommending an untitled letter, or requesting a written corrective action plan and periodic progress reports. The agency's progress should be monitored and a follow-up inspection should be scheduled, within a reasonable time consistent with the noted violations to confirm correction of the violations. Recommend Issuing a Warning Letter if the agency does not provide assurance of corrective action or does not complete corrective actions within agreed timeframes. The appropriate Center should review and concur with the issuance of a Warning Letter. The Warning Letter should be addressed to the headquarters office of the government agency.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

4-1-3 Issuing Warning Letters - Factors To Consider

The Warning Letter is the Agency's principal means of notifying regulated industry of violations and of achieving prompt voluntary correction. Warning Letters can be issued at the discretion of the district director without center concurrence, except in specific program areas that require prior center concurrence. (See Center Concurrence and Letters Issued by Centers.) Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.)

In determining whether to issue a Warning Letter, District Directors should consider whether:

1. Evidence shows that a firm, product, and/or individual is in violation of the law or regulations and that failure to achieve adequate and prompt correction may result in enforcement action.
2. The Agency policy is clear concerning the violation(s) and the violation(s) are determined to be of regulatory significance.
3. There is a reasonable expectation that prompt correction will occur.
4. The nature of and the circumstances surrounding the violation(s) are appropriate to issuance of a Warning Letter.
5. The violations do not fall within the specific program areas requiring Center concurrence.

4-1-4 Center Concurrence And Letters Issued By Centers

Center concurrence is required prior to issuing Warning Letters in the following areas, or Warning Letters are issued directly by the Center.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

A. ALL CENTERS

1. All labeling violations - except where specific guidance has been provided, e.g., Compliance Programs, Compliance Policy Guides, and Drug Health Fraud Bulletins.
2. Computer application and software violations.
3. Bioresearch Monitoring Program violations.
4. Product advertising violations.

Note: Only the Centers issue Warning Letters for violations associated with product advertising, OTC drug monographs, and the Bioresearch Monitoring Program.

B. CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

1. New drug charges - including unapproved changes in processes or formulations and recommendations to withhold approvals of applications or supplements.
2. Adverse drug reaction reporting violations.
3. Novel and unusual tamper-resistant packaging violations.
4. Prescription Drug Marketing Act violations.
5. Investigational drug use violations.
6. CGMP** charges involving active pharmaceutical ingredients and other drug component manufacturing deficiencies.
7. CGMP** charges involving all dosage forms, including medical gases.
8. CGMP** charges involving Team Biologics (Core Team) inspections of facilities for therapeutic biologic products regulated by CDER

** CGMP Warning Letters covered by items 6, 7 and 8 above - Forward copies of the proposed Warning Letter, the FDA 483 supporting the alleged violations identified in the proposed Warning Letter, the EIR (without Exhibits), and any written response by the firm (without

attachments) electronically. Attachments to written responses to the FDA 483 and/or Exhibits should be forwarded electronically upon request of the Center. CDER has established a separate mailbox for electronic submission of Warning Letters from district offices. The address is: CDER Drug WL. Send the information to the attention of the Branch Chief, Case Management and Guidance Branch. For any questions, contact the Branch Chief, Case Management and Guidance Branch, HFD-326, voice 301-827-9022, fax 301-827-8908.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

C. CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (CBER)

1. Donor re-entry violations (e.g., HBsAg, anti-HIV-1).
2. Violations relating to drug or device GMPs.
3. Violative inspections of federal government agencies.
4. Violative inspections of Team Biologics (Core Team) inspection of facilities for biologic products regulated by CBER.
5. Viral marker test run deficiencies.** (See below)
6. Violations in areas where specific guidance has not been provided.** (See below)
7. Human tissue for transplantation - the issuance of a Warning Letter to a firm following the issuance of an Order for Recall, Retention, and Destruction is not usually appropriate since enforcement action will have already been taken. If a District identifies circumstances in which a Warning Letter seems to be appropriate, the recommendation should be submitted to CBER for review.

****Viral marker testing violations:** The Districts no longer need Center concurrence regarding viral marker testing violations. However, Center concurrence is required for Warning Letters based on invalidation of viral marker test run deficiencies since Center guidance on this issue is relatively recent.

****Violations in areas where specific guidance has not been provided:** The Center would not be in a strong position to issue a Warning Letter if there is no policy on an issue, or if the agency's policy is not clear. In these situations, we encourage the District to contact the Division of Case Management in CBER's Office of Compliance and Biologics Quality before recommending a Warning Letter to the Center.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for

submitting such letters to OCC, and include timeframes and routing information.

D. CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH)

1. All 21 U.S.C. 352(j) danger to health violations.
2. Medical device reporting violations which cite failure to report malfunctions as defined in 803.3(n). Center medical and technical expertise is necessary for these evaluations.
3. Restricted device violations.
4. Radiation Control for Health and Safety Act violations - except for sunlamp products and x-ray assemblers.
5. Violation of requirements for post market surveillance studies.
6. Any violation of device tracking regulations other than failure of the firm to implement any form of a tracking system.
7. All suspected violations of the user reporting regulations.
8. Failure to submit a premarket notification (510(k)) or Premarket Approval (PMA) Application.
9. Failure to submit a 510(k) or a PMA supplement for a significant modification(s) and/or the addition of a new intended use(s) to a previously cleared or approved device.
10. All violations arising from pre-approval PMA inspections including supplements to a previously approved PMA application.
11. Mammography Quality Standards Act (MQSA) violations in the following situations, unless superseded by a relevant Compliance Program or other directive:
 - (a) Where numerous Level 2 or 3 inspection findings were observed, but no single noncompliance constitutes a Level 1 or repeat Level 2 inspection finding; or
 - (b) Any situations not specifically identified as a Level 1 noncompliance or repeat Level 2 noncompliance.

Note: For direct reference situations regarding MQSA violations, reference the instructions contained in Part V of the Compliance Program or other directive.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

E. CENTER FOR VETERINARY MEDICINE (CVM)

1. Product approval violations.
2. Tissue residue violations where no tolerance has been established**, or which involve the use of compounded products.
3. Feed contaminant violations where no tolerance has been established.
4. Adverse drug reaction reporting violations.
5. Low acid canned pet food violations requiring technical review.
6. CGMP violations for medicated feed [21 CFR Part 225], Type A Medicated Articles [21 CFR Part 226], and dosage form drugs [21 CFR Part 211]. Submit complete recommendation package (recommendation, EIR, CRs, all exhibits, and other supporting documents).

**Direct reference authority for tissue residue violations where no tolerance has been established may be given to districts on a case-by-case basis.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

F. CENTER FOR FOOD SAFETY AND APPLIED NUTRITION (CFSAN)

All violations not covered by direct reference authority, in a Compliance Policy Guide, or Compliance Program. These include, but are not limited to, the following examples:

1. Pesticide and chemical contamination violations not covered by direct reference authority.
2. Dietary Supplements, medical foods, and infant formulas.
3. Low acid and acidified canned foods (LACF) violations.
4. Food and color additive violations.
5. Seafood HACCP violations not covered by direct reference authority in the Compliance Program.
6. All situations involving violations of section 402 (a) (4) of the Act, including deviations of CGMP regulations for foods, low acid and acidified canned foods, bottled water and any other CGMP regulation concerning CFSAN issues, e.g., dietary supplements.

7. Mycotoxins
8. Animal drugs in foods (aquaculture chemotherapeutic agents).
9. Food standards

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

4-1-5 Letters For Illegal Promotional Activities

Centers should issue Warning Letters, not untitled letters, for promotional activities if the nature of the activity is such that the Center would support further regulatory action. Do not use Warning Letters or untitled letters if the Center would not support regulatory action. The Center should alert the district office of the violation and ask that they bring the promotional activity to the attention of the firm on the next scheduled visit. If the district inspection reveals additional problems, this violation may be included as part of their regulatory action plan. If the problem is urgent the district could request a meeting with the firm to discuss the violations.

4-1-6 Multiple Center Review

When the district is aware that the issues in a Warning Letter will require multiple Center review, the Warning Letter recommendation should be submitted concurrently to each Center involved. However, when the district is unaware that the issues involve more than one Center, then the Centers will review the Warning Letter in sequence. Each Center's 15 working day review time frame will begin at the time the submission is received at that Center. To facilitate a timely review, the lead Center should forward a copy of the recommendation to the other Center(s) and incorporate the other Center's comments into a single document.

4-1-7 Time Frames

Within fifteen (15) working days after completion of the inspection, or, if applicable, sample analysis, the district should submit a Warning Letter recommendation to the appropriate reviewing office for concurrence.

Within fifteen (15) working days after receipt of the Warning Letter recommendation, the Center should review the Warning Letter and notify the district office of its decision. If the Warning Letter is disapproved, the Center will notify the district office of its decision within 15 days of receipt, and will issue a memorandum stating its reasons for disapproval within 30 days, or as soon after that as possible. A copy of the disapproval memorandum should be provided to HFC-210 and HFC-230. If the Warning Letter is approved, the Center will forward its approval memo and the proposed Warning Letter, as appropriate, for further review and concurrence. See Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning

Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

The District compliance officer (or, the Center CSO/Scientist, if the Warning Letter was Center-initiated) assigned to the Warning Letter should diligently pursue and actively monitor the progress of the case through the Agency review process to its conclusion (i.e., voluntary compliance or enforcement action). The Office of Enforcement (Division of Compliance Management and Operations) can assist in situations where significant delays are experienced or assistance is needed to resolve technical, scientific, or policy issues. (Also, see section on Ad Hoc Committees in Chapter 10.)

4-1-8 Warning Letter Follow-Up

The issuing district or Center will evaluate the response to the Warning Letter. If the response is inadequate, or if no response is received, the district or Center will begin follow-up action as necessary to achieve correction.

If the response appears adequate, the district or Center will verify that commitments have been fulfilled and that correction has been achieved, and will notify other appropriate Agency units. Follow-up inspections should be conducted promptly after the agreed upon date of completion of the promised corrections, if necessary to assure that corrections have been implemented

A. ACKNOWLEDGMENT OF RESPONSE TO A WARNING LETTER

The district or Center that issued the Warning Letter should acknowledge responses received to Warning Letters with an appropriate written response with copies to other Agency units involved.

B. FOLLOW-UP ENFORCEMENT

If a firm has been issued a Warning Letter, and it continues to operate out of compliance, districts and Centers should consider further enforcement options. A second Warning Letter should not be issued for similar violations. However, Districts and Centers have the option of conducting a meeting with firm's management prior to pursuing an enforcement action. If prompt voluntary compliance is not achieved, such meetings serve as further prior notice. (See section on Prior Notice in Chapter 10.)

C. INSPECTION CLASSIFICATION

A Warning Letter constitutes official Agency action. Inspections will be classified Official Action Indicated, OAI, whenever a Warning Letter is Issued. This procedure provides greater consistency and uniformity in the classification system and regulatory policy. Inspections should not be re-classified from OAI due to failure to meet the 15 working day timeframe for issuing a Warning Letter.

OAI classifications based on tissue residue violations should not have mandated follow-up inspections unless additional violations have been reported to the Agency by the Department of Agriculture's Food Safety and Inspection Service.

For further information on classification of inspections see Field Management Directive No. 86, or refer to the web site at http://www.fda.gov/ora/inspect_ref/fmd/fmd86.htm

4-1-9 Firm Profile Updates In Facts

The district or Center must promptly update the firm profile in FACTS when a drug, biologic or medical device Warning Letter is issued. Update the profile again when it is determined that corrections have been achieved, if the Warning Letter has been disapproved and the inspections status is changed from OAI to VAI, or when further enforcement action is recommended or taken. For Warning Letters issued under a Bioresearch Monitoring Program, corrective actions may not be verified until the next inspection as requested by the Center. The Centers update the FACTS firm profile for foreign inspections of drug, device, and biologic manufacturers. For more detailed instructions, refer to the Office of Enforcement, Division of Compliance Information and Quality Assurance (DCIQA) Intranet Homepage. Please contact DCIQA, HFC-240 with questions.

4-1-10 Warning Letter Format

Warning Letters can vary in form, style, and content to provide the flexibility needed to accurately and effectively state the nature of the violation(s) found and the response expected. However, the elements listed below are common to Warning Letters:

1. Titled "WARNING LETTER."
2. Delivery - Warning Letters should be sent to ensure overnight delivery and receipt of delivery (e.g., return receipt requested, FedEx) should be documented.
3. Issued to the responsible individual who, based on currently available evidence, is most closely related to the violation, to that person's superior, and to the highest known official (original of letter) in the organization. Each person in the organization issued a copy is identified on the Warning Letter.
4. The dates of the inspection and a description of the violative condition, practice, or product in brief but sufficient detail to provide "prior notice" and provide the respondent opportunity to take corrective action. Include citation of the section of the law or regulation violated.
5. The Warning Letter should appropriately acknowledge corrections promised during the inspection, or annotated on the 483, or provided to the district in a written response.
6. A request for correction and a written response within a specific period of time after the date of receipt of the letter, usually fifteen (15) working days. At the district's discretion, the recipient may be offered an opportunity to discuss the letter with district officials or, when appropriate, with Center officials.
7. A statement in drug and medical device Warning Letters that: "Federal agencies are advised of all Warning Letters about drugs and devices so they may take this information into account when considering the award of contracts." This does not apply to Warning

Letters issued to IRBs, clinical investigators, sponsors, and monitors involved in clinical trials.

8. Instructions, as appropriate, that the response include: (1) each step that has been or will be taken to completely correct the current violations and to prevent similar violations; (2) the time within which correction will be completed; (3) any reason the corrective action has not been completed within the response time; and (4) any documentation necessary to show that correction has been achieved.
9. A warning statement that failure to achieve prompt correction may result in enforcement action without further notice. Examples of such actions may be cited. Do not include a commitment to take enforcement action.
10. A designated district or Center official to whom the response should be addressed.
11. Issued by the District Director, division director, or higher Agency official. Some program areas will require Center concurrence before issuance.

4-1-11 Warning Letter Distribution

Warning Letter distribution is as follows:

1. Original – Addressee(s)
2. One redacted copy to HFI-35 for public display under FOI regulations. Do not send credit page with drafting, clearance record, or blind copies to HFI-35. Include the name or initials of the person redacting the letter and the date redacted for release on the redacted copy for future reference.
3. One copy each to:

Each person identified in the Warning Letter

HFA-224

HFC-210 (Division of Compliance Management and Operations)

HFC-230 (Division of Compliance Policy)

Center Compliance unit (by special mail, fax, or as otherwise directed by the governing Compliance Program Guidance Manual (CPGM), which may request sending electronic copies to a specified e-mail account). For example:

HFD-300 (CDER)

HFM-610 (CBER)

HFZ-300 (CDRH) and, for MDR letters only, HFZ-533

HFV-230 (CVM)

HFS-605 (CFSAN)

HFC-130 ORA - DFI (Foreign (International) letters only)

HFC-170 ORA - DIOP - for Import letters only

Appropriate district office, for all Center-issued Warning Letters.

Appropriate district office, for all establishment locations that receive either an original or a copy of Warning Letter.

HFC-240 (Division of Compliance Information and Quality Assurance) only for drugs, devices and any biological drug or device

Local Distribution, factory file, WL file, resident post, and appropriate federal and state agencies.

4. Offices or individuals identified as blind copies (bcc) on credit page.

4-1-12 Warning Letters To Importers And Foreign Firms

A. IMPORTER WARNING LETTERS

See Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for Issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information. Center concurrence is not required, except in certain program areas that require prior Center concurrence.

Warning Letters may be issued to importers of FDA regulated products that engage in business practices that appear designed to evade the lawful regulation of imports. The "Priority Enforcement Strategy for Problem Importers," chapter provides guidance for the use of Warning Letters, and other enforcement actions, against importers.

Generally, it is not appropriate to take enforcement action against a customs broker. The owner, consignee, or importer is normally the responsible party for imported goods. However, if the broker is the owner, consignee, or importer identified on the import documents, or if the broker has authority over the product through prior arrangement with the importer, it may be appropriate to issue a Warning Letter to the broker. Assure that the broker is responsible for the violation.

Import Alert #00-17 contains a list of Warning Letters issued to importers.

Contact DIOP, Policy and Enforcement Branch (HFC-172) 301-443-6553 about issuing or using a Warning Letter involving an importer, consignee, owner, or broker of imported goods.

B. IMPORT BROKERS

By statute, 19 U. S. C. Section 1641, the United States Customs Service (Customs) has the responsibility for ensuring that brokers comply with the law. Customs, not FDA, has the authority to follow through on regulatory action against violators. When a broker fails to fulfill his statutory obligations as a broker, and FDA decides that a warning is appropriate, FDA should send an untitled letter telling the broker of the violation and warning that any future violation will be reported to customs.

There are some cases in which it may be appropriate to send a Warning Letter to a broker such as when the broker is functioning as the importer of record and violates a provision of the Act. The Warning Letter is issued to the broker in his capacity as importer of record. It is often difficult to distinguish between a broker performing his duties as a broker or as an importer of record. The only guidance the Act or its implementing regulations offers on the definition of

owner or consignee is found in 21 CFR 1.83(a). Section 1.83(a) defines an owner or consignee as "the person who has the rights of a consignee under the provisions of Sections 483, 484, and 485 of the Tariff Act of 1930, as amended (19 U.S.C. 1483, 1484, and 1485)." [21 CFR 1.83(a)] Section 483 of the Tariff Act was repealed in 1983. Under Sections 484 and 485, a consignee's rights consist primarily of filing any documentation required to allow foreign goods entry into the United States. [19 U.S.C. 1484, 1485]

The former Section 483 of the Tariff Act says the consignee of imported goods is the consignee declared on the bill of lading or air waybill, unless the consignee conferred its rights to other persons through endorsements on such documents. [19 U.S.C. Section 1483 (repealed 1983)]. The current Section 484(a)(2)(C) says the documentation required to make entry of goods "shall be filed either by the owner or purchaser of the goods or, when appropriately designated by the owner, purchaser, or consignee of the goods, a person holding a valid license under Section 1641 of this title." [19 U.S.C. Section 1484(a)(2)(C)]. While the person "appropriately designated" (that is, a customs broker licensed under 19 U.S.C. Section 1641) is often the importer of record, Sections 484 and 485 of the Tariff Act recognize, as did the former Section 483, that neither the consignee nor the importer of record is necessarily the true owner of the imported goods. So under Sections 484 and 485, only the importer of record (owner or purchaser, or a broker or broker designee) may make customs entry. [Id.; 19 U.S.C. 1485 (a)]

Usually, the broker will not be the party responsible for causing the violation of the import provisions of the Act. While the broker files the entry documentation, he exercises little, if any control over the goods itself. The owner/consignee/importer usually controls the movement of the goods and, therefore, bears the legal responsibility for complying with the Act.

To determine the proper addressee of a Warning Letter, send the letter to the person or entity identified on the entry documents as the importer. Under Sections 484 and 485 of the Tariff Act, the importer of record always has the rights of the consignee. In other words, one must be an owner, consignee, or the authorized agent of either (the customs broker engaged to make entry) to be the importer of record. If there are other individuals with an interest in the goods but FDA is unsure of the extent of the interest, the importer of record should be able to identify those individuals and notify them of the violation. If FDA is aware of other persons or entities with an interest in the goods, the Agency should send courtesy copies of the Warning Letter to them.

C. FOREIGN FIRMS

A Warning Letter may be appropriate if FDA has regulatory authority over the company and is prepared to exercise that control. Firms are placed on detention without physical examination because of repeatedly offering violative products for import. Unless the foreign firm is under the regulatory purview of FDA, issuing Warning Letters should be discussed with the Office of the Chief Counsel. For foreign manufacturers of devices, and drugs, CDRH and CDER issue Warning Letters based on review and concurrence with district recommendations in the foreign inspection reports. For CBER regulated products, administrative actions may also be considered for licensed foreign establishments.

4-1-13 Freedom Of Information (FOI)

Send a redacted copy of all Warning Letters to the Freedom of Information Staff, HFI-35, when

the letters are issued. Do not send the credit page with drafting and/or clearance records, or blind copies to HFI-35. Caution: See procedures below for Release of Warning Letters.

Include the name or initials of the person redacting the letter and the date redacted for release on the redacted copy for future reference.

Warning Letters are available on FDA's Internet Website at <http://www.fda.gov/foi/warning.htm> and are on public display at the Freedom of Information Staff office.

A. RELEASE OF WARNING LETTERS

District and Centers should use the following procedures before the release of a Warning Letter through a FOI request:

FOI requests for Warning Letters should be sent to the FOI Staff (HFI-35) for response. FOI requests can also be sent by facsimile to (301) 443-1726. Do not accept telephone or electronic requests for Warning Letters.

The address to send written requests for Warning Letters is:

Freedom of Information Staff (HFI-35)
Food and Drug Administration
Room 12A16
5600 Fishers Lane
Rockville, MD 20857
(301) 827-6567

The district or Center may release a redacted Warning Letter directly, if the Warning Letter either needs no non-public information to be redacted or the non-public information has been redacted, the Warning Letter is readily available, and no prepayment is necessary. (See the Information Disclosure Manual, "Freedom of Information Act," "Responsibilities of a Component FOIA Officer," item 2, for further details.) Assure that the addressee has received the original letter prior to releasing a redacted copy of the letter to another party. In that case, the component FOIA Officer may release the Warning Letter and then send a copy of the request, the response, and if appropriate, a copy of the records to the Division of FOI (HFI-35), noting the name and address of the requester, and the charges, if any.

4-1-14 Center For Biologics Evaluation And Research (CBER)

The compliance programs for CBER regulated products are located at: www.fda.gov/cber/cpg/cpg.htm. Evaluate violations to decide if they warrant administrative or regulatory action or both. To help in this determination, refer to Part V of each Compliance Program, which provides information on deviations that may warrant action.

The organizational unit in the CBER Office of Compliance and Biologics Quality (OCBQ) which handles warning letter recommendations is the Division of Case Management, HFM-610. They can be reached at (301) 827-6201.

A. CBER PROGRAM WARNING LETTERS

1. All correspondence to licensed establishments should be addressed to the most responsible person. A copy of the correspondence should also be sent to the authorized official. For unlicensed establishments, correspondence should be addressed to the most responsible individual, e.g., blood bank director or hospital administrator.
2. The lists of significant deviations (those that may lead to enforcement action if not promptly and adequately corrected) serve as guides for determining the recommended course of action. (See Attachments A and B of CP 7342.001 and CP 7342.002.) Any significant deviation, whether repetitive or an isolated occurrence, may warrant the issuance of a Warning Letter. Additionally, districts may consider issuance of a Warning Letter to a firm with a history of similar or substantially similar significant deficiencies about which the manufacturer has been advised.
3. The specific areas that require CBER concurrence for District Directors to issue a Warning Letter are listed above in "Center Concurrence and Letters Issued by Centers." In addition, districts do not have direct reference authority to issue a Warning Letter to other federal agencies. Once the appropriate reviews are completed, Warning Letters are issued directly by the district, with the exception of Team Biologics Warning Letters, which issue from the OE after CBER concurrence.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.
4. Schedule a follow-up inspection approximately 30 days after the response to the Warning Letter is received to determine the adequacy of the reported corrective actions. When corrective action has not been made or the firm has failed to respond, the district should consider suitable follow-up.
5. Send copies of all Warning Letters to Division of Case Management (HFM-610).
6. Districts should routinely provide copies of Warning Letters to the appropriate state agency or agencies. If the state regulatory office for these products is not known, contact ORA, Division of Federal-State Relations, HFC-150, (301) 827-6906. The letter should be redacted to protect confidential commercial information unless the state officials are commissioned. See Chapter 3 for commissioning procedures.

B. FEDERAL-STATE RELATIONS FOR BLOOD BANK INSPECTIONS

Currently, the Agency has no formal cooperative program with state or local jurisdictions for the inspection or regulation of blood banks. Cooperation with these authorities is encouraged especially if a state or local jurisdiction has a regulatory program for blood banks. Exchange of information should occur with all levels of state government whenever possible.

C. CURRENT GOOD MANUFACTURING PRACTICES (CGMPs) REGULATIONS FOR FINISHED PHARMACEUTICALS: REGULATORY ACTIONS FOR BLOOD ESTABLISHMENTS

21 CFR Part 211, CGMPs, applies to blood establishments. CBER review and concurrence is required for Warning Letters about deviations from Part 211 that are not associated with Part 606, e.g. 21 CFR 211.68. Direct reference authority does not include citing blood establishments for deviations from Part 211 CGMPs in Warning Letters.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

D. ADVERTISING AND PROMOTIONAL LABELING BRANCH PROCEDURAL GUIDE

The Advertising and Promotional Labeling Branch (APLB) in the Division of Case Management, Office of Compliance and Biologics Quality, may initiate regulatory action if the advertising and promotional labeling are not consistent with the approved labeling (package insert), clinical data used to approve the product, or applicable sections of the Act and regulations for labeling and advertising by notifying the manufacturer in writing of the violations.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

E. WARNING LETTERS RECOMMENDATIONS

Send tissue establishment Warning Letter recommendations to CBER for review and concurrence. When an Order for Recall, Retention, and Destruction has been issued for violations involving human tissue for transplantation it is not usually appropriate to issue a Warning Letter because the enforcement action has already been taken.

Send Warning Letter recommendations for CBER to Office of Compliance and Biologics Quality.

For Blood, Plasma and Tissue:
Chief, Blood and Tissue Compliance Branch
Division of Case Management, HFM-614

For Biological Drugs and Devices:
Chief, Biological Drug and Device Compliance Branch
Division of Case Management, HFM-624

Direct CBER Warning Letter questions to the Division of Case Management, HFM-610 301-827-6201.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

4-1-15 Center For Drug Evaluation And Research (CDER)

A. PREAPPROVAL INSPECTIONS/PENDING APPLICATIONS - WITHHOLD APPROVAL

Warning Letters are not to be recommended by the District Offices as a follow-up to a preapproval inspection for pending drug or device applications (ANDAs, NDA, PMAs) if no other FDA regulated products are marketed by the firm.

Warning Letters may be recommended by the District Offices for preapproval inspections of drug and device firms if other FDA regulated products are marketed by the firm. These letters should include the following statement: "Due to the deficiencies listed on the attached FDA-483 we are recommending to the Center that approval of the "... application be withheld."

In 2003, there has been a reassignment of regulatory program responsibility for certain biologic drug products from CBER to CDER. Generally, these products are monoclonal antibodies for diagnosis and therapy, cytokines, immunomodulators, growth factors and thrombolytics. The preapproval inspection operations for these drugs will be conducted by CDER staff.

B. SURVEILLANCE INSPECTIONS FOR ASSESSING CONFORMANCE WITH CGMPs

Warning Letters may be recommended by the District Offices based on findings from surveillance inspections made to assess conformance of a manufacturing site with the CGMP requirement in the Act. See *Standard Charge # 6* in *Section C*, below. In therapeutic biologic drugs, operations to assess their conformance to the CGMP's will be conducted by Team Biologics Investigators. These drugs will be subject to the same regulatory procedures and actions as other drugs regulated by CDER, however, Team Biologics Compliance Officers (rather than the district) will be responsible for initiating and preparing these actions. If there is a question of which regulatory group presides over a therapeutic biologic drug, contact the Branch Chief, Therapeutic Biologic Drug Branch, Division of Manufacturing and Product Quality at 301-827-6886.

C. STANDARD CDER CHARGES

1. Grandfather New Drug Charge: The charge for drugs that claim to have been on the market before 1938 or before 1962:

505(a) The articles are new drugs within the meaning of Section 201(p) of the Act and approval of an application filed under Section 505(b) of the Act is not effective for such drugs and a Notice of Claimed Investigational Exemption under Section 505(i) of the Act

and Part 312 of the CFR is not on file for such drugs, and documentation in support of such drugs, and "grandfather" exemption has not been submitted per 21 CFR 314.200(e)(2) which constitutes a waiver of such claims.

2. Back Door New Drug Charge: When the new drug charge (505) cannot be used because of lack of interstate movement of the article to be seized but there is documentation of the interstate movement of a component as a 301(k) sample then the charge is that the product was misbranded while held for sale:

502(f)(1) The article of drug, (DRUG NAME), is misbranded in that its labeling fails to bear adequate directions for the use for which the article is represented or suggested (as described above), and it is not exempt from this requirement under regulation 21 CFR 201.115, since the article is a new drug within the meaning of Section 201(p) of the Act and no approval of an application filed pursuant to Section 505(b) of the Act is effective for this drug.

A 502(f)(1) charge is appropriate for OTC drugs for which the directions are "Inadequate in fact." These are drugs which: a) have no directions; b) have directions that deviate from those required by a final monograph; or c) have directions, but those directions lack information which is necessary for the drug to be used safely, such as dosage or frequency of administration. (See 21 CFR 201.5.) However, a 502(f)(1) charge should not be used if "adequate directions for common uses thereof are known to the ordinary individual." (See 21CFR 201.116.)

A 502(f)(1) charge is appropriate for all prescription drugs that are unapproved new drugs. This includes a drug with an indication that is generally not amenable to lay diagnosis, even if the drug would not ordinarily be thought of as a prescription drug (e.g., shark fin cartilage for the treatment of cancer.)

When the product is not a new drug, the simple misbranding charge should read:

502(f)(1) The article of drug, (DRUG NAME) is misbranded in that its labeling fails to bear adequate directions for use for which the article is represented or suggested.

3. Prescription Drug Where There Is No Labeling Bearing Directions for Use
The charge is as follows:

502(f)(1) The article(s), (DRUG NAME), is subject to the provisions of Section 503(b)(1) of the Act and it is not exempt from Section 502(f)(1) of the Act in that its labeling fails to bear information required by regulation 21 CFR 201.100, providing adequate directions for use under which a practitioner licensed by law can use the drug safely and for the purposes for which it is intended, including indications; effects, dosages, routes, methods, frequency and duration of administration, relevant hazards; contraindications, side effects, and precautions.

4. Drug Registration and Listing

The charge is misbranding under section 502(o) of the Act but the violation is failure to register and list:

502(o) The articles, (DRUG NAMES), are misbranded in that they were manufactured in

an establishment not duly registered under Section 510 of the Act and the articles have not been listed as required by Section 510(j) of the Act.

5. Prescription Drugs

Section 503(b)(1) provides criteria for determining if the article is a prescription drug. Section 503(b)(1) is not a violation charge:

503(b)(1) The article, (DRUG NAME), because of its toxicity or other potential for harmful effect, or the method of use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug, and is misbranded because it is not dispensed upon prescription by a licensed practitioner.

The charge is:

For a prescription drug:

503(b)(4)(A) The article of drug, (DRUG NAME), is subject to Section 503(b)(1) of the Act and is misbranded in that its label fails to bear the symbol, "Rx only."

For an OTC drug that is not to bear the symbol, "Rx only":

The article of drug, (DRUG NAME), is not subject to Section 503(b)(1) of the Act and is misbranded in that its label bears the symbol, "Rx only" and it is not entitled to bear such symbol.

The following straight UNAPPROVED NEW DRUG charge may be used when there is interstate movement of the finished, labeled drug product.

505(a) The article of drug, (DRUG NAME), is a drug within the meaning of Section 201(g) of the Act which may not be introduced or delivered for introduction into interstate commerce under Section 505(a) of the Act, since it is a new drug within the meaning of Section 201(p) of the Act and no approval of an application filed pursuant to Section 505(b) of the Act is effective for such drug.

For information regarding health fraud issues, contact the Internet and Health Fraud Team at (301) 827-8931.

6. Adulteration Due To Inadequate Conformance with CGMPs

The charge is as follows:

501(a)(2)(B) The article(s), (DRUG NAME), is (are) adulterated within the meaning of Section 501(a)(2)(B) of the Act in that the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding fails to conform to, or is not operated or administered in conformity with, CGMP regulations [21 CFR 210, 211].

4-1-16 Center For Devices And Radiological Health (CDRH)

A. VIOLATIONS UNDER THE MAMMOGRAPHY QUALITY STANDARDS ACT (MQSA)

For routine Level 1 or repeat Level 2 noncompliances found during MQSA inspections, districts will not need CDRH concurrence before sending Warning Letters. Also, districts may send a Warning Letter without CDRH concurrence when a facility has performed mammography without a certificate. Under other circumstances, where inspections show numerous Level 2 and 3 noncompliances but no Level 1 or repeat Level 2 noncompliances, districts will need CDRH concurrence before sending a Warning Letter. For any of the situations mentioned above where CDRH concurrence is needed for an MQSA Warning Letter, the district should send the draft Warning Letter to the Division of Mammography Quality and Radiation Programs. (See Part V of the Compliance Program or other directive for additional case guidance.)

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

B. SAMPLE WORDING FOR CHARGES

1. Adulteration

Section 501(f)(1)(B) - in that it is a Class III device under Section 513(f) and does not have an approved application for premarket approval in effect pursuant to Section 515(a) or an approved application for an investigational device exemption under Section 520(g).

Section 501(c) - in that its strength, purity, or quality falls below that which it purports or is represented to possess.

Section 501(h) - in that the methods used in, or the facilities or controls used for, the manufacture, packing, storage, or installation are not in conformance with the Current Good Manufacturing Practice (CGMP) requirements for medical devices which are set forth in the Quality System regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820.

2. Misbranding Charges

Section 502(a) INEFFECTIVE or QUACK DEVICE - In that the labeling for the device represents or suggests that the device is adequate and effective for (.....), which representations or suggestions are false or misleading or otherwise contrary to fact because the device is not adequate or effective for such purposes.

Section 502(a) REFERENCE TO SECTION 510(k) # - in that the labeling of the device contains the statement, (e.g., "US FDA #K912345"), which is misleading in accordance with 21 CFR 807.97, because such statements create an impression of official approval of the device which is complying with the premarket notification regulations. This device was not approved by the FDA, but was determined to be substantially equivalent within

the meaning of section 513(l)(1)(A) of the Act.

Section 502(a) REFERENCE TO ESTABLISHMENT REGISTRATION OR REGISTRATION # - in that the labeling of the device contains the statement, (e.g. "It is licensed as a Medical Device Establishment by the U.S. Food and Drug Administration" or "Medical Device Establishment Registration Number 1234567"), which is misleading in accordance with 21 CFR 807.39, because such statements create an impression of official approval due to registration or possession of a registration number. Registration of a device establishment or assignment of a registration number does not in any way denote approval of the establishment or its products.

Section 502(b) - In that the device is in package form and its label fails to contain: (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count.

Section 502(f)(1) INEFFECTIVE or QUACK DEVICE - in that the labeling for the device fails to bear adequate directions for the purposes for which it is intended, because adequate directions cannot be written for (e.g., such purposes, etc.).

Section 502(f)(1) EXPIRATION DATES FOR IVDS - in that the labeling for the device fails to bear adequate directions for use because the labeled expiration dates have not been established by reliable, meaningful, and specific test methods, as required by 21 CFR 809.10.

Section 502(o) - In that the device was manufactured, prepared, propagated, compounded, or processed in an establishment not duly registered under Section 510, was not included in a list required by Section 510(j), and a notice or other information respecting the device was not provided to FDA as required by Section 510(k).

Section 502(o) MODIFICATION OF THE DEVICE in that a notice or other information respecting the device was not provided to FDA as required by 21 CFR 807.81(a)(3)(i), when the device was significantly changed or modified by (describe change).

There is a model plain English Warning Letter for small businesses describing violations associated with the failure to obtain premarket clearance, which is available on the internet at: <http://www.cdrh.fda.gov/offices/oc/engwarn.htm>.

For examples of model Quality System regulation/MDR Warning Letters, see Compliance Program 7382.845 - Inspection of Medical Device Manufacturers.

CDRH has established a separate mailbox for electronic submission of device Warning Letters from district offices. The address is: CDRH FPB Device WL. Typing "deviceWL" in the address bar will insert the correct address.

C. LETTERS TO X-RAY ASSEMBLERS

Letters issued to assemblers of diagnostic x-ray systems as a result of routine compliance field testing which uncover Class B Violations (see CP 7386.003) will be issued as untitled letters. Letters issued for more serious radiation hazard violations (Class A Violations) which require

immediate corrective action will be issued as Warning Letters. Warning Letters may also issue to x-ray assemblers for "pattern of violations" situations where the Agency is prepared to take enforcement action if the violations continue and/or if failure to correct violations continues. Subchapter C - Electronic Product Radiation Control (formerly the Radiation Control for Health and Safety Act of 1968) of Chapter V of the Act requires the Secretary to notify the assembler/manufacture concerning noncompliant or defective radiation emitting devices and solicit follow-up corrective action by the assembler/manufacture whether or not the Agency is prepared to take follow-up enforcement action. If there are specific cases to discuss or a need for further information on this subject, contact CDRH, Office of Compliance, HFZ-300, (301) 594-4692.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

4-1-17 Center For Food Safety And Applied Nutrition (CFSAN)

CFSAN will provide instructions for priority areas to be covered in Warning Letters in Compliance Programs.

4-1-18 Tracking

IDENTIFICATION OF WARNING LETTERS

To facilitate the tracking of Warning Letters, every Warning Letter issued by a district or Center office should bear a sequential code number. This code number should identify the fiscal year issued, the district or Center issuing the letter, and a sequential number for the Warning Letters issued by that office.

4-2 UNTITLED LETTERS

4-2-1 Policy

An untitled letter cites violations that do not meet the threshold of regulatory significance for a Warning Letter. Therefore, the format and contents of an untitled letter should clearly distinguish it from a Warning Letter. For example:

The letter is not titled.

The letter does not include a statement that FDA will advise other federal agencies of the issuance of the letter so that they may take this information into account when considering the awarding of contracts.

The letter does not include a warning statement that failure to take prompt correction may result in enforcement action.

The letter does not evoke a mandated district follow-up.

The letter requests (rather than requires) a written response from the firm within a reasonable amount of time (e.g., "Please respond within 30 days"), unless more specific instructions are provided in a relevant Compliance Program.

Any appropriate Agency compliance official may issue an untitled letter.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

4-3 EXHIBIT

4-1 Procedures for Clearing FDA Warning Letters and Untitled Letters

Exhibit 4-1**Procedures for Clearing FDA Warning Letters and Untitled Letters**

Revised April 24, 2004

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1. Purpose

To facilitate the Office of Chief Counsel's review of all Warning Letters and Untitled Letters, prior to their issuance, for legal sufficiency and consistency with Agency policy.

2. Policy / Scope

These procedures apply to all of the agency components that are responsible for recommending, evaluating or issuing Warning Letters and Untitled Letters. Therefore, the applicability of these procedures is not limited to ORA and the Centers' Offices of Compliance.

3. Background

On November 29, 2001, the Deputy Secretary of the Department of Health and Human Services directed "...the Food and Drug Administration (FDA) to submit all Warning Letters and Untitled Letters to FDA's Office of Chief Counsel (OCC) prior to their issuance so that they can be reviewed for legal sufficiency and consistency with Agency policy." To implement this directive, a cross-agency working group established procedures to integrate OCC review into

the agency's existing procedures for the review of enforcement correspondence. These procedures were implemented in March 2002 (see 8. Change History).

4. Definitions

For the purpose of these procedures:

- 4.1 A **Warning Letter**, as explained in the *Regulatory Procedures Manual*, is a correspondence that notifies regulated industry about violations that FDA has documented during its inspections or investigations. Typically, a Warning Letter notifies a responsible individual or firm that the Agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act (the Act), its implementing regulations and other federal statutes. Warning Letters should only be issued for violations of regulatory significance, i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected. A Warning Letter is one of the Agency's principal means of achieving prompt voluntary compliance with the Act.
- 4.2 An **Untitled Letter** is an initial correspondence with regulated industry that cites violations that do not meet the threshold of a Warning Letter as defined in the *Regulatory Procedures Manual*. Untitled Letters are intended to cover those circumstances where the Agency has a need to communicate with regulated industry about violations that do not meet the threshold of regulatory significance as described above. The three types of letters related to licensed products that are issued by CBER and CDER, pursuant to sections 6, 7, and 8, of these procedures, do not necessarily fall within this definition of an untitled letter; however, they are still untitled letters that are covered by the scope of these procedures.

5. Responsibilities

- 5.1 The Office of Enforcement will review these procedures every twelve (12) months to evaluate their scope and effectiveness. Any refinements that become identified through the evaluation or otherwise, that may facilitate the review, streamline or focus the process, or enable better management of the workload, while maintaining the overall intent, are implemented through established, internal agency review procedures. In addition, the Council will monitor the timeframes to determine whether they need to be modified based on the agency's experience with these procedures.
- 5.2 Each Office involved in implementing these procedures is responsible for documenting additional internal procedures as needed.
- 5.3 Violation letters are tracked using FDA's Agency Information Management System (AIMS). The system provides the capability to enter and track Warning and Untitled Letters upon submission through the approval process. The action office (i.e. the District or Center initiating the recommendation) is responsible for submitting recommendations to AIMS as well as updating data related to their submissions. Instructions for using the AIMS system can be found at the OE Warning Letter Home Page on FDA's Intranet. Submissions are entered into the system via a tracking form and assigned a number (VL number).

6. Procedures

6.1 Timeframes

6.1.1 Warning Letters

The Agency did not establish new timeframes for ORA and the Centers. In these procedures, the agency recommit to the established timeframes at each level of review. To ensure the applicability of evidence to the present situation, the agency will strive to issue warning letters within four months from the appropriate reference date. Examples of the appropriate reference date are: the last day of the inspection, the date of sample analysis, or the date of evidence collection.

The timeframe for OCC review of all Warning Letters is fifteen (15) working days. If OCC does not respond to Direct Reference Warning Letters and those issued pursuant to foreign inspections within this timeframe, the District or Center can presume concurrence and may send the letter out without additional input. All other categories of letters should await an OCC decision prior to being issued. For all categories of warning letters receiving a decision by OCC, OCC will either concur, concur with changes, not concur with written reasons, or flag the letter because it raises significant issues and questions, e.g., jurisdictional issues or insufficient evidentiary support. The period for OCC review officially begins once OCC has received the full packet of materials that serve as support for the agency's issuance of the Warning Letter. If the basic elements of the case are not provided (the basic elements are identified in the district and center responsibility sections of these procedures), OCC will return the materials to the originator. If, as a part of their review, OCC asks for an exhibit or attachment that accompanied the Establishment Inspection Report (EIR) or Form FDA 483 response, a copy of the document should be sent to OCC electronically, via fax or by mail.

6.1.2 Warning Letter Responses

If it is reasonably clear from the Warning Letter response that the individual or firm is going to contest the findings as set out in the Warning Letter, OCC should be consulted and provided with the relevant documents. This is not necessary when the disputed issues are scientific or technical. For further guidance, refer to *Instructions and Frequently Asked Questions Regarding Warning Letter Responses* on the Warning Letter Home Page on FDA's Intranet.

6.1.3 Untitled Letters

There are no agency timeframes for the issuance of Untitled Letters. However, pursuant to these procedures, the working group established timeframes for the review of Untitled Letters. In most cases, the timeframes for Warning Letters are tripled for the review of Untitled Letters. The exceptions to this rule are the letters for licensed products that are issued by CBER or CDER pursuant to section 6.3 of these procedures. To ensure the applicability of evidence to the present situation, the agency will strive to issue untitled letters within six months from the last day of the inspection, the date of sample analysis, or the date of evidence collection.

Pursuant to OCC's review of Untitled Letters, OCC will either concur, concur with changes, not concur with *written* reasons, or flag the letter because it raises significant issues and

questions, e.g., jurisdictional issues or insufficient evidentiary support. However, the default provisions do not apply to Direct Reference Untitled Letters and Untitled Letters issued pursuant to a foreign inspection. The period for OCC review officially begins once OCC has received the full packet of materials that serve as support for the agency's issuance of the Untitled Letter. If the basic elements of the case are not provided (the basic elements are identified in the district and center responsibility sections of these procedures), OCC will return the materials to the originator. If, as a part of their review, OCC asks for an exhibit or attachment that accompanied the EIR or Form FDA 483 response, a copy of the document should be sent to OCC electronically, via fax or by mail.

6.2. Procedures for the Review of Agency Warning and Untitled Letters

6.2.1. General Procedures for Direct Reference Warning and Untitled Letters

(a) District Office Responsibilities

- (1) Within 15 working days after the completion of an inspection, the sample analysis, or date of evidence collection, submit a draft "final" Warning Letter to OCC for concurrence, and send a copy to ORA's Office of Enforcement's (OE) email account **ORA Warning Letter**.
- (2) Within 45 working days after the completion of an inspection, the sample analysis, or date of evidence collection, submit a draft "final" Untitled Letter to OCC for concurrence, and send a copy to OE's email account **ORAWarning Letter**.
- (3) To facilitate OCC's review of the Warning or Untitled Letters, send the Form FDA 483, the endorsement page of the EIR or the FACTS coversheet, the narrative portion of the EIR, and, if applicable, the summary of any sample analysis to OCC electronically. Do *not* send the EIR attachments or exhibits to OCC.
- (4) If there is no Form FDA 483 or EIR, send the evidence to OCC that supports the issuance of the letter.
- (5) If the District receives the Form FDA 483 response prior to submitting the draft "final" Warning or Untitled letter to OCC, a copy of the Form FDA 483 response (without the exhibits or the attachments) and the District's assessment of the response should accompany the draft "final" Warning or Untitled Letter.
- (6) If the District receives the Form FDA 483 response while OCC is reviewing the draft "final" Warning or Untitled letter, the District should notify the attorney that is conducting the review. A copy of the Form FDA 483 response (without the exhibits or the attachments) and the District's assessment of the response (including whether the response has changed the District's view on whether to issue the letter) should also be submitted to the assigned attorney electronically, via fax, or by mail. The review clock will stop when OCC is notified and restart upon OCC's receipt of the Form FDA 483 response and the District's assessment. Any changes to the proposed letter as a result of the FDA-483 response will be discussed with the initiating office, as appropriate, and drafted by OCC.
- (7) If OCC concurs, or if OCC does not review the draft "final" Warning Letter within 15 working days, issue the letter.

- (8) If OCC concurs with the draft "final" Untitled Letter, issue the letter.
- (9) If the District receives the Form FDA 483 response after OCC has concurred with the issuance of the draft "final" Warning or Untitled Letter, you should issue the letter.
- (10) Upon issuance, send a signed copy of the Warning or Untitled Letter to OE's email account **ORA Warning Letter** and the Center whose products are the subject of the letter. Additional copies should be distributed to all Agency components identified in the Compliance Program and/or RPM Chapter 4.
- (11) In the case of *non*concurrence or the letter is flagged because it raises significant issues, the District will work with OCC, and the Director of Compliance, OE and the Center as necessary, to quickly address OCC's concerns.

(b) OCC Responsibilities

- (1) Review the draft "final" Warning Letter and Untitled Letter within 15 working days.
- (2) If concurrence, send concurrence to the District's Director of the Compliance Branch along with a copy of the draft "final" letter with any edits (the District can then issue the letter).
- (3) Send a copy of the concurrence to OE's email account **ORA Warning Letter**.
- (4) If *non*concurrence or the letter is flagged because it raises significant issues, contact the District, state *in writing* the reason for nonconcurrence, and send a copy to the Director of Compliance of OE at OE's email account **ORA Warning Letter Nonconcur**.

(c) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued.

6.2.2. General Procedures for Warning and Untitled Letters Pursuant to a Foreign Inspection

(a) Center Responsibilities

- (1) Within 15 working days after the receipt of the EIR, the Center will determine if a Warning Letter is appropriate.
- (2) Within 45 working days after the receipt of the EIR, the Center will determine if an Untitled Letter is appropriate.
- (3) Send a copy of the draft "final" letter to OCC for concurrence.
- (4) To facilitate OCC's review of the Warning or Untitled Letters, send the Form FDA 483, the endorsement page of the EIR or the FACTS coversheet, the narrative portion of the EIR, and, if applicable, the summary of any sample analysis to OCC electronically. Do *not* send the EIR attachments or exhibits to OCC.
- (5) If there is no Form FDA 483 or EIR, send the evidence to OCC that supports the issuance of the letter.
- (6) If the agency receives the Form FDA 483 response prior to submitting the draft "final"

Warning or Untitled letter to OCC, a copy of the Form FDA 483 response (without the exhibits or the attachments) and the agency's assessment of the response should accompany the draft "final" Warning or Untitled Letter.

- (7) If the agency receives the Form FDA 483 response while OCC is reviewing the draft "final" Warning or Untitled letter, the Center should notify the attorney that is conducting the review. A copy of the Form FDA 483 response (without the exhibits or the attachments) and the agency's assessment of the response (including whether the response has changed the agency's view on whether to issue the letter) should also be submitted to the assigned attorney electronically, via fax, or by mail. The review clock will stop when OCC is notified and restart upon OCC's receipt of the Form FDA 483 response and the agency's assessment. Any changes to the proposed letter as a result of the FDA-483 response will be discussed with the initiating office, as appropriate, and drafted by OCC.
- (8) If OCC concurs, or if OCC does not review the draft "final" Warning Letter within 15 working days, issue the letter.
- (9) If OCC concurs with the draft "final" Untitled Letter, issue the letter.
- (10) If the agency receives the Form FDA 483 response after OCC has concurred with the issuance of the draft "final" Warning or Untitled Letter, the letter should be issued.
- (11) Upon issuance, send a signed copy of the Warning or Untitled Letter to OE's email account **ORA Warning Letter** and ORA's Office of Regional Operations (ORO), Division of Field Investigations (DFI). Additional copies should be distributed to all Agency components identified in the Compliance Program and/or RPM Chapter 4.
- (12) In the case of *non*concurrence or the letter is flagged because it raises significant issues, the Center will work with OCC and the Director of Compliance, OE and ORO's DFI as necessary to quickly address OCC's concerns.

(b) OCC Responsibilities

- (1) Review the draft "final" Warning Letter and Untitled Letter within 15 working days.
- (2) If concurrence, send concurrence to the Center along with a copy of the draft "final" letter with any edits (the Center can then issue the letter).
- (3) Send a copy of the concurrence to OE's email account **ORA Warning Letter**.
- (4) If *non*concurrence or the letter is flagged because it raises significant issues, contact the Center, state *in writing* the reason for nonconcurrence, and send a copy to the Director of Compliance of OE at OE's email account **ORA Warning Letter Nonconcur**.

(c) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued.

6.2.3. Warning and Untitled Letters that Require Center Concurrence

(a) District Office Responsibilities

- (1) Within 15 working days after the completion of the inspection, the sample analysis, or collection of evidence, submit a recommendation and a draft "final" Warning Letter to the Center and send a copy to OE's email account **ORA Warning Letter**.
- (2) Within 45 working days after the completion of the inspection, the sample analysis, or collection of evidence, submit a recommendation and a draft "final" Untitled Letter to the Center and send a copy to OE's email account **ORA Warning Letter**.
- (3) To the extent that this information is not included in the recommendation, and to facilitate the Center's review of the Warning or Untitled Letters, send the Form FDA 483, the endorsement page of the EIR or the FACTS coversheet, the narrative portion of the EIR, the relevant exhibits, and, if applicable, the summary of any sample analysis to the Center electronically. (Refer to the Warning Letter Website on FDA's intranet for instructions regarding electronic submission of information to specific Centers.)
- (4) If the District receives the Form FDA 483 response prior to submitting the draft "final" Warning or Untitled letter recommendation, a copy of the Form FDA 483 response (without the exhibits or the attachments) and the District's assessment of the response should accompany the draft "final" Warning or Untitled Letter.
- (5) If the District receives the Form FDA 483 response while the draft "final" Warning or Untitled letter is being reviewed, the District should notify the Center and attorney that is conducting the review, as appropriate. A copy of the Form FDA 483 response (without the exhibits or the attachments) and the District's assessment of the response (including whether the response has changed the District's view on whether to issue the letter) should also be submitted to the appropriate reviewer(s) electronically, via fax, or by mail. The review clock will stop when OCC is notified and restart upon OCC's receipt of the Form FDA 483 response and the agency's assessment. Any changes to the proposed letter as a result of the FDA-483 response will be discussed with the initiating office, as appropriate, and drafted by the office conducting the review (the Center or OCC).
- (6) If the Center approves the recommendation and OCC concurs, issue the letter.
- (7) If the agency receives the Form FDA 483 response after OCC has concurred with the issuance of the draft "final" Warning or Untitled Letter, the letter should be issued.
- (8) Upon issuance, send a signed copy of the Warning or Untitled Letter to the Center and OE's email account **ORA Warning Letter**. Additional copies should also be distributed, as necessary, to all Agency components identified in the Compliance Program and/or RPM Chapter 4.
- (9) In the case of *non*concurrence or the letter is flagged because it raises significant issues, the District will work with OCC and the Director of Compliance, OE and the Center as necessary to quickly address OCC's concerns.

(b) Center Responsibilities

- (1) Within 15 working days after the receipt of the recommendation, the accompanying documents, and the draft "final" Warning Letter, the Center should review and approve or nonconcur with the issuance of the letter. The Center will issue the approval memo within the 15 working day timeframe.

- (2) Within 45 working days after the receipt of the recommendation, the accompanying documents, and the draft "final" Untitled Letter, the Center should review and approve or nonconcur with the issuance of the letter. The Center will issue the approval memo within the 45 working day timeframe.
- (3) If the recommendation is approved, the Center will send its concurrence and the draft "final" letter with any edits to OCC for concurrence. The Center should also copy the District and send a copy of the draft "final" letter to OE's email account **ORA Warning Letter**.
- (4) To facilitate OCC's review of the Warning or Untitled Letters, send the Form FDA 483, the endorsement page of the EIR or the FACTS coversheet, the narrative portion of the EIR, and, if applicable, the summary of any sample analysis to OCC electronically. Do *not* send the EIR attachments or exhibits to OCC.
- (5) If there is no Form FDA 483 or EIR, send the evidence to OCC that supports the issuance of the letter.
- (6) If the Warning Letter recommendation is *not* approved, the Center will notify the District's Director of the Compliance Branch, OCC, and OE of its decision within 15 working days. (OE has an email account for this purpose entitled **ORAWarning Letter Nonconcur**) The Center will also issue a memorandum to the District's Director of the Compliance Branch that states its reasons for nonconcurrence within 30 working days, or as soon as possible.
- (7) If the Untitled Letter recommendation is *not* approved, the Center will notify the District's Director of the Compliance Branch, OCC, and OE of its decision within 45 working days. (The same OE email account entitled **ORA Warning Letter Nonconcur** should be used for this purpose.) The Center will also issue a memorandum to the District's Director of the Compliance Branch that states its reasons for nonconcurrence within 60 working days, or as soon as possible.

(c) OCC Responsibilities

- (1) Once the Center has approved the recommendation, review the draft "final" Warning Letter within 15 working days.
- (2) Once the Center has approved the recommendation, review the draft "final" Untitled Letter within 45 working days.
- (3) If concurrence, send concurrence to the District's Director of the Compliance Branch along with a copy of the draft "final" letter with any edits (the District can then issue the letter).
- (4) Send a copy of the concurrence to the Center and to OE's email account **ORA Warning Letter**.
- (5) If *nonconcurrence* or the letter is flagged because it raises significant issues, contact the District, state *in writing* the reason for nonconcurrence, and send a copy to the Director of Compliance, OE at OE's email account **ORA Warning Letter Nonconcur**.

(d) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued.

6.2.4. Warning and Untitled Letters that Issue Directly from the Center

(a) Center Responsibilities

- (1) Make the decision to issue a Warning Letter or an Untitled Letter
- (2) Submit a draft "final" Warning Letter or Untitled Letter to OCC.
- (3) To facilitate OCC's review of the Warning or Untitled Letters, send the Form FDA 483, the endorsement page of the EIR or the FACTS coversheet, the narrative portion of the EIR, and, if applicable, the summary of any sample analysis to OCC electronically. Do *not* send the EIR attachments or exhibits to OCC.
- (4) If there is no Form FDA 483 or EIR, send the evidence to OCC that supports the issuance of the letter.
- (5) If the agency receives the Form FDA 483 response prior to submitting the draft "final" Warning or Untitled letter to OCC, a copy of the Form FDA 483 response (without the exhibits or the attachments) and the agency's assessment of the response should accompany the draft "final" Warning or Untitled Letter.
- (6) If the agency receives the Form FDA 483 response while OCC is reviewing the draft "final" Warning or Untitled letter, the Center should notify the attorney that is conducting the review. A copy of the Form FDA 483 response (without the exhibits or the attachments) and the agency's assessment of the response (including whether the response has changed the agency's view on whether to issue the letter) should also be submitted to the assigned attorney electronically, via fax, or by mail. The review clock will stop when OCC is notified and restart upon OCC's receipt of the Form FDA 483 response and the agency's assessment. Any changes to the proposed letter as a result of the FDA-483 response will be discussed with the initiating office, as appropriate, and drafted by OCC.
- (7) If OCC concurs, the Center can issue the letter.
- (8) If the agency receives the Form FDA 483 response after OCC has concurred with the issuance of the draft "final" Warning or Untitled Letter, the letter should be issued.
- (9) Upon issuance send a signed copy of the Warning or Untitled Letter to the District's Director of the Compliance Branch where the recipient of the letter is located and to OE's email account **ORA Warning Letter**. Additional copies should be distributed, as necessary, to all Agency components identified in the Compliance Program and/or RPM Chapter 4.
- (10) In the case of *non*concurrence or the letter is flagged because it raises significant issues, the Center will work with OCC and the Director of Compliance, OE as necessary, to quickly address OCC's concerns.

(b) OCC Responsibilities

- (1) Review the draft "final" Warning Letter within 15 working days.

- (2) Review the draft "final" Untitled Letter within 45 working days.
- (3) If concurrence, send concurrence to the Center along with a copy of the draft "final" letter with any edits (the Center can then issue the letter).
- (4) Send a copy of the concurrence to OE's email account **ORA Warning Letter**.
- (5) If *non*concurrence or the letter is flagged because it raises significant issues, contact the Center, state *in writing* the reason for nonconcurrence, and send a copy to the Director of Compliance, OE at OE's email account **ORA Warning Letter Nonconcur**.

(c) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued.

6.2.5. Letters that Issue Directly from the Centers' Promotion and Advertising Staffs

(a) Center Responsibilities

- (1) Make the decision to issue a Warning Letter or an Untitled Letter.
- (2) Send a copy of the draft "final" letter to OCC for concurrence.
- (3) To facilitate OCC's review of the Warning or Untitled letter, send the evidence to OCC that supports the issuance of the letter.
- (4) If OCC concurs, issue the letter.
- (5) Upon issuance, send a signed copy of the Warning or Untitled Letter to OE's email account **ORA Warning Letter**. Additional copies should be distributed, as necessary, to all Agency components identified in the Compliance Program and/or RPM Chapter 4.
- (6) In the case of *non*concurrence or the letter is flagged because it raises significant issues, the Center will work with OCC to quickly address OCC's concerns.

(b) OCC Responsibilities

- (1) Review the draft "final" Warning Letter within 15 working days.
- (2) Review the draft "final" Untitled Letter within 45 working days.
- (3) If concurrence, send concurrence to the Center along with a copy of the draft "final" letter with any edits (the Center can then issue the letter).
- (4) Send a copy of the concurrence to OE's email account **ORA Warning Letter**.
- (5) If *non*concurrence or the letter is flagged because it raises significant issues, contact the Center and state *in writing* the reasons for nonconcurrence.

(c) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued.

6.3 Licensed Products Letters

Violation Letters associated with licensed biological therapeutics may fall under CBER or CDER responsibility. A listing of such products that have been transferred under CDER's jurisdiction can be viewed at: <http://www.fda.gov/cber/transfer/transfprods.htm>. Additional information can be found at: <http://www.fda.gov/cder/biologics/default.htm>.

Recommendations and other correspondence related to 6, 7, and 8 (below) that are associated with CDER products should be forwarded to CDER, Office of Compliance, Division of Manufacturing and Product Quality (HFD-320). Recommendations and correspondence related to CBER products should be referred to CBER, Office of Compliance and Biologics Quality, Division of Case Management (HFM-610).

6.3.1 License Suspension

(a) **Center Responsibilities**

- (1) Within three (3) working days after receiving information that a danger to health exists, the Center will gather the pertinent evidence, convene a Health Hazard Evaluation meeting with the applicable product office, and draft a Letter of Suspension.
- (2) If the determination is made that a danger to health exists, a draft "final" Letter of Suspension will be submitted by the Center to OCC within the 3 working day period.
- (3) To facilitate OCC's review of the letter, the Health Hazard Evaluation and the pertinent evidence that establishes that a danger to health exists should be submitted to OCC electronically.
- (4) If OCC concurs, the Center's Office of Compliance and the Office of the Center Director will process and issue the letter.
- (5) In the case of *non*concurrence or the letter is flagged because it raises significant issues, the Center will work with OCC to quickly address OCC's concerns.
- (6) Upon issuance, send a signed copy of the letter to OE's email account **ORA Warning Letter**. Additional copies should be distributed, as necessary, to all Agency components identified in the Compliance Program and/or RPM Chapter 4.

(b) **OCC Responsibilities**

- (1) Review the draft "final" letter within 5 working days.
- (2) If concurrence, send concurrence to the appropriate Center along with a copy of the draft "final" letter with any edits.
- (3) Send a copy of the concurrence to OE's email account **ORA Warning Letter**.
- (4) If *non*concurrence or the letter is flagged because it raises significant issues, contact the appropriate Center and state *in writing* the reason for nonconcurrence.

(c) **OE Responsibilities**

Maintain a repository of all Untitled Letters that have been issued.

6.3.2 License Revocation (For Cause)

(a) Center Responsibilities

- (1) Within 30 working days after receipt of a Recommendation for a License Revocation, the Center will evaluate the recommendation to determine whether the issuance of a letter requesting the revocation of a license is appropriate.
- (2) If the issuance of a letter is appropriate, submit a draft "final" letter to OCC for their concurrence.
- (3) To facilitate OCC's review of the letter, the Center should send the recommendation and any additional supporting documents to OCC electronically.
- (4) If OCC concurs, issue the letter.
- (5) Upon issuance, send a signed copy of the letter to OE's email account **ORA Warning Letter**.
- (6) In the case of *non*concurrence or the letter is flagged because it raises significant issues, the Center will work with OCC to quickly address OCC's concerns.

(b) OCC Responsibilities

- (1) Review the draft "final" letter within 30 working days.
- (2) If concurrence, send concurrence to the Center along with a copy of the draft "final" letter with any edits.
- (3) Send a copy of the concurrence to OE's email account **ORA Warning Letter**.
- (4) If *non*concurrence or the letter is flagged because it raises significant issues, contact the Center, and state *in writing* the reason for nonconcurrence.

(c) OE Responsibilities

Maintain a repository of all Untitled Letters that have been issued.

6.3.3 Notice of Intent to Revoke

(a) Center Responsibilities

- (1) Within 30 working days after the receipt of a Recommendation for a Notice of Intent to

Revoke (NOIR), the Center will evaluate the recommendation to determine whether the issuance of a (NOIR) letter is appropriate.

- (2) If the issuance of a NOIR is appropriate, submit a draft "final" NOIR letter and any accompanying documentation to OCC for their concurrence.
- (3) To facilitate OCC's review of the NOIR letter, the recommendation should be sent to OCC electronically.
- (4) If OCC concurs, Issue the letter.
- (5) Upon issuance, send a signed copy of the letter to OE's email account **ORA Warning Letter**.
- (6) In the case of *non*concurrence or the letter is flagged because it raises significant issues, the Center will work with OCC.

(b) OCC Responsibilities

- (1) Review the draft "final" letter within 30 working days.
- (2) If concurrence, send concurrence to the Center, along with a copy of the draft "final" NOIR letter with any edits.
- (3) Send a copy of the concurrence to OE's email account **ORA Warning Letter**.
- (4) If *non*concurrence or the letter is flagged because it raises significant issues, contact the Center and state *in writing* the reason for nonconcurrence.

(c) OE Responsibilities

Maintain a repository of all Untitled Letters that have been issued.

6.4 Enforcement Correspondence Under an Audit Review

Periodically, the agency may determine, through the periodic evaluations or otherwise, that certain untitled and warning letters may be reviewed by OCC on an audit basis rather than a letter-by-letter review. The agency may institute such an audit review under those circumstances in which policy is clear and well established, and model letters have been developed and cleared through OCC for use by the originating organization. Specific areas and criteria for audit review will be developed for the relevant letters.

If, during the evaluation or otherwise, any problems are identified in the use of the models, quality of issued letters, conformance with the audit requirements or other criteria in this procedure, audit review may revert back to full letter by letter review.

(a) Introduction

Districts are required to submit every fifth Warning Letter and every fifth Untitled Letter

through the routine procedures in this document. For all other letters that meet the criteria for direct reference authority in this program, districts may issue them directly, using the model letters identified for such use (available on the Warning Letter Website on FDA's Intranet). These model letters must be followed for all letters under this program issued on or after the associated effective date

At the district's discretion, letters that represent unique circumstances that warrant OCC review, may continue to be submitted for review through the routine procedures in this document, in addition to the required submission of every fifth letter.

(b) District Responsibilities

Use the model letter for all untitled letters and warning letters issued on or after the effective date. Each district must set up a system whereby every fifth untitled letter and every fifth warning letter are submitted for OCC review using the procedures in this document. All other letters matching the audit review criteria may issue without OCC review. The system established must be available for review to determine conformance with these procedures.

Districts must continue to be diligent to ensure the high quality and timeliness of any letters that are issued and must otherwise follow the appropriate procedures in the RPM, Compliance Programs, or elsewhere.

Conformance with these procedures and use of the model letter is required. Audit review can be rescinded if warranted.

(c) Center Responsibilities

None. This option relates only to letters for which the field has direct reference authority.

(d) OCC Responsibilities

Review untitled letter and warning letter recommendations submitted by the field, representing every fifth letter in each category to be issued by a particular district on or after the effective date, in accordance with the routine procedures in this document. Determine conformity with the model letter. Report any perceived problems to the Office of Enforcement.

(e) OE Responsibilities

Maintain a repository of all untitled letters and warning letters issued. Review conformance with these procedures as part of the periodic evaluation.

6.4.1 Radiological Health Letters

Currently, the only model letter approved under this audit program is the Notification to X-Ray Assemblers of Defect or Noncompliance as the Result of Field Testing. The link to this letter can be found on the Warning Letter Website on FDA's intranet. The effective

date for use of this letter is March 1, 2004.

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1125 TRENTON-HARBOURTON ROAD, TITUSVILLE, NEW JERSEY 08560-0200

18 APR 2002

Russell Katz, MD, Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
U.S. Food and Drug Administration
Attn: Document Control Room 10B-40
1451 Rockville Pike
Rockville, MD 20852

Subject: NDA 20-272/SLR-024
Cross reference: NDA 20-588/SLR-015
RISPERDAL[®] (risperidone) Tablets and Oral Solution
Amendment to Pending CBE Labeling Supplement - Postintroduction
Reports Section

Dear Dr. Katz:

On behalf of Janssen Pharmaceutica Products, L.P., please refer to our New Drug Application, NDA 20-272, for Risperdal (risperidone) Tablets. In accordance with 21 CFR 314.70(c)(2), Johnson & Johnson Pharmaceutical Research & Development, L.L.C. is submitting an amendment to supplement SLR-024 to provide the supporting documentation not included with the original supplement. The supplement is for the addition of the term "hyperglycemia" to the **ADVERSE REACTIONS: Postintroduction Reports** section of the package insert for Risperdal (risperidone) tablets and oral solution. Immediately following this letter is Form 356h, a copy of the original supplement cover letter, table of contents, marked and clean copies of the package insert, and two supporting safety reports.

For your convenience, this amendment is being supplied with a CD-ROM as a review aid. This CD-ROM has been virus scanned using McAfee VirusScan (virus Definition 4.0.4064/Scan Engine E 4.0.25) and is virus free.

Please contact me at (609) 730-2712 if you have any questions regarding this submission.

Sincerely,



Susan J. Merchant
Manager, Regulatory Affairs

cc: S. Hardeman (DNDR RMO)

JJRP 00557338

Confidential/Produced in Litigation Pursuant to Protective Order

D-6211.1

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1125 TRENTON-HARBOR TON ROAD, TITUSVILLE, NEW JERSEY 08560-0200

18 APR 2002

Russell Katz, MD, Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
U.S. Food and Drug Administration
Attn: Document Control Room 10B-40
1451 Rockville Pike
Rockville, MD 20852

Subject: NDA 20-272/SLR-024
Cross reference: NDA 20-588/SLR-015
RISPERDAL[®] (risperidone) Tablets and Oral Solution
Amendment to Pending CBE Labeling Supplement – Postintroduction
Reports Section

Dear Dr. Katz:

On behalf of Janssen Pharmaceutica Products, L.P., please refer to our New Drug Application, NDA 20-272, for Risperdal (risperidone) Tablets. In accordance with 21 CFR 314.70(c)(2), Johnson & Johnson Pharmaceutical Research & Development, L.L.C. is submitting an amendment to supplement SLR-024 to provide the supporting documentation not included with the original supplement. The supplement is for the addition of the term "hyperglycemia" to the ADVERSE REACTIONS: Postintroduction Reports section of the package insert for Risperdal (risperidone) tablets and oral solution. Immediately following this letter is Form 356h, a copy of the original supplement cover letter, table of contents, marked and clean copies of the package insert, and two supporting safety reports.

For your convenience, this amendment is being supplied with a CD-ROM as a review aid. This CD-ROM has been virus scanned using McAfee VirusScan (virus Definition 4.0.4064/Scan Engine E 4.0.25) and is virus free.

Please contact me at (609) 730-2712 if you have any questions regarding this submission.

Sincerely,



Susan J. Merchant
Manager, Regulatory Affairs

cc: S. Hardeman (DNDP RMO)

JJRP 00557338
Confidential/Produced in Litigation Pursuant to Protective Order

D-6211.1

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. 0910-0038 Expiration Date: April 30, 2000 See OMB Statement on last page
		FOR FDA USE ONLY
		APPLICATION NUMBER
APPLICANT INFORMATION		
NAME OF APPLICANT Janssen Pharmaceutica Products, L.P.		DATE OF SUBMISSION 18 APR 2002
TELEPHONE NO. (Include Area Code) (609) 730-2712		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) Johnson & Johnson Pharmaceutical Research & Development, L.L.C. 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
On behalf of Janssen Pharmaceutica Products, L.P. 1125 Trenton-Harbourton Road Titusville, New Jersey 08560-0200		
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/AN 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-pyrido[1,2-a]pyrimidin-4-one		CODE NAME (if any) R064766
DOSAGE FORM: Tablet	STRENGTHS: 0.25, 0.5, 1, 2, 3, 4 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: Treatment of schizophrenia		
APPLICATION INFORMATION		
APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABREVIATED 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 ☐ PRE-SUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER		
REASON FOR SUBMISSION Amendment to CBE Labeling Supplement to NDA 20-272/SLR-024		
PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED 1	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 (combination sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CPN), DMCP 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, FMAAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application) NDA 20-588, IND 31,931		

FORM FDA 356 (4/97)

JJRP 00557339
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D-6211.2

This application contains the following items: (Check all that apply)		
X	1. Index	
X	2. Labeling (check one)	☒ Draft Labeling ☐ Final Printed Labeling
	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)	
	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))	
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)	
X	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 (d) (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, 406, 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 <i>Susan J. Merchant</i>		TYPED NAME AND TITLE Susan J. Merchant, Manager, Regulatory Affairs DATE 18 APR 2002
ADDRESS (Street, City, State, and ZIP Code) 1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560-0200		Telephone Number (609) 730-2712
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 (0910-0038) Hubert H. Humphrey Building, Room 531-B 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.
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FORM FDA 356b (4/97)

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Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1125 TRENTON-HARBOR TON ROAD, TITUSVILLE, NEW JERSEY 08560-0200

12 APR 2002

Russell Katz, MD, Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
U.S. Food and Drug Administration
Attn: Document Control Room 10B-40
1451 Rockville Pike
Rockville, MD 20852

Subject: NDA 20-272

Cross reference: NDA 20-588
RISPERDAL[®] (risperidone) Tablets and Oral Solution
Special Supplement - Changes Being Effectuated

Dear Dr. Katz:

On behalf of Janssen Pharmaceutica Products, L.P., please refer to our New Drug Application, NDA 20-272, for Risperdal (risperidone) Tablets. In accordance with 21 CFR 314.70(c)(2), Johnson & Johnson Pharmaceutical Research & Development, L.L.C. is submitting a "Special Supplement - Changes Being Effectuated" to add "hyperglycemia" to the ADVERSE REACTIONS: Postintroduction Reports section of the package insert for Risperdal (risperidone) tablets and oral solution. "Hyperglycemia" is added immediately preceding "diabetes mellitus aggravated" in the first sentence. Copies of two reports entitled, "Update of Post-Marketing Reports of Disorders of Glucose Metabolism" and "Evaluation of the effects of risperidone on glucose metabolism in Phase 2-3 clinical trials" are appended as supporting documentation for this change.

Final printed labeling will be submitted as soon as it is available and implemented immediately thereafter. Please contact me at (609) 730-2712 if you have any questions.

Sincerely,



Susan J. Merchant
Manager, Regulatory Affairs

cc: S. Hardeman (DNDP RMO)

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Marked Package Insert

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DRAFT
JANSSEN
PHARMACEUTICA
PRODUCTS, L.P.

RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{28}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:

(insert structure)

Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide, the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1mg/mL oral solution. The inactive ingredients for this solution are; tartaric acid, benzoic acid, sodium hydroxide and purified water.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that this drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (K_i of 0.12 to 7.3 nM) for the serotonin type 2 ($5HT_2$), dopamine type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® antagonizes other receptors, but with lower potency.

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RISPERDAL[®] has low to moderate affinity (K_i of 47 to 253 nM) for the serotonin 5HT_{1C}, 5HT_{1D}, and 5HT_{2A} receptors, weak affinity (K_i of 620 to 800 nM) for the dopamine D₂, and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-8}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of ¹⁴C-risperidone as a solution in three healthy male volunteers. Total recovery of radioactivity at one week was 85%, including 70% in the urine and 15% in the feces.

Risperidone is extensively metabolized in the liver by cytochrome P₄₅₀IID₆ to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating specie, and appears approximately equi-effective with risperidone with respect to receptor binding activity and some effects in animals. (A second minor pathway is *N*-dealkylation). Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. Plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) when compared to a solution. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone was 70% (CV=25%).

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is cytochrome P₄₅₀IID₆, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. Cytochrome P₄₅₀IID₆ is subject to genetic polymorphism (about 6-8% of Caucasians, and a very low percent of Asians have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers. Following oral administration of solution or tablet, mean peak plasma concentrations occurred at about 1 hour. Peak 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of risperidone was three hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Because risperidone and 9-hydroxyrisperidone are approximately equi-effective, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of risperidone and 9-hydroxyrisperidone, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours. In analyses comparing adverse reaction rates in extensive and poor metabolizers in controlled and open studies, no important differences were seen.

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Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of cytochrome $P_{450}1D_6$ could interfere with conversion of risperidone to 9-hydroxyrisperidone. This in fact occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The favorable and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number ($n=70$) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by cytochrome $P_{450}1D_6$. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (See PRECAUTIONS and DRUG INTERACTIONS).

The plasma protein binding of risperidone was about 90% over the in vitro concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of α_1 -acid glycoprotein. The plasma binding of 9-hydroxyrisperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfamethazine (100 μ g/mL), warfarin (10 μ g/mL) and carbamazepine (10 μ g/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Special Populations

Renal Impairment: In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment: While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1 -acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly: In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (See DOSAGE AND ADMINISTRATION).

Race and Gender Effects: No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4 to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed; these included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=180) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (> 20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

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Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

INDICATIONS AND USAGE

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6 to 8 weeks) controlled trials of schizophrenic inpatients (See CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS**Neuroleptic Malignant Syndrome (NMS)**

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Potential for Proarrhythmic Effects: Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12-16 mg/day, well above the recommended dose. Other drugs that prolong

the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrhythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL® treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (See DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of Risperdal® and antihypertensive medication.

Seizures: During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL® treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia: As with other drugs that antagonize dopamine D₂ receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (See CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERDAL[®] treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL[®] 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL[®] 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL[®] has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL[®] therapy does not affect them adversely.

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

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL[®] in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL[®] therapy is unknown.

Antiemetic effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with Risperdal[®] use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for RISPERDAL[®] should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with RISPERDAL[®] in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL[®] in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL[®] has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. The electrocardiograms of approximately 380 patients who received RISPERDAL[®] and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the data revealed one finding of potential concern, i.e., 8 patients taking RISPERDAL[®]

whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen in the smaller placebo group. There were 3 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²), and an increase in the free fraction of the risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (See DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance: Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed an infant if they are taking RISPERDAL®.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

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

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

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Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Fluoxetine may increase the plasma concentration of the anti-psychotic fraction (risperidone plus 9-hydroxyrisperidone) by raising the concentration of risperidone, although not the active metabolite, 9-hydroxyrisperidone.

Drugs that Inhibit Cytochrome $P_{450}IID_6$ and Other P_{450} Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome $P_{450}IID_6$, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers ($n=70$) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other P_{450} isozymes, including 1A1, 1A2, IIC9, MP, and IIIA4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome $P_{450}IID_6$: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome $P_{450}IID_6$. Therefore, RISPERDAL[®] is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

TUMOR TYPE	SPECIES	SEX	MULTIPLE OF MAXIMUM HUMAN DOSE in mg/m ² (mg/kg)	
			LOWEST EFFECT LEVEL	HIGHEST NO EFFECT LEVEL
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	None
	rat	female	0.4 (2.4)	None
	rat	male	6 (37.5)	1.5 (9.4)
Mammary gland neoplasms, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (See Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis: No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose on a mg/m² basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the human dose on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum

testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C: The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats and in one Segment II study in New Zealand rabbits. The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the human dose on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses 0.1 to 3 times the human dose on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose 1.5 times higher than the human dose on a mg/m² basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERDAL[®] therapy is unknown.

RISPERDAL[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL[®] on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone were excreted in breast milk. It has been demonstrated that risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving RISPERDAL[®] should not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL[®] did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (See PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

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

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events ($\geq 0.3\%$) associated with discontinuation and considered to be possibly or probably drug-related included:

<u>Adverse Event</u>	<u>RISPERDAL®</u>	<u>Placebo</u>
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL® related adverse event (See PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients but 3.8% in active-control patients in the phase 2-3 trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: In two 6 to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events were present at at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgasmic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Patients: The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL®-treated patients treated at doses of ≤ 10 mg/day than among placebo-treated patients in the pooled results of two 6 to 8-

week controlled trials. Patients received RISPERDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1: Treatment-Emergent Adverse Experience Incidence in 6 to 8-Week Controlled Clinical Trials¹

	RISPERDAL®		Placebo
Body System/ Preferred Term	≤ 10 mg/day (N = 324)	16 mg/day (N = 77)	(N = 142)
Psychiatric Disorders			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Nervous System			
Extrapyramidal symptoms ²	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal System			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%

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Toothache	2%	0%	0%
Respiratory System			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a Whole			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

¹ Events reported by at least 1% of patients treated with RISPERDAL[®] ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL[®] 16 mg/day and placebo are provided as well. Events for which the RISPERDAL[®] incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

² Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '≤ 10 mg/day' group and

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placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (See DOSE DEPENDENCY OF ADVERSE EVENTS).

Dose Dependency of Adverse Events:

Extrapyramidal symptoms: Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing four fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events: Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL[®] (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p < 0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

Vital Sign Changes: RISPERDAL[®] is associated with orthostatic hypotension and tachycardia (See PRECAUTIONS).

Weight Changes: The proportions of RISPERDAL[®] and placebo-treated patients meeting a weight gain criterion of $\geq 7\%$ of body weight were compared in a pool of 6 to 8-week placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL[®] (18%) compared to placebo (9%).

Laboratory Changes: A between group comparison for 6 to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL[®]/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology,

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or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (See PRECAUTIONS).

ECG Changes: The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (See WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® (risperidone) were administered to 2607 patients in phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology (Note: These events are marked with an asterisk in the listings that follow).

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders: *Frequent:* increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction,

euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: *Frequent:* increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoaesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-intestinal Disorders: *Frequent:* anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: *Frequent:* fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: *Infrequent:* hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders: *Frequent:* increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: *Infrequent:* palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders: *Infrequent:* abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: *Infrequent:* hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders: *Frequent:* polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-skeletal System Disorders: *Infrequent:* myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female: *Frequent:* menorrhagia*, orgasmic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: *Infrequent:* increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: *Infrequent:* epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: *Rare:* tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: *Infrequent:* anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male: *Frequent:* erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders: *Rare:* leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders: *Rare:* gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: *Rare:* bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, *hyperglycemia*, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving Risperdal®. A causal relationship with Risperdal® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychologic Dependence: RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

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OVERDOSAGE

Human Experience: Premarketing experience included eight reports of acute Risperdal® overdose with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure. Postmarketing experience includes reports of acute Risperdal® overdose, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia and hypotension. Other adverse events reported since market introduction which were temporally, (but not necessarily causally) related to RISPERDAL® overdose, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage: In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose: RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early short-term clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent short-term controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. In a long-term controlled trial in stable patients, RISPERDAL® was administered on a QD schedule at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1 - 2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in short-term clinical trials supporting effectiveness of RISPERDAL®, however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy: While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

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

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of the risperidone, possibly resulting in an enhanced effect (See CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for

whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (See PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL[®], the initial titration schedule should be followed.

Switching from Other Antipsychotics: There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL[®], or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL[®] therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

RISPERDAL[®] (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "1" and the strength "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL[®] (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

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Tests indicate that Risperdal® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

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R. 7148

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F).
Protect from light and moisture.

Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F).

Protect from light and freezing.

Keep out of reach of children.

75032207503221

US Patent 4,804,663

January *February* 2002, *April* 2002

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RISPERDAL® tablets are manufactured by:

JOLLC, Gurabo, Puerto Rico or
Janssen-Cilag, SpA, Latina, Italy

RISPERDAL® oral solution is manufactured by:

Janssen Pharmaceutica N.V.
Beerse, Belgium

RISPERDAL® tablets and oral solution are distributed by:

Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

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PHARMACEUTICA
PRODUCTS, L.P.

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Clean Package Insert

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D-6211.31

DRAFT
JANSSEN
PHARMACEUTICA
PRODUCTS, L.P.

RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:

(insert structure)

Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide, the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1mg/mL oral solution. The inactive ingredients for this solution are: tartaric acid, benzoic acid, sodium hydroxide and purified water.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that this drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (K_i of 0.12 to 7.3 nM) for the serotonin type 2 ($5HT_2$), dopamine type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® antagonizes other receptors, but with lower potency.

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RISPERDAL® has low to moderate affinity (K_i of 47 to 253 nM) for the serotonin 5HT₁₀, 5HT_{1D}, and 5HT_{1A} receptors, weak affinity (K_i of 620 to 800 nM) for the dopamine D₁ and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-6}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of ¹⁴C-risperidone as a solution in three healthy male volunteers. Total recovery of radioactivity at one week was 85%, including 70% in the urine and 15% in the feces.

Risperidone is extensively metabolized in the liver by cytochrome P₄₅₀IID₆ to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating specie, and appears approximately equi-effective with risperidone with respect to receptor binding activity and some effects in animals. (A second minor pathway is *N*-dealkylation). Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. Plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) when compared to a solution. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone was 70% (CV=25%).

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is cytochrome P₄₅₀IID₆, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. Cytochrome P₄₅₀IID₆ is subject to genetic polymorphism (about 6-8% of Caucasians, and a very low percent of Asians have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers. Following oral administration of solution or tablet, mean peak plasma concentrations occurred at about 1 hour. Peak 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of risperidone was three hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Because risperidone and 9-hydroxyrisperidone are approximately equi-effective, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of risperidone and 9-hydroxyrisperidone, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours. In analyses comparing adverse reaction rates in extensive and poor metabolizers in controlled and open studies, no important differences were seen.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of cytochrome P₄₅₀IID₆ could interfere with conversion of risperidone to 9-hydroxyrisperidone. This in fact occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The favorable and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by cytochrome P₄₅₀IID₆. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (See PRECAUTIONS and DRUG INTERACTIONS).

The plasma protein binding of risperidone was about 90% over the in vitro concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of α_1 -acid glycoprotein. The plasma binding of 9-hydroxyrisperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfamethazine (100 μ g/mL), warfarin (10 μ g/mL) and carbamazepine (10 μ g/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Special Populations

Renal Impairment: In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL[®] doses should be reduced in patients with renal disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment: While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1 -acid glycoprotein. RISPERDAL[®] doses should be reduced in patients with liver disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly: In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (See DOSAGE AND ADMINISTRATION).

Race and Gender Effects: No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4 to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed; these included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (> 20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

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Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

INDICATIONS AND USAGE

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6 to 8 weeks) controlled trials of schizophrenic inpatients (See CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS**Neuroleptic Malignant Syndrome (NMS)**

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) Immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Potential for Proarrhythmic Effects: Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12-16 mg/day, well above the recommended dose. Other drugs that prolong

the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrhythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL® treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (See DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of Risperdal® and antihypertensive medication.

Seizures: During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL® treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia: As with other drugs that antagonize dopamine D₂ receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (See CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERDAL[®] treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL[®] 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL[®] 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL[®] has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL[®] therapy does not affect them adversely.

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

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL[®] in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL[®] therapy is unknown.

Antiemetic effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with Risperdal[®] use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for RISPERDAL[®] should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with RISPERDAL[®] in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL[®] in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL[®] has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. The electrocardiograms of approximately 380 patients who received RISPERDAL[®] and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the data revealed one finding of potential concern, i.e., 8 patients taking RISPERDAL[®]

whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen in the smaller placebo group. There were 3 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²), and an increase in the free fraction of the risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (See DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance: Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed an infant if they are taking RISPERDAL®.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

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

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

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Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Fluoxetine may increase the plasma concentration of the anti-psychotic fraction (risperidone plus 9-hydroxyrisperidone) by raising the concentration of risperidone, although not the active metabolite, 9-hydroxyrisperidone.

Drugs that Inhibit Cytochrome $P_{450}IID_6$ and Other P_{450} Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome $P_{450}IID_6$, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other P_{450} isozymes, including 1A1, 1A2, 11C9, MP, and 11A4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome $P_{450}IID_6$: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome $P_{450}IID_6$. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

TUMOR TYPE	SPECIES	SEX	MULTIPLE OF MAXIMUM HUMAN DOSE in mg/m ² (mg/kg)	
			LOWEST EFFECT LEVEL	HIGHEST NO EFFECT LEVEL
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas Mammary gland neoplasms, Total	mouse	female	0.2 (2.4)	None
	rat	female	0.4 (2.4)	None
	rat	male	6 (37.5)	1.5 (9.4)
	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (See Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis: No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose on a mg/m² basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the human dose on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum

testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C: The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats and in one Segment II study in New Zealand rabbits. The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the human dose on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses 0.1 to 3 times the human dose on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose 1.5 times higher than the human dose on a mg/m² basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERDAL[®] therapy is unknown.

RISPERDAL[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL[®] on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone were excreted in breast milk. It has been demonstrated that risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving RISPERDAL[®] should not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL[®] did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (See PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

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

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events ($\geq 0.3\%$) associated with discontinuation and considered to be possibly or probably drug-related included:

<u>Adverse Event</u>	<u>RISPERDAL®</u>	<u>Placebo</u>
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL® related adverse event (See PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients but 3.8% in active-control patients in the phase 2-3 trials.

Incidence In Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: In two 6 to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events were present at at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgasmic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Patients: The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL®-treated patients treated at doses of ≤ 10 mg/day than among placebo-treated patients in the pooled results of two 6 to 8-

week controlled trials. Patients received RISPERDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1: Treatment-Emergent Adverse Experience Incidence in 6 to 8-Week Controlled Clinical Trials¹

	RISPERDAL®		Placebo
Body System/ Preferred Term	≤ 10 mg/day (N = 324)	16 mg/day (N = 77)	(N = 142)
Psychiatric Disorders			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Nervous System			
Extrapyramidal symptoms ²	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal System			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva Increased	2%	0%	1%

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Toothache	2%	0%	0%
Respiratory System			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a Whole			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

¹ Events reported by at least 1% of patients treated with RISPERDAL[®] ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL[®] 16 mg/day and placebo are provided as well. Events for which the RISPERDAL[®] incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

² Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '≤ 10 mg/day' group and

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placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (See DOSE DEPENDENCY OF ADVERSE EVENTS).

Dose Dependency of Adverse Events:

Extrapyramidal symptoms: Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing four fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events: Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p < 0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

Vital Sign Changes: RISPERDAL® is associated with orthostatic hypotension and tachycardia (See PRECAUTIONS).

Weight Changes: The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of $\geq 7\%$ of body weight were compared in a pool of 6 to 8-week placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes: A between group comparison for 6 to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology,

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or urinalysis parameters. Similarly, there were no RISPERDAL[®]/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL[®] administration was associated with increases in serum prolactin (See PRECAUTIONS).

ECG Changes: The electrocardiograms of approximately 380 patients who received RISPERDAL[®] and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL[®] whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (See WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL[®]

During its premarketing assessment, multiple doses of RISPERDAL[®] (risperidone) were administered to 2607 patients in phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL[®] varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology (Note: These events are marked with an asterisk in the listings that follow).

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL[®] who experienced an event of the type cited on at least one occasion while receiving RISPERDAL[®]. All reported events are included except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL[®], they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders: *Frequent:* increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction,

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euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: *Frequent:* increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoaesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-intestinal Disorders: *Frequent:* anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: *Frequent:* fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: *Infrequent:* hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders: *Frequent:* increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: *Infrequent:* palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders: *Infrequent:* abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: *Infrequent:* hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders: *Frequent:* polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-skeletal System Disorders: *Infrequent:* myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female: *Frequent:* menorrhagia*, orgasmic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: *Infrequent:* increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: *Infrequent:* epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: *Rare:* tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: *Infrequent:* anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male: *Frequent:* erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders: *Rare:* leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders: *Rare:* gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: *Rare:* bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, hyperglycemia, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving Risperdal®. A causal relationship with Risperdal® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychologic Dependence: RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

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OVERDOSAGE

Human Experience: Premarketing experience included eight reports of acute Risperdal[®] overdose with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure. Postmarketing experience includes reports of acute Risperdal[®] overdose, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia and hypotension. Other adverse events reported since market introduction which were temporally, (but not necessarily causally) related to RISPERDAL[®] overdose, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage: In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL[®]. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose: RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early short-term clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent short-term controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. In a long-term controlled trial in stable patients, RISPERDAL® was administered on a QD schedule at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1 - 2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in short-term clinical trials supporting effectiveness of RISPERDAL®, however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy: While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

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

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of the risperidone, possibly resulting in an enhanced effect (See CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for

whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (See PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL[®], the initial titration schedule should be followed.

Switching from Other Antipsychotics: There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL[®], or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL[®] therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

RISPERDAL[®] (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL[®] (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

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Tests indicate that Risperdal® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

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R. 7173

Storage and Handling

RISPERDAL[®] tablets should be stored at controlled room temperature 15°-25°C (59°-77°F).
Protect from light and moisture.

Keep out of reach of children.

RISPERDAL[®] 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F).

Protect from light and freezing.

Keep out of reach of children.

7503221

US Patent 4,804,663

February 2002, April 2002

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RISPERDAL[®] tablets are manufactured by:

JOLLC, Gurabo, Puerto Rico or
Janssen-Cilag, SpA, Latina, Italy

RISPERDAL[®] oral solution is manufactured by:

Janssen Pharmaceutica N.V.
Beerse, Belgium

RISPERDAL[®] tablets and oral solution are distributed by:

Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

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DRUG SAFETY AND SURVEILLANCE REPORT	
R - number: R064766	Non-proprietary name: Risperidone
GRIPS No.: EDMS-PSDB-1633862	Report Date: 17 January 2002
Title:	Drug Safety and Surveillance update of Post-Marketing Reports of Disorders of Glucose Metabolism
Authors:	D. Upmalis
Department:	Drug Safety and Surveillance

CONFIDENTIALITY STATEMENT

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This trial was performed according to the principles of Good Clinical Practice.

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1. Introduction

The CPMP Pharmacovigilance Working Party (January 2000) raised the question of whether there is a possible class effect for atypical neuroleptics concerning an influence on glucose metabolism resulting in impaired glucose intolerance/diabetes mellitus. The Swedish Medical Products Agency (MPA) was appointed to analyze this question on behalf of the Pharmacovigilance Working Party. In a request, dated 10 April 2000, the MPA requested the Janssen-Cilag affiliate in Sweden to compile all clinical reports regarding the influence of risperidone on glucose metabolism. The UK Medicines Control Agency and US Food and Drug Administration (FDA) made similar, but not identical requests in 2000 also. The response to the US FDA summarized the nonclinical, clinical and pharmacovigilance data available for risperidone regarding the occurrence of diabetes and other disturbances in glucose metabolism¹. The response to FDA was also submitted to the MCA and MPA.

As a part of the full submission, the Janssen Research Foundation pharmacovigilance report reviewed worldwide reports of disturbance of glucose metabolism associated with the use of risperidone received for the period May 1993 through 31 March 2000. The report discussed 202 spontaneous case reports received over that time period. Forty-one (41) cases (20% of total AEs reported) represented newly diagnosed diabetes. It was concluded that the number of cases reported, given the extensive exposure to drug, was extremely low. Furthermore, review of the cases led to the conclusion that there did not appear to be evidence for a relationship between the use of risperidone and disturbances in glucose homeostasis.

The CPMP Pharmacovigilance Working Party produced an internal report in June 2001 after their review of the data submitted, including the pharmacovigilance data. The review included an opinion that proposed a revision to the Summary of Product Characteristics (SmPC) for Risperdal (risperidone). While a rationale was not provided, the report recommended that wording referring to hyperglycaemia and diabetes mellitus be added to the SmPC. The purpose of this document is to review those case reports received since the submission to the CPMP to determine whether there are sufficient data to change the CDS for risperidone.

2. Methods

On 25-October-2001, the pharmacovigilance database was searched for cases that had been reported since 1-April-2000, the day following the data cut-off for the previous report. Cases reported included initial and follow-up serious and non-serious reports obtained from health care professionals, physicians, regulatory agencies, the literature and from consumers. Clinical trial reports were specifically excluded, as they will be discussed in a separate document. Search terms covered those cases coded in the WHO-ART medical dictionary to: *acidosis, hypoglycemia, hyperglycemia, coma diabetic, glycosuria, glucose tolerance abnormal, hypoglycemic reaction, ketosis, diabetes mellitus, diabetes mellitus aggravated, osmolar gap abnormal, diabetes mellitus*

reactivated or ketosis. Diagnoses were defined as coded by the WHO-ART dictionary based on reporting terms.

3. Results

A total of fifty-one cases were found, reported by health care professionals, physician, consumers, Regulatory Authorities or from literature. Adverse experiences from clinical trials were not included in this review. CIOMS line listings of these cases are attached in Annex 1. A total of 34 cases were reported by health care professionals or physicians, three from regulatory authorities, and one from the literature. Thirteen cases were reported by consumers and could not be verified with health care professionals.

There are fourteen (14) cases that appear to represent new onset of diabetes mellitus and five (5) cases of hypoglycemia. Frequency of distribution of relevant reported adverse events are shown in Table 1.

Table 1. Frequency distribution of all relevant reported adverse events

REACTION TERMS	Total Number of reports (N=51)		Total Number in Previous Review (N=202)	
	N	%	N	%
Acidosis, metabolic	4	7.8	4	2.0
Blood Sugar Decreased	1	2.0	2	1.0
Blood Sugar Increased	3	5.9	13	6.4
Diabetes Mellitus	16	31.4	54	26.7
Diabetes Mellitus Aggravated	3	5.9	44	21.8
Diabetic Ketoacidosis	8	15.7	1	0.5
Hyperglycemia	12	23.5	46	22.8
Hypoglycemia	5	9.8	30	14.8
Ketosis	1	2.0	0	0

Note: more than one term may describe one case

The distribution of adverse experiences is similar to that reported in the previous review. The majority of cases reported involve hyperglycemia or diabetes mellitus. There are a number of cases of hypoglycemia reported as well.

3.1 Diabetic Ketoacidosis

One item of note is the increase in reports of diabetic ketoacidosis over the most recent reporting period. There were 8 cases coded to ketoacidosis or diabetic ketoacidosis in this report, including one that was initially reported in the previous report (JRFUSA1999000568). The one case was the only case reported in the previous report. Review of the cases coded to diabetic ketoacidosis in this report represent no clear signal that would allow attribution to risperidone. Three of these cases are poorly characterized. Of the remaining cases, one case presented with neuroleptic malignant syndrome (EMADSS2001005607). Another patient (JAOCAN2000000803) had been on

prednisolone for a renal transplant for an extended period of time and was on a number of other medications. Another patient was reported to have experienced weight gain over the four years he had been on medication (JRFUSA2000002754). Finally, one case was reported to have occurred after risperidone therapy had been discontinued (NSADSS2001013504).

3.2 Review of Selected Cases other than DKA

There are a few cases that suggest a possible link between administration of risperidone and glucose intolerance. These cases are reviewed below.

APCDSS2001001114 – This case describes a 42-year-old male, known diabetic with stable blood sugars, who was switched from olanzapine to risperidone and was reported to have experienced increased blood sugars. Previously, his sugars had ranged from 6-10 mmol/L, but went up to 14 mmol/L.

EMADSS2001001421 – This report was received from the MCA regarding a 90-year-old male who had been on risperidone 1 mg b.i.d. for four days when his blood sugars were found to be elevated (18-23 mmol/L). He was not a known diabetic but had been started on prednisolone one day earlier.

EMADSS2001001925 – This case describes an 85-year-old woman, known diabetic controlled by diet who was placed on risperidone in August 2000. In September, her blood sugar was elevated to 300 mg/dl. Risperidone was stopped, with a drop in glucose to 120-160 mg/dl. Risperidone was then re-introduced in October with a "positive" response. This case may represent a positive de-challenge and re-challenge.

JACFRA2000000661 – A 37-year-old male experienced polyuria, polydipsia and weight decrease while on risperidone, cyamemazine and zopiclone. A diagnosis of Diabetes Mellitus was made one month later (fasting glucose 20 mmol/L). Risperidone was withdrawn and the patient was said to have improved.

JACGER2000001341 – This is a report from a psychologist about a 67-year-old male who was on risperidone for approximately one month and then noted to be hyperglycemic. This was reported to have resolved after stopping risperidone.

JRFUSA2000009493 – This is a report from a consumer (not medically confirmed) regarding his diabetic, 23-year-old wife. It is stated that the patient started therapy with risperidone 3 mg/day and, on the second day of therapy, experienced hyperglycemia (300 mg/dl) requiring additional insulin.

NSADSS2001001997 – This is a report received from a physician who stated that a 42-year-old male patient had experienced diabetic ketoacidosis while on risperidone therapy. No further details were provided.

NSADSS2001008332 – This is a report from a consumer (not medically confirmed) regarding her 11-year-old son. She stated that he was diagnosed as diabetic shortly after initiating risperidone therapy. Furthermore, she has noted that his blood glucose levels are lower when he misses a dose of risperidone.

NSADSS2001009151 – This is a pharmacist report of a 54-year-old patient with known non-insulin dependent diabetes mellitus who was started on risperidone 3 mg/day and, within a matter of weeks experienced hyperglycemia, with blood sugars going from 7 to 17 mmol/L. Increase in glibenclamide dose did not control the sugars, but when therapy was changed from risperidone to perphenazine, the sugars normalized.

4. Conclusions

In the most recent periodic safety update review, covering 1-June-2000 to 31-May-2001, it was estimated that the total patient exposure over that time was 28,363,737 patient-months. As the search period for this report extends beyond both the start and stop dates of the PSUR, the 51 cases here represent an incidence over an exposure greater than that. While the number of reports is very small, there are a very few cases in this report, in addition to some cases reported earlier, that suggest that there is a possibility for very rare drug-associated events characterized by impairment of glucose metabolism.

-
- i De Smedt G, Mahmoud R, Grogg A, Derivan A. Integrated summary of the effects of risperidone on glucose metabolism and weight. Janssen Research Foundation August 2000, Integrated Summary Report. EDMS-BEBE-1788252.

De Smedt, G

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Johnson & Johnson Pharmaceutical Research and Development, L.L.C.

CLINICAL SUMMARY REPORT	
R - number: R064766	Non-proprietary name: Risperidone
EDMS PSDB-1647076	Report Date: 13 February 2002
Title:	Evaluation of the effects of risperidone on glucose metabolism in Phase 2-3 clinical trials.
Authors:	G. De Smedt, E. Eerdekens, J. Rosenberg
Department:	Global Clinical R&D and Regulatory Affairs, Worldwide, and Global Biometrics and Reporting

ABSTRACT

The data from over 9000 patients treated in short-term and nearly 5000 treated in long-term Phase 2-3 trials were collected for a review of adverse events associated with abnormalities in glucose metabolism and abnormal glucose levels.

Adverse events

The following were considered glucose-related adverse events: 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. In short-term trials (<3 months) for all age groups combined the incidence of reported glucose-related adverse events was low among risperidone-treated patients (0.69% of 6849 patients) and comparable to, if not lower than, the incidence among placebo-treated patients (0.96% of 1145 patients) and olanzapine-treated patients (0.93% of 536 patients). In the long-term trials (≥6 months), the incidence of glucose-related adverse events was lower with risperidone treatment (1.02% of 4415 patients) than with the typical agent, haloperidol (2.98% of 302 subjects). There were no placebo-controlled long-term trials.

In the short-term trials, there were no glucose-related adverse events in the pediatric population. In adults, the incidence of glucose-related adverse events was very low with risperidone treatment (0.45% of 5835 subjects) and lower than with placebo (0.60% of 501 subjects). Disturbances in glucose metabolism appeared to be age dependent. Elderly subjects had a higher incidence of glucose-related adverse events compared to younger subjects, regardless of the treatment or duration of treatment. The incidence of glucose-related adverse events was slightly higher with risperidone treatment (2.53% of 830 patients) than with placebo (1.74% of 461 patients) among the elderly.

Serious adverse events

Among all risperidone-treated patients, there was only one fatal case in which, among other symptoms, a glucose-related adverse event was present. This was an elderly patient with hyperglycemia and hyperosmolar non-ketotic state as a complication of urinary sepsis and acute renal failure.

The incidence of serious adverse events related to abnormalities in glucose metabolism with short- (0.1% of 6849 patients) or long-term (0.2% of 4415 patients) risperidone treatment was comparable to short-term placebo (0.30% of 1145 patients) or short-term haloperidol treatment (0% of 712 patients), and lower than with long-term haloperidol treatment (1% of 302 patients). No serious adverse events in the 536 patients treated with olanzapine or patients treated with neuroleptics other than haloperidol (293 and 234 patients in short-term and long-term trials, respectively) were related to abnormalities of glucose metabolism.

Discontinuations due to adverse events

The incidence of discontinuations due to adverse events related to abnormalities in glucose metabolism with risperidone treatment in short- and long-term trials (0.03% and 0.02%, respectively) was lower than for placebo treatment (0.1%, short-term only) and long-term haloperidol treatment (0.3%). No discontinuations were related to abnormalities of glucose metabolism with short-term haloperidol treatment, or in smaller groups with olanzapine or other neuroleptics.

Random glucose levels

Random glucose levels were categorized using the WHO criteria for diabetes (≥ 11 mmol/L = suggestive of diabetes; ≥ 8.9 and < 11 mmol/L = suggestive of hyperglycemia). Glucose was not measured in the pediatric trials. Among subjects with glucose levels available, there were 5274 patients with normal (≤ 7.8 mmol/L) random glucose levels at baseline. Among risperidone-treated adults with normal baseline glucose levels in short-term trials, the incidences of glucose levels suggestive of diabetes or hyperglycemia during treatment (0.4% and 0.7% of 2092 subjects, respectively) were comparable to those with placebo (0.4% and 1.2% of 257 subjects) and other treatments (0.2% and 1.7% of 464 subjects). Elderly patients had slightly higher incidences of glucose levels suggestive of diabetes or hyperglycemia (3.2% and 7.2% of 570 subjects) with risperidone relative to placebo (2.2% and 4.7% of 318 subjects) and other treatments (2.1% and 2.1% of 142 subjects). Among risperidone-treated adults in long-term trials, 1.9% had levels suggestive of diabetes and 2.2% suggestive of hyperglycemia, lower than the 3.0% incidences of hyperglycemic and diabetic levels observed for patients who received other treatments in the long-term trials. Among elderly patients in the long-term trials, 12 (4.3% of 276) had levels suggestive of diabetes, and 34 (12.3% of 276) had levels suggestive of hyperglycemia. There were no elderly comparator groups in the long-term trials.

In the subgroup of subjects with both glucose levels and medical history available (2819 in short-term trials, 936 in long-term trials), records were reviewed by a clinician for evidence of prior diabetes. The results suggest that abnormalities of glucose metabolism in this clinical database (as reflected in adverse event reports and random glucose levels) most commonly represent dysregulation or worsening of

existing diabetes rather than new-onset diabetes. In the short-term trials, among patients without pre-existing diabetes, 0.3% of the risperidone-treated and 0.8% of the placebo-treated patients had glucose-related adverse events; glucose levels were suggestive of diabetes for 0.5% of the risperidone-treated and 0.8% of the placebo-treated patients, and suggestive of hyperglycemia for 1.0% of the risperidone patients and 3.2% of the placebo patients. Among subjects with pre-existing diabetes, the rates of glucose-related adverse events were 8.0% of risperidone patients and 9.7% of the placebo patients. Among patients with pre-existing diabetes and normal glucose levels at baseline, postbaseline glucose levels were suggestive of diabetes for 9.1% of risperidone patients and 6.3% of placebo patients, and suggestive of hyperglycemia in 18.2% and 18.8% of risperidone- and placebo-treated patients, respectively.

Conclusion

The information derived from a large number of clinical trials reporting on more than 9000 subjects supports the conclusion that disturbances of glucose metabolism during risperidone treatment are very rare. Overall, the incidence of glucose-related adverse events was lower with risperidone than placebo. In the pediatric and adult population, risperidone was indistinguishable from placebo in terms of percentage of individuals with abnormalities in glucose metabolism. Elderly patients showed a slightly higher incidence of abnormalities in glucose metabolism with risperidone compared to placebo in short-term trials. Hyperglycemia and dysregulation or worsening of existing diabetes were more commonly observed than new-onset diabetes which was very rare.

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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}

Risperidone (Risperdal[®]) has been marketed world-wide in more than 70 countries since 1993. The Company Core Data Sheet lists the following indications. Risperidone 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 schizophrenic patients. Risperidone is indicated for the treatment of behavioral disturbances in patients with dementia who are aggressive, psychotic or have activity disturbances, and for conduct and other disruptive behaviour disorders in children and adults with subaverage IQ. Based on extensive clinical experience including short- and long-term use, risperidone has been shown to be well tolerated.

An evaluation of available adverse event data related to abnormalities of glucose metabolism from Phase 2- 3 trials on risperidone sponsored by Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (formerly Janssen Research Foundation) from 1 December 1985 to 1 April 2000 was performed in August 2000. This was done upon a request by the regulatory authorities to follow the effects of novel antipsychotic treatment on glucose metabolism. This clinical report updates that information with data from recent trials. In addition, random glucose levels from the Phase 3 clinical trials were evaluated.

2. SUBJECTS AND METHODS

2.1. Subjects

2.1.1. SUBJECTS EVALUATED FOR GLUCOSE-RELATED ADVERSE EVENTS IN PHASE 2-3 TRIALS

All Phase 2-3 trials in the risperidone program, that were completed and where data were fully analyzed as of November 2001, were reviewed (Table 1). The program consisted of trials with oral and depot (microspheres) formulations of risperidone. Those trials with adverse event data in a format that could be merged with the other trials were included, as shown in the table. Data from 4 of the trials (GBR-17, GER-11, BEL-6, and BEL-9, italicized in the table) 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. However, data from these trials are not expected to greatly influence the overall conclusions of this report due to the relatively small percentage (approximately 4%) of patients involved.

Indications studied included schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar mania, dementia and behavioral disturbances

(mainly in elderly patients), and conduct or other disruptive behaviour disorders (mainly in children and adolescents). Trial medication doses given for indications other than schizophrenia and other psychotic disorders were generally lower.

Data from patients treated in 64 of the Phase 2-3 trials listed in Table 1 (non-italicized) were evaluated for glucose-related adverse events (data in the electronic database). When only short-term trials (≤ 3 months) were considered, 1145 patients were treated with placebo, 6849 with risperidone, 712 with haloperidol, 536 with olanzapine, and 293 with other neuroleptics. Because BEL-11 was a cross-over trial, 37 patients provided data for both risperidone and placebo analysis and therefore were counted twice in the total number of patients evaluated for glucose-related adverse events in short-term trials.

In long-term trials (≥ 6 months), there were no patients with placebo, 4415 with risperidone, 302 with haloperidol, no patients with olanzapine, and 234 patients with other neuroleptics. These totals include patients who also participated in short-term trials, and continued into long-term extension trials.

Table 1: Phase 2-3 risperidone trials completed with full analysis of data as of Nov 2001

Trial	Total Patients	Risperidone	Haloperidol	Other Neuroleptics ^a	Olanzapine	Placebo
TRIALS IN ADULT SUBJECTS (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 ⁴	98	48	0	50	0	0
FRA-3 ⁵	62	21	20	21	0	0
GER-5 ⁶	59	39	0	20	0	0
INT-10 ⁷	211	211	0	0	0	0
INT-2 ⁸	1362	1136	226	0	0	0
INT-3 ⁹	523	348	87	0	0	88
INT-5	183	99	84	0	0	0
INT-7 ¹⁰	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	0
INT-46 ^c	150	75	0	0	0	75
INT-61	779	779	0	0	0	0
KOR-1 ¹¹	39	19	20	0	0	0
SUI-1 ¹²	86	43	0	43	0	0
USA-1 ¹³	160	53	53	0	0	54
USA-60	441	441	0	0	0	0
USA-72	246	163	0	0	0	83
USA-102 ^c	156	52	53	0	0	51
USA-112	407	202	0	0	205	0
USA-121	507	400	0	0	0	107
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
INT-32	86	86	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 ¹⁴	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 ^b	0	0
INT-47/GBR-29	58	58	0	0	0	0
INT-57 ^d	762	762	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

Table 1: Phase 2-3 risperidone trials completed with full analysis of data as of Nov 2001 (continued)

Trial	Total Patients	Risperidone	Haloperidol	Other Neuroleptics ^a	Olanzapine	Placebo
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^b	11640	9270	899	527	448	496

TRIALS IN ELDERLY SUBJECTS (>65 yrs)

Double-blind short-term trials

AUS-5 ^c	337	167				170
BEL-14	39	20	0	0	0	19
INT-24	344	115	115	0	0	114
INT-50	175	87	0	0	88	0
USA-63	625	462	0	0	0	163

Open short-term trials

BEL-6	50	50	0	0	0	0

Double-blind long-term trials

None

Open long-term trials

BEL-9	9	9	0	0	0	0
INT-23	180	180	0	0	0	0
INT-26	83	83	0	0	0	0
USA-34	22	22	0	0	0	0
USA-64	103	103	0	0	0	0
USA-70	330	330	0	0	0	0
TOTAL^d	2297	1628	115	0	88	466

TRIALS IN PEDIATRIC SUBJECTS (<18 yrs)

Double-blind short-term trials

BEL-11 ^e	37 ^f	37 ^f	0	0	0	37 ^f
BEL-24	13	6	0	0	0	7
NED-9	38	19	0	0	0	19
CAN-19	110	53	0	0	0	57
USA-93	118	55	0	0	0	63

Open short-term trials

BEL-21	6	6	0	0	0	0
BEL-22	7	7	0	0	0	0

Double-blind long-term trials

NA

Open long-term trials

CAN-20	77	77	0	0	0	0
INT-41	504	504	0	0	0	0
USA-97	107	107	0	0	0	0
TOTAL^g	1017	871	0	0	0	183

OVERALL TOTAL	14954^h	11769	1014	527	536	1145

Table 1: Phase 2-3 risperidone trials completed with full analysis of data as of Nov 2001 (continued)

- 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 in any treatment group reported a glucose-related adverse event.

- Trials marked in italics are those that were not included in the evaluation of glucose-related adverse events because their databases were not in an appropriate format for merging electronically at the time of this report. This accounted for 505 patients, all of whom received risperidone. These patients are included in the calculation of the total number of patients and the total number treated with risperidone.

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

b: Only conventional neuroleptics were used. Specific drug names are unavailable.

c: Patients in the risperidone group were simultaneously receiving a mood stabilizer. Patients in the placebo groups were taking mood stabilizer alone.

d: RIS-INT-57 permitted inclusion of elderly patients (n=75).

e: Patients enrolled in AUS-5 had to be 55 years or older. Median age was 84 years.

f: BEL-11 was a cross-over study; the same patients were counted in the risperidone as well as the placebo group. Of the 37 patients in trial BEL-11, 2 were under the age of 18.

g: Includes patients counted in more than one group. Also includes patients counted in both a short-term and long-term trial.

Source: Display GAE.2 and Clinical Trial Reports

Patients could be exposed to risperidone during double-blind trials and could continue to open-label treatment in subsequent trials. The relationship of the trials is shown in Table 2.

The open-label, long-term trial, USA-7 (n=105 with 5 patients having glucose-related adverse events) was the only trial that followed other open-label, long-term trials. These 105 patients were counted only once, in their first open-label, long term trial (USA-6, USA-5, or USA-9).

Table 2: 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)	
CAN-19 (110) →	CAN-20 (77) + INT-41 (23)	

Numbers in parentheses are the numbers of patients included.

2.1.2. SUBJECTS EVALUATED FOR LABORATORY GLUCOSE DATA

Analysis of glucose levels was based on Phase 3 trials for which the protocol specified the collection of glucose laboratory data (Table 3). In none of the pediatric trials were glucose levels determined.

Table 3: Phase 3 trials with glucose data available

Trial	Total Patients	Risperidone	Haloperidol	Other Neuroleptic ^a	Olanzapine	Placebo
TRIALS IN ADULT SUBJECTS (18-65 yrs)						
Double-blind short-term trials						
FIN-1	98	48	0	50	0	0
INT-10	211	211	0	0	0	0
INT-2	1362	1136	226	0	0	0
INT-3	523	348	87	0	0	88
INT-5	183	99	84	0	0	0
INT-9	149	75	0	74	0	0
INT-46 ^b	150	75	0	0	0	75
SUI-1	86	43	0	43	0	0
USA-1	160	53	53	0	0	54
USA-60	441	441	0	0	0	0
USA-72	246	163	0	0	0	83
USA-102 ^b	156	52	53	0	0	51
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						
INT-12	483	483	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 ^c	105	105	0	0	0	0
USA-9	107	107	0	0	0	0
TOTAL^d	5252	3929	805	167	0	35
TRIALS IN ELDERLY SUBJECTS (>65 yrs)						
Double-blind short-term trials						
AUS-5 ^c	337	167				170
INT-24	344	115	115	0	0	114
INT-50	175	87	0	0	88	0
USA-63	625	462	0	0	0	163
Open long-term trials						
INT-23	180	180	0	0	0	0
INT-26	83	83	0	0	0	0
USA-70	330	330	0	0	0	0
TOTAL^d	2074	1424	115	0	88	798
OVERALL TOTAL^d	7326	5353	920	167	88	798

Trials marked in italics are those with medical history information available.

a: Other neuroleptics include zuclopenthixol (FIN-1), remoxipride (INT-9), clozapine (SUI-1), and olanzapine (INT-50).

b: In trials INT-46 and USA-102, patients who received placebo/haloperidol during the double-blind phase and then received risperidone during the open-label phase were counted in both the risperidone and placebo/haloperidol groups for this analysis.

c: Patients enrolled in AUS-5 had to be 55 years or older. Median age was 84 years.

d: Includes patients counted in more than one group. Also includes patients counted in both a short-term and long-term trial.

2.1.2.1. Patients with medical history information

A subset of patients in the glucose laboratory database had specific information recorded about their medical history. The short-term trials with this data available were AUS-5, INT-2, INT-24, INT-46, INT-5, INT-50, and USA-102, with a total of 2707 distinct patients. Long-term trials were INT-6, INT-12, INT-23, and INT-26, with a total of 936 distinct patients. All are italicized in Table 3.

2.2. Methods of analysis

2.2.1. GLUCOSE-RELATED ADVERSE EVENTS

In the population described in section 2.1.1, the incidence of adverse events related to abnormalities of glucose metabolism (glucose-related) adverse events was determined. The events summarized are worsenings of pre-existing conditions, or newly diagnosed diabetes or abnormalities in glucose metabolism. The following were considered glucose-related adverse events: 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.

Pre-trial adverse events and post-trial/follow-up non-serious adverse events were excluded from the summary tabulations.

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 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), and by age. Adverse events were described in detail if they were serious or if death or discontinuation occurred due to a glucose-related adverse event. In addition, the incidence of glucose-related adverse events among the population described in section 2.1.2.1 was summarized by history of pre-existing diabetes.

2.2.2. RANDOM GLUCOSE LEVELS

Glucose levels were examined in the subject sample as described in section 2.1.2. Because fasting conditions were not required, results were treated as random samples. Using the WHO criteria for diabetes¹⁵, subjects with a glucose level ≤ 7.8 mmol/L at baseline were considered to have a normal value. Levels ≥ 8.9 mmol/L and < 11 mmol/L during the trial were categorized as suggestive of hyperglycemia. Levels ≥ 11 mmol/L were categorized as suggestive of diabetes. The incidence of glucose levels

beyond these limits among patients with normal baseline levels was examined by trial duration, by age, and by history of diabetes.

2.2.3. MEDICAL HISTORY

In the database used for analysis of glucose levels, a physician reviewed the subjects' medical histories, when available, to determine the presence of diabetes at baseline. (See section 2.1.2.1.)

3. RESULTS

3.1. Adverse events related to abnormalities in glucose metabolism

3.1.1. OVERALL INCIDENCE

Table 4 shows the incidence of glucose-related adverse events in short-term trials only. The incidence with risperidone treatment (0.69% of 6849 patients) was very low and comparable to, if not lower than, with placebo or olanzapine. Relative to haloperidol and other neuroleptics (0.28% of 712 patients and 0.34% of 293, respectively) the incidence was higher with both risperidone and placebo. Other neuroleptics included zuclopenthixol (FIN-1), perphenazine (INT-7), remoxipride (INT-9), clozapine (GER-5, SUI-1), methotrimeprazine (FRA-3).

Table 4: 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=1145	Risperidone N=6849	Haloperidol N=712	Olanzapine N=536	Other Neuroleptics ^a N=293
Any glucose-related adverse event	11 (0.96%)	47 (0.69%)	2 (0.28%)	5 (0.93%)	1 (0.34%)
Acidosis	0	1 (0.01%)	0	0	0
Blood sugar increased	0	2 (0.03%)	0	0	0
Coma diabetic ^b	0	1 (0.01%)	0	0	0
Diabetes mellitus	1 (0.09%)	7 (0.1%)	0	2 (0.37%)	1 (0.34%)
Diabetes mellitus aggravated	0	2 (0.03%)	0	0	0
Glycosuria	0	2 (0.03%)	0	1 (0.19%)	0
Hyperglycaemia	7 (0.61%)	28 (0.41%)	2 (0.28%)	3 (0.56%)	0
Hypoglycaemia	3 (0.26%)	7 (0.1%)	0	0	0
Ketosis	0	1 (0.01%)	0	0	0
Plasma osmolality increased	0	1 (0.01%)	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, AUS-5, INT-32, INT-50, INT-61, USA-121

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 and died one day later.

Source: Display GAE.1, GAE.4, GAE.4A GLUCOSE

In long-term trials, there was a lower incidence of glucose-related adverse events with risperidone treatment (1.02 % of 4415 patients) or other neuroleptics (0% of 293 patients) than with haloperidol treatment (2.98% of 302 patients) (Table 5). There were no long-term, double-blind trials with placebo or olanzapine.

Table 5: 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=4415	Haloperidol N=302	Other neuroleptics ^a N=234
Any glucose-related adverse event	45 (1.02%)	9 (2.98%)	0
Acidosis	1 (0.02%)	0	0
Diabetes mellitus	12 (0.27%)	5 (1.66%)	0
Glycosuria	5 (0.11%)	0	0
Hyperglycaemia	25 (0.57%)	5 (1.66%)	0
Hypoglycaemia	5 (0.11%)	1 (0.33%)	0
Ketosis	1 (0.02%)	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, CAN-20, INT-41, INT-57

a: Conventional neuroleptics, not specified (INT-17)

Source: Display GAE.1, GAE.4, GAE.4A GLUCOSE

3.1.2. SERIOUS ADVERSE EVENTS AND DISCONTINUATIONS DUE TO ADVERSE EVENTS RELATED TO ABNORMALITIES IN GLUCOSE METABOLISM

The incidence of serious adverse events related to abnormalities in glucose metabolism with short-term risperidone treatment (0.1% of 6849 patients) was comparable to, if not lower than, short-term placebo (0.30% of 1145 patients) or short-term haloperidol treatment (0% of 712 patients). No serious adverse events with neuroleptics other than haloperidol were related to abnormalities of glucose metabolism. The incidence of discontinuations due to adverse events related to abnormalities in glucose metabolism with risperidone treatment in short-term trials (0.03%) was lower than for placebo treatment (0.1%). No discontinuations due to adverse events related to abnormalities of glucose metabolism were reported in the groups treated with olanzapine or neuroleptics other than haloperidol in short-term trials (Table 6). However, the number of subjects in these groups was too small to draw any conclusions.

One fatal outcome was reported (#1204 in trial USA-63) and concerned an 85-year-old black man. He had a history of multiple medical problems, including insulin-dependent diabetes and chronic renal insufficiency. He discontinued treatment with risperidone after 13 days, when he was hospitalized 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 hyperosmolarity syndrome, and died one day later. The investigator considered the adverse events unrelated to trial medication.

Table 6: Incidence of deaths, serious adverse events and discontinuations due to adverse events related to abnormalities in glucose metabolism in short-term trials

	Placebo N=1145	Risperidone N=6849	Haloperidol N=712
Deaths	0	1 (0.01%) ^{a,b}	0
Serious adverse events	4 (0.30%)	7 (0.1%)	0
Discontinuations due to adverse events	1 (0.1%)	2 (0.03%)	0

a: One patient (#4113 in USA-63) died from non-glucose-related adverse events but did report a glucose-related adverse event during treatment. The narrative is included for completeness in Annex 1 but is not included in the summary table.

b: Although originally coded as "coma diabetic", this elderly patient (#1204 in USA-63) experienced hyperglycemia with a hyperosmolar non-ketotic state as a complication of urinary sepsis and acute renal failure.

No deaths, discontinuations 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, FRA-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 AUS-5, INT-32, INT-61, INT-50, USA-121,

Source: Display GAE.5A GLUCOSE, GAE.5B GLUCOSE, GAE.5C GLUCOSE and Clinical Trial Reports

The incidence of serious adverse events with long-term risperidone treatment (0.2% of 4415 patients) was lower than with long-term haloperidol treatment (1% of 302

patients). The incidence of discontinuations in long-term trials was lower in patients receiving risperidone (0.02%) than in those receiving haloperidol (0.3%) (Table 7).

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

	Placebo	Risperidone	Haloperidol
	N=0	N=4415	N=302
Deaths	—	0 ^a	0
Serious adverse events	—	8 (0.2%)	3 (1.0%)
Discontinuations due to adverse events	—	1 (0.02%)	1 (0.3%)

a: One patient (#A00367 from INT-23) died from non-glucose-related adverse events but did report a glucose-related adverse event during treatment. The narrative is included for completeness in Annex 1 but not included in the summary table.

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

Trials: 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, INT-57, CAN-20, INT-41

Source: Display GAE.5A GLUCOSE, GAE.5B GLUCOSE, GAE.5C GLUCOSE and Clinical Trial Reports

Glucose-related serious adverse events are listed in Table 8. Among 15 risperidone-treated patients who had a serious adverse event, 6 patients experienced hyperglycemia, 6 patients experienced diabetes mellitus (worsening or new onset), and 4 patients experienced hypoglycemia. The patient who died had a serious adverse event listed as diabetic coma (described above). Nine (9) of those patients had a pre-existing glucose-related condition. Among haloperidol-treated patients, serious adverse events included diabetes mellitus, hypoglycemia, and hyperglycemia. Serious adverse events among placebo patients were uncontrolled diabetes, hypoglycemia, and hyperglycemia.

Four (4) of the 5 patients who discontinued due to adverse events related to abnormalities in glucose metabolism were elderly. Three (3) of the 5 patients who discontinued had pre-existing abnormalities in glucose metabolism.

Individual narratives for deaths, other serious adverse events and adverse events leading to discontinuation are provided in Annex 1.

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)					
INT-61 (Double-blind short-term)					
A30445 ^a	RIS oral	Hyperglycemia		X	
A30755	RIS oral	Diabetes mellitus		X	
USA-79 (Double-blind long-term)					
0054	RIS	Diabetes mellitus		X	
0601 ^a	RIS	Diabetes mellitus		X	
0084 ^a	HAL	Diabetes mellitus Hypoglycemia		X	
0302	HAL	Diabetes mellitus		X	
0349 ^a	HAL	Hyperglycemia	X	X	
INT-45 (Double-blind short-term)					
A30142 ^a	RIS	Hyperglycemia Hypoglycemia		X	
USA-102 (Double-blind short-term)					
A30030	PLA	Uncontrolled diabetes		X	
USA-6 (Open-label long-term)					
0254	RIS	Hypoglycemia		X ^b	
ELDERLY (>65 years)					
AUS-5 (Double-blind short-term)					
160	PLA	Hypoglycemia		X	
USA-63 (Double-blind short-term)					
0911 ^a	PLA	Hyperglycemia		X	
4113 ^{a,d}	PLA	Hyperglycemia	X	X	(X ^c)
0115 ^a	RIS	Hypoglycemia		X	
1204 ^d	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 long-term)					
A00118 ^a	RIS	Diabetes mellitus		X	
A00367	RIS	Hypoglycemia		X	(X ^c)
USA-70 (Open-label long-term)					
2916 ^a	RIS	Diabetes mellitus		X	
4118	RIS	Hyperglycemia	X	X	
4206	RIS	Hyperglycemia		X	
TOTAL			5^c	22	1^c

Table 8: Patients who died, had serious adverse events or discontinued due to glucose-related adverse events (continued)

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

A patient narrative is provided in Annex 1 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 an endocrine disorder other than a glucose-related one.

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

c: Patient 0076 from trial USA-79 (HAL) was listed in the August 2000 report as having discontinued due to a glucose-related event, but is not included in this table as the discontinuation was due to other reasons. A narrative is provided.

d: This patient died but the cause of death was not due to a glucose-related adverse event. A narrative is provided in Annex 1 for completeness.

e: One patient is indicated because this 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.

3.1.3. SUBGROUP ANALYSIS

3.1.3.1. Age

Overall, the incidence of glucose-related adverse events in all age groups was very low. Incidence of glucose-related adverse events appeared to be age-dependent, with elderly patients having a higher incidence than younger groups regardless of 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.^{16, 17}

In the short-term trials, there were no glucose-related adverse events in the pediatric population. In adults, the incidence of glucose-related adverse events was low with risperidone treatment (0.45% of 5835 subjects) and comparable to, if not lower than, with placebo (0.60% of 501 subjects). Elderly patients treated with risperidone showed a slightly higher incidence of adverse events compared to placebo-treated patients (2.53% of 830 subjects and 1.74% of 461 subjects, respectively) (Table 9).

In long-term trials, the incidence of glucose-related adverse events was 0.15% of 688 pediatric subjects, 0.74% of 2958 adults, and 2.86% of 769 elderly among risperidone-treated patients. The incidence was 2.98% among 302 haloperidol-treated adults and 0% for the 234 adults who received other neuroleptics. There were no comparator groups of elderly or pediatric subjects (Table 9).

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

Trial duration Treatment	Pediatric		Adult		Elderly	
	<18 years		18 - 65 years		>65 years	
	N	n (%)	N	n (%)	N	n (%)
Short-term trial (≤3 months)						
Placebo	183	0	501	3 (0.60%)	461	8 (1.74%)
Risperidone	184	0	5835	26 (0.45%)	830	21 (2.53%)
Haloperidol	—	—	597	1 (0.17%)	115	1 (0.87%)
Olanzapine	—	—	458	4 (0.87%)	78	1 (1.28%)
Other Neuroleptic	—	—	293	1 (0.34%)	—	—
Long-term trial (≥6 months)						
Risperidone	688	1 (0.15%)	2958	22 (0.74%)	769	22 (2.86%)
Haloperidol	—	—	302	9 (2.98%)	—	—
Other Neuroleptic	—	—	234	0	—	—

Source: Display GAE.5, Table GAE.4A.AGE.GLUCOSE

3.1.3.2. Medical history of diabetes

In the population described in section 2.1.2.1, there were 116 distinct patients with pre-existing diabetes and 2591 distinct patients without pre-existing diabetes in the short-term trials. Among patients with no prior history of diabetes, the percentage with glucose-related adverse events was low (0.3%) with risperidone, and similar to groups treated with placebo (0.8%) and other neuroleptics (0.4%) in short-term trials (Table 10).

Table 10: Incidence of glucose-related adverse events by medical history in short-term trials

	No pre-existing diabetes			Pre-existing diabetes		
	RIS	Placebo	Other	RIS	Placebo	Other
Subjects with medical history	1793	379	531	50	31	35
Glucose-related adverse event	5 (0.3%)	3 (0.8%)	2 (0.4%)	4 (8.0%)	3 (9.7%)	1 (2.9%)
Hyperglycemia	4 (0.2%)	1 (0.3%)	2 (0.4%)	4 (8.0%)	2 (6.5%)	0
Glycosuria	1 (0.1%)	0	0 (0%)	0	0	0
Diabetes mellitus	0	1 (0.3%)	0	0	0	1 (2.9%)
Hypoglycemia	0	1 (0.3%)	0	0	1 (3.2%)	0

Source: Table GAE.6A.diab.glucose

In long-term trials, 40 distinct patients had pre-existing diabetes and 896 distinct patients did not. Among patients without prior history of diabetes one patient had a glucose-related adverse event. There were few events among those with a positive prior history but the number of patients with data available was too small for any firm conclusions (38 risperidone-treated patients) (Table 11).

Table 11: Incidence of glucose-related adverse events by medical history in long-term trials

	No pre-existing diabetes		Pre-existing diabetes	
	RIS	Other	RIS	Other
Subjects with medical history	799	97	38	2
Glucose-related adverse event	1 (0.1%)	0	3 (7.9%)	0
Acidosis	0	0	1 (2.6%)	0
Hyperglycemia	0	0	1 (2.6%)	0
Diabetes mellitus	0	0	1 (2.6%)	0
Hypoglycemia	1 (0.1%)	0	0	0

Source: Table GAE.6A.diab.glucose

3.1.3.3. Age and medical history of diabetes

The subgroups described in section 3.1.3.2 above were further subdivided by age. All glucose-related adverse events among patients in short-term trials with a prior history of diabetes (Table 10) occurred in patients older than age 65. In the long-term trials the subgroups of patients with a history of diabetes were simply too small to consider (27 risperidone-treated adults, 11 risperidone-treated elderly) (Display GAE.6A.diab.age.glucose).

3.2. Random glucose levels suggestive for disturbances in glucose metabolism**3.2.1. OVERALL INCIDENCE**

Random glucose levels were available in short-term trials for 3862 patients. In the short-term trials, the percentage of glucose levels suggestive of diabetes (≥ 11 mmol/L) in patients with baseline levels ≤ 7.8 mmol/L was comparable among the different treatment groups. The percentage with levels suggestive of hyperglycemia (≤ 8.9 and < 11 mmol/L) was lower with risperidone (2.1% of 2676 patients) than placebo treatment (3.1% of 575 patients) (Table 12).

Table 12: Incidence of elevated glucose levels in short-term trials

Glucose levels at any postbaseline time	Risperidone	Placebo	Other
Suggestive of diabetes	26/2676 (1.0%)	8/575 (1.4%)	4/611 (0.7%)
Suggestive of hyperglycemia	56/2676 (2.1%)	18/575 (3.1%)	12/611 (2.0%)

Patients with random glucose levels at baseline ≤ 7.8 mmol/L.

Source: Display SAF.1A glucose

In the long-term trials the percentage of levels suggestive of diabetes was 2.5% for risperidone-treated patients and 3.0% for patients treated with other neuroleptics. The percentage of patients with levels suggestive of hyperglycemia was 4.6% in the risperidone group and 3.0% in the "other" group (Table 13).

Table 13: Incidence of elevated glucose levels in long-term trials

Glucose levels at any postbaseline time	Risperidone	Other
Suggestive of diabetes	29/1182 (2.5%)	7/230 (3.0%)
Suggestive of hyperglycemia	54/1182 (4.6%)	7/230 (3.0%)

Patients with random glucose levels at baseline ≤ 7.8 mmol/L.

Source: Display SAF.1A glucose

3.2.2 SUBGROUP ANALYSIS

3.2.2.1. Age

Because incidence of diabetes in the general population increases with age, the data were also examined by age group. In addition to the expected age relationship, there appeared to be a slightly higher incidence of abnormal glucose levels among elderly patients treated with risperidone than those treated with placebo or other neuroleptics in short-term trials. In contrast, among adults the percentages for risperidone were similar to, if not lower than, those for other treatments (Table 14). In long-term trials, the percentage of glucose abnormalities was lower among adult patients receiving risperidone than those receiving other treatment; there was no comparator group for elderly patients in long-term trials. (Table 15).

Table 14: Incidence of elevated glucose levels in short-term trials by age

Glucose levels at any postbaseline time	Risperidone	Placebo	Other
Adults			
Suggestive of diabetes	8/2092 (0.4%)	1/257 (0.4%)	1/464 (0.2%)
Suggestive of hyperglycemia	15/2092 (0.7%)	3/257 (1.2%)	8/464 (1.7%)
Elderly			
Suggestive of diabetes	18/570 (3.2%)	7/318 (2.2%)	3/142 (2.1%)
Suggestive of hyperglycemia	41/570 (7.2%)	15/318 (4.7%)	3/142 (2.1%)

Patients with random glucose levels at baseline ≤ 7.8 mmol/L.

Age was missing for 6 patients treated with risperidone, none of whom had abnormal glucose levels, and 2 in the other treatment group, one of whom had levels suggestive of hyperglycemia.

Source: Display SAF.2A glucose

Table 15: Incidence of elevated glucose levels in long-term trials by age

Glucose levels at any postbaseline time	Risperidone	Other
Adults		
Suggestive of diabetes	17/900 (1.9%)	7/230 (3.0%)
Suggestive of hyperglycemia	20/900 (2.2%)	7/230 (3.0%)
Elderly		
Suggestive of diabetes	12/276 (4.3%)	--
Suggestive of hyperglycemia	34/276 (12.3%)	--

Patients with random glucose levels at baseline ≤ 7.8 mmol/L.

Age was missing for 2 risperidone-treated patients, neither of whom had elevated glucose levels.

Source: Display SAF.2A glucose

3.2.2.2. Medical history of diabetes

Of the subjects with both information on medical history and glucose levels, 2004 in the short-term trials and 494 in the long-term trials had normal glucose levels at baseline. The majority (97%) had no prior history of diabetes. Elevations of glucose levels were observed in a higher percentage of patients with a history of diabetes than in those without such history (Table 16 and Table 17).

Table 16: Incidence of elevated glucose levels in short-term trials by medical history

Glucose levels at any postbaseline time	No pre-existing diabetes			Pre-existing diabetes		
	RIS	Placebo	Other	RIS	Placebo	Other
Suggestive of diabetes	6/1316 (0.5%)	2/252 (0.8%)	0/382 (0%)	2/22 (9.1%)	1/16 (6.3%)	3/16 (18.8%)
Suggestive of hyperglycemia	13/1316 (1.0%)	8/252 (3.2%)	3/382 (0.8%)	4/22 (18.2%)	3/16 (18.8%)	2/16 (12.5%)

Source: Display SAF.5A.glucose

Patients with random glucose levels at baseline ≤ 7.8 mmol/L, and with postbaseline assessments.

Table 17: Incidence of elevated glucose levels in long-term trials by medical history

Glucose levels at any postbaseline time	No pre-existing diabetes		Pre-existing diabetes	
	Risperidone	Other	Risperidone	Other
Suggestive of diabetes	1/408 (0.2%)	0/79 (0%)	1/5 (20%)	0/2 (0%)
Suggestive of hyperglycemia	4/408 (1.0%)	0/79 (0%)	1/5 (20%)	1/2 (50%)

Source: Display SAF.5A.glucose

Patients with random glucose levels at baseline ≤ 7.8 mmol/L, and with postbaseline assessments.

4. CONCLUSION

The information derived from a large number of clinical trials reporting on more than 9000 subjects supports the conclusion that disturbances of glucose metabolism during risperidone treatment are very rare. Overall, the incidence of glucose-related adverse events was lower with risperidone than placebo. In the pediatric and adult population, risperidone was indistinguishable from placebo in terms of percentage of individuals with abnormalities in glucose metabolism. Elderly patients showed a slightly higher incidence of abnormalities in glucose metabolism with risperidone compared to placebo in short-term trials. Hyperglycemia and dysregulation or worsening of existing diabetes were more commonly observed than new-onset diabetes which was very rare.

5. REFERENCES

- 1 Niemegeers CJE, et al. Pharmacology of risperidone (R64 766), a new antipsychotic with serotonin 5₂ and dopamine D₂ antagonistic properties. *J Pharmacol Exp Ther* 1988;244/2: 685-693.
- 2 Leysen JE, et al. The biochemical profile of risperidone, a new antipsychotic. *J Pharmacol Exp Ther* 1988;247/2: 661-670.
- 3 Claus A, Bollen J, De Cuyper H, Eneman M, et al. Risperidone versus haloperidol in the treatment of chronic schizophrenic in subjects: a multicentre double-blind comparative trial. *Acta Psychiatr Scand* 1992;85:295-305.
- 4 Huttunen MO, Pieppori T, Rantanen H, Larmo I, Nyholm R, Raitang V. Risperidone versus zuclopenthixol in the treatment of acute schizophrenic episodes: a double-blind parallel-group trial. *Acta Psychiatr Scand* 1995;91:271-277.
- 5 Blin O, Azorin JM, Bouhours P. Antipsychotic and anxiolytic properties of risperidone, haloperidol, and methotrimeprazine in schizophrenic patients. *J Clin Psychopharmacol* 1996;16:38-44.
- 6 Klier E, Lehmann E, Hinzler E, Wurthmann C, Heinrich K. Randomized, double-blind, controlled trial of risperidone versus clozapine in patients with chronic schizophrenia. *J Clin Psychopharmacol* 1995;15 (Suppl. 1):455-515.
- 7 Nair NPV, and this Risperidone Study Group. Therapeutic equivalence of risperidone given once daily and twice daily in patients with schizophrenia. *J Clin Psychopharmacol* 1998;18:103-110.
- 8 Peuskens J. Risperidone in the treatment of chronic schizophrenic patients: a multinational, multicentre double-blind, parallel-group study versus haloperidol. *Br J Psychiatry* 1995;166:712-726.
- 9 Chouinard G, et al. A Canadian multi-center placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacology* 1993;13:25-40.
- 10 Hoyberg OJ, Penberg C, Remvig J, Lingjaering O, Sloth Nielsen M, Salveren I. Risperidone versus perphenazine in the treatment of chronic schizophrenic patients with acute exacerbations. *Acta Psychiatr Scand* 1993;88:395-402.
- 11 Min SK, Rime CS, Kim C-E, Kang D-Y. Risperidone versus haloperidol in the treatment of chronic schizophrenic patients: a parallel group double-blind comparative trial. *Yonsei Med J* 1993;34:179-190.
- 12 Bondolf G, Dufour H, Ptak M et al. on behalf of the Risperidone Study Group. Risperidone versus clozapine in treatment-resistant chronic schizophrenic: a randomised double-blind study. *Am J Psychiatry* 1998;155:499-504.
- 13 Borison RL, et al. Risperidone: clinical safety and efficacy in schizophrenia. *Psychopharmacology Bulletin* 1992;28:213-218.

- 14 Moller H-J, Gaoiang CA, Addiminton DE, von Knorring L, Tores-Plank J-F, Gaussaros C. Long-term treatment with risperidone in patients with chronic schizophrenia. *Int Clin Psychopharmacol* 1998;13:99-100.
- 15 WHO Study Group on Diabetes Mellitus. World Health Organisation Technical Report series 727. Geneva, Switzerland: World Health Organisation; 1985.
- 16 Berger B, Stenstrom G, Sundkvist G. Incidence, prevalence, and mortality of diabetes in a large population. A report from the Skaraborg Diabetes Registry. *Diabetes Care*. 1999;22:773-8.
- 17 Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. *Diabetic Medicine* 1997;14: S7-S85.

6. SUPPORTING DATA

6.1. Displays

Risperidone: Integrated Clinical Report dp 329 safety - glucose

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

August 2000

	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- olep- tics	Plac- ebo	Risp- erid- one	Halo- peri- dol	Olan- zapi- ne	Neur- olep- tics	Plac- ebo	Risp- erid- one	
n	a	n	a	n	n	n	n	n	n	a	n		
ADVERSE EVENT PREFERRED TERM													
ACIDOSIS	-	1	-	-	-	-	-	-	-	-	-	1	
BLOOD SUGAR INCREASED	-	-	-	-	-	-	2	-	-	-	-	2	
COMA DIABETIC	-	-	-	-	-	-	1	-	-	-	-	1	
DIABETES MELLITUS	5	11	-	1	1	1	4	5	1	1	1	15	
DIABETES MELLITUS AGGRAVATED	-	2	-	-	-	-	2	-	-	-	-	2	
GLYCOSURIA	-	2	-	1	-	-	-	-	1	-	-	3	
HYPERGLYCAEMIA	5	23	2	3	-	5	20	7	3	-	5	43	
HYPOGLYCAEMIA	1	5	-	-	-	1	7	1	-	-	-	12	
KETOSIS	-	1	-	-	-	-	1	-	-	-	-	2	
PLASMA OSMOLALITY INCREASED	-	-	-	-	-	-	1	-	-	-	-	1	

Risperidone: Integrated Clinical Report dp 329 safety - glucose

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

August 2000

AGE GROUP	TRIAL BLINDING BY DESIGN	TRIAL DURATION	TRIAL ID	Treatment					Total
				Haloperidol	Olanzapine	Ocher-Mesulc	Placebo	Risperidone	
				n	n	n	n	n	
18 - 65	DOUBLE-BLIND	LONG-TERM	INT-6	99	-	-	-	91	190
			USA-79	203	-	-	-	192	395
			AUT-1	-	-	33	-	34	67
			BEL-5	22	-	-	-	22	44
			BEL-7	32	-	-	-	28	60
			FIM-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	346	523
			INT-39	-	-	-	25	29	54
			INT-45	-	243	-	-	247	490
			INT-46	-	-	-	75	75	150
			INT-5	84	-	-	-	99	183
			INT-7	-	-	52	-	93	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-60	-	-	-	-	441	441
			USA-72	-	-	-	83	163	246
	OPEN-LABEL	LONG-TERM	BEL-17	-	-	-	-	116	116

Risperidone: Integrated Clinical Report dp 329 safety - glucose

(CONTINUED)

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

AGE GROUP	TRIAL BLINDING BY DESIGN	TRIAL DURATION	TRIAL ID	Treatment					Total
				Malo-peri-dol	Olan-zapi-ne	Other Neur-olep-tics	Plac-ebo	Risp-erid-one	
				n	n	n	n	n	
18 - 65	OPEN-LABEL	LONG-TERM	GBR-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	74
			BEL-24	-	-	-	7	6	13
			CAN-19	-	-	-	57	53	110
			NED-9	-	-	-	19	25	38
			Total	-	-	-	113	101	214

Risperidone: Integrated Clinical Report dp 329 safety - glucose

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

				Treatment					Total
				Haloperi- dol	Olan- zapine	Ocher Neur- oleptics	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-26	-	-	-	-	83	83
			USA-34	-	-	-	-	22	22
			USA-64	-	-	-	-	103	103
			USA-70	-	-	-	-	320	330
	Total			115	-	-	296	1315	1726
Total				1014	448	527	868	8402	11259

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

August 2000

	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

Risperidone: Integrated Clinical Report dp 329 safety - glucose

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

August 2000

			AGE GROUP								Total n
			18 - 65		< 18		> 65				
			n	t	n	t	n	t	n	t	
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		
		Olansapine	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		
	Olansapine		444	99.11	-	-	-	-	444		
	Other Neuroleptics		526	99.81	-	-	-	-	526		
	YES	LONG-TERM	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			
SHORT-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		
		Olansapine	4	0.89	-	-	-	-	4		

Risperidone: Integrated Clinical Report dp 329 safety - glucose

(CONTINUED)
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							
YES	SHORT-TERM	Other Neuroleptics	1	0.34	-	-	-	-	
		Placebo	2	0.51	-	-	5	1.69	7
		Risperidone	18	0.40	-	-	15	2.51	33
		All treatments	26	0.41	-	-	21	2.08	47
	Short + Long Term	Treatment							
		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
	Total	Treatment							
		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
		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
All treatments	6277	100.0	366	100.0	1008	100.0	7651		

Risperidone: Integrated Clinical Report dp 329 safety - glucose

(CONTINUED)

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

			AGE GROUP								Total
			18 - 65		< 18		> 65				
			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	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		

Risperidone: Integrated Clinical Report dp 329 safety - glucose

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

			SEX								Total n
			FEMALE				MALE				
			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		
		SHORT-TERM	Treatment								
	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			
	Short + Long Term	Treatment									
		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	6186	98.98	6968	99.25	11163		
	YES	TRIAL DURATION	Treatment								
	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			
SHORT-TERM		Treatment									
Haloperidol		-	-	1	0.40	1	0.22	2			
Olanzapine	-	-	1	0.76	3	0.95	4				

Risperidone: Integrated Clinical Report dp 329 safety - glucose

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

			SEX								Total n
			FEMALE				MALE				
			n	%	n	%	n	%	n	%	
Glucose related AE	TRIAL DURATION	Treatment									
YES	SHORT-TERM	Other Neuroleptics	-	-	-	-	1	0.53			
		Placebo	-	-	2	0.55	5	0.59			7
		Risperidone	-	-	16	0.81	17	0.51			33
		All treatments	-	-	20	0.71	27	0.56			47
		Treatment									
	Short + Long Term	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	0.59			7
		Risperidone	-	-	35	1.09	38	0.73			73
		All treatments	-	-	43	1.02	53	0.75			96
		Treatment									
		LONG-TERM									
	Total	Haloperidol	-	-	107	100.0	195	100.0			302
		Other Neuroleptics	1	100.0	75	100.0	158	100.0			234
		Risperidone	2	100.0	1213	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
		LONG-TERM									

Risperidone: Integrated Clinical Report dp 329 safety - glucose

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

			SEX								Total n
			FEMALE				MALE				
			n	%	n	%	n	%	n	%	
Total	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	

Risperidone: Integrated Clinical Report dp 329 safety - glucose

(CONTINUED)

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

Glucose related AE	TRIAL DURATION	Treatment	RACE									
			Other		Black		White		Total		n	
			n	%	n	%	n	%	n	%		
NO	LONG-TERM	Treatment										
		Haloperidol	-	-	21	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	203	99.51	292	
		Placebo	75	100.0	58	98.31	116	100.0	612	99.03	861	
		Risperidone	377	100.0	510	99.62	707	99.19	1683	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	122	97.06	135	97.83	600	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	611	100.0	794	99.25	944	97.72	5960	99.25	8329	
		All Treatments	816	100.0	1052	98.87	1277	97.93	7998	99.28	11163	
YES	LONG-TERM	Treatment										
		Haloperidol	-	-	4	11.43	2	2.70	3	1.55	9	
		Risperidone	-	-	4	1.43	5	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	

Risperidone: Integrated Clinical Report dp 329 safety - glucose

(CONTINUED)
Display GR5.5 Number of patients with/without glucose related AEs by demographics

			RACE										Total n		
					Other		Black		White						
			n	%	n	%	n	%	n	%	n	%			
Glucose related AE	TRIAL DURATION	Treatment													
YES	SHORT-TERM	Other Neuroleptics	-	-	-	-	-	-	1	0.49					
		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		
		Treatment													
	Short + Long Term	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		
		Treatment													
	Total	TRIAL DURATION	Treatment												
			LONG-TERM	Haloperidol	-	-	35	100.0	74	100.0	193	100.0			302
			Other Neuroleptics	2	100.0	20	100.0	-	-	312	100.0			234	
			Risperidone	254	100.0	268	100.0	246	100.0	2104	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	
			All treatments	560	100.0	741	100.0	984	100.0	3346	100.0			7651	
Treatment															

Risperidone: Integrated Clinical Report dp 329 safety - glucose

(CONTINUED)

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

		RACE									
		Other		Black		White		Total			
		n	%	n	%	n	%	n	%	n	%
Total	Short : Long Term	Treatment									
		Haloperidol	56	100.0	126	100.0	138	100.0	694	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	628	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

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GLUCOSE RELATED ANALYSIS

TABLE QAR.4A GLUCOSE , INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION

POPULATION: ALL SUBJECTS
DURATION: SHORT TERM

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO ----- NO. SUBJECTS (%)	RISPERIDONE NO. SUBJECTS (%)	----- OLANZAPINE ----- NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	277	1519	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	4 (1.4)	14 (0.9)	1 (1.1)
METABOLIC AND NUTRITIONAL DISORDERS	4 (1.4)	14 (0.9)	1 (1.1)
HYPERGLYCAEMIA	2 (0.7)	8 (0.5)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	3 (0.2)	1 (1.1)
GLYCOBURIA	0 (0.0)	2 (0.1)	0 (0.0)
ACIDOSIS	0 (0.0)	1 (0.1)	0 (0.0)
HYPOGLYCAEMIA	2 (0.7)	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : AUS-8, INT-32, INT-61, INT-50, USA-121
LONG TERM : CAN-20, INT-41, INT-57

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GLUCOSE RELATED ANALYSIS

TABLE GAE.4A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG TERM

--- RISPERIDONE ---	
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)

TOTAL NUMBER OF SUBJECTS	1343
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	5 (0.4)
METABOLIC AND NUTRITIONAL DISORDERS	5 (0.4)
GLYCOSURIA	3 (0.2)
HYPERGLYCAEMIA	2 (0.1)
DIABETES MELLITUS	1 (0.1)

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GLUCOSE RELATED ANALYSIS

TABLE GAE.4A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SEQT + LONG TERM

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (n)	NO. SUBJECTS (n)	NO. SUBJECTS (n)
TOTAL NUMBER OF SUBJECTS	277	2862	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	4 (1.4)	19 (0.7)	1 (1.1)
METABOLIC AND NUTRITIONAL DISORDERS	4 (1.4)	19 (0.7)	1 (1.1)
HYPERGLYCAEMIA	2 (0.7)	10 (0.3)	0 (0.0)
GLYCOURIA	0 (0.0)	5 (0.2)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	4 (0.1)	1 (1.1)
ACIDOSIS	0 (0.0)	1 (0.0)	0 (0.0)
HYPOGLYCAEMIA	2 (0.7)	0 (0.0)	0 (0.0)

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GLUCOSE RELATED ANALYSIS

TABLE GAE.SA GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S WITH ACTION TAKEN PERM STOP OF TRIAL MEDICATION

POPULATION: ALL SUBJECTS
DURATION: SHORT TERM

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREPARED TERM	PLACEBO	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	277	1519	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : AUS-5, INT-32, INT-61, INT-50, USA-121
LONG TERM : CAN-20, INT-41, INT-67

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GLUCOSE RELATED ANALYSIS

TABLE GAB.5A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S WITH ACTION TAKEN PERM STOP OF TRIAL MEDICATION (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG TERM

ADVERSE EVENT SYSTEM ORGAN CLASS	--- RISPERIDONE --- NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	1343
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

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GLUCOSE RELATED ANALYSIS

TABLE QAB.5A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S WITH ACTION TAKEN PERM STOP OF TRIAL MEDICATION (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM

	----- PLACEBO -----	RISPERIDONE -----	OLANZAPINE -----
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.	NO.	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)	SUBJECTS (%)	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	277	2862	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

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GLUCOSE RELATED ANALYSIS

TABLE 042.58 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S

POPULATION: ALL SUBJECTS

DURATION: SHORT TERM

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO ----- NO. SUBJECTS (%)	RISPERIDONE NO. SUBJECTS (%)	----- OLANZAPINE ---- NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	277	1519	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.4)	2 (0.1)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.4)	2 (0.1)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	1 (0.1)	0 (0.0)
HYPERGLYCAEMIA	0 (0.0)	1 (0.1)	0 (0.0)
HYPOGLYCAEMIA	1 (0.4)	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : AUS-5, INT-32, INT-61, INT-50, USA-121
LONG TERM : CUB-20, INT-41, INT-57

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GLUCOSE RELATED ANALYSIS

TABLE GAE.58 GLUCOSE , INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG TERM

--- RISPERIDONE ---	
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)

TOTAL NUMBER OF SUBJECTS	1343
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

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GLUCOSE RELATED ANALYSIS

TABLE 04R.58 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO -----	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	277	2862	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.4)	2 (0.1)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.4)	2 (0.1)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	1 (0.0)	0 (0.0)
HYPERGLYCAEMIA	0 (0.0)	1 (0.0)	0 (0.0)
HYPOGLYCAEMIA	1 (0.4)	0 (0.0)	0 (0.0)

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GLUCOSE RELATED ANALYSIS

TABLE QAR.5C GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S WITH OUTCOME DEATH

POPULATION: ALL SUBJECTS

DURATION: SHORT TERM

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	277	1519	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : AUS-5, INT-32, INT-61, INT-56, USA-121
LONG TERM : CAN-20, INT-41, INT-57

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GLUCOSE RELATED ANALYSIS

TABLE GAE.SC GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S WITH OUTCOME DEATH (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG TERM

--- RISPERIDONE ---	
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	1343
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

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GLUCOSE RELATED ANALYSIS

TABLE C4E.5C GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S WITH OUTCOME DEATH (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACIBO	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	277	2862	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)	0 (0.0)

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GLUCOSE RELATED ANALYSIS

TABLE GAS.4A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS

POPULATION: ALL SUBJECTS

DURATION: SHORT TERM

AGE CLASS: <18 years

--- RISPERIDONE ---	
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	1
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : ADS-5, INT-32, INT-61, INT-50, USA-121
LONG TERM : CAN-20, INT-41, INT-57

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GLUCOSE RELATED ANALYSIS

TABLE GAE.4A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT TERM
AGE CLASS: 18-65 years

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	112	1285	10
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.9)	8 (0.6)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.9)	8 (0.6)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	3 (0.2)	0 (0.0)
HYPERGLYCAEMIA	0 (0.0)	3 (0.2)	0 (0.0)
ACIDOSIS	0 (0.0)	1 (0.1)	0 (0.0)
GLYCOSURIA	0 (0.0)	1 (0.1)	0 (0.0)
HYPOGLYCAEMIA	1 (0.9)	0 (0.0)	0 (0.0)

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GLUCOSE RELATED ANALYSIS

TABLE GAB.1A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT TERM
AGE CLASS: >65 years

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEO	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	165	233	78
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	3 (1.8)	6 (2.6)	1 (1.3)
METABOLIC AND NUTRITIONAL DISORDERS	3 (1.8)	6 (2.6)	1 (1.3)
HYPERGLYCAEMIA	2 (1.2)	5 (2.1)	0 (0.0)
GLUCOSURIA	0 (0.0)	1 (0.4)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	0 (0.0)	1 (1.3)
HYPOGLYCAEMIA	1 (0.6)	0 (0.0)	0 (0.0)

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GLUCOSE RELATED ANALYSIS

TABLE GAR.4A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG TERM
AGE CLASS: <16 years

--- RISPERIDONE ---		
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.	
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)	
TOTAL NUMBER OF SUBJECTS	581	
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	

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GLUCOSE RELATED ANALYSIS

TABLE 4A.4A. AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS

DURATION: LONG TERM

AGE CLASS: 18-65 years

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	
	NO.	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	711	
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	5 (0.7)	
METABOLIC AND NUTRITIONAL DISORDERS	5 (0.7)	
GLYCOSURIA	3 (0.4)	
HYPERGLYCAEMIA	2 (0.3)	
DIABETES MELLITUS	1 (0.1)	

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GLUCOSE RELATED ANALYSIS

TABLE GAR.4A AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AB'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG TERM
AGE CLASS: >65 years

--- RISPERIDONE ---	
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	51
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

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GLUCOSE RELATED ANALYSIS

TABLE QAS.4A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM
AGE CLASS: <18 years

--- RISPERIDONE ---		
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.	
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)	
TOTAL NUMBER OF SUBJECTS	582	
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	

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GLUCOSE RELATED ANALYSIS

TABLE GAE.4A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM
AGE CLASS: 18-65 years

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	312	1996	10
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.9)	13 (0.7)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.9)	13 (0.7)	0 (0.0)
HYPERGLYCAEMIA	0 (0.0)	5 (0.3)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	4 (0.2)	0 (0.0)
GLYCOSURIA	0 (0.0)	4 (0.2)	0 (0.0)
ACIDOSIS	0 (0.0)	1 (0.1)	0 (0.0)
HYPOGLYCAEMIA	1 (0.9)	0 (0.0)	0 (0.0)

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GLUCOSE RELATED ANALYSIS

TABLE GAS.4A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM
AGE CLASS: >65 years

	----- PLACEBO -----	RISPERIDONE	----- OLANZAPINE -----
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.	NO.	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)	SUBJECTS (%)	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	165	284	78
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	3 (1.8)	6 (2.1)	1 (1.3)
METABOLIC AND NUTRITIONAL DISORDERS	3 (1.8)	6 (2.1)	1 (1.3)
HYPERGLYCAEMIA	2 (1.2)	5 (1.8)	0 (0.0)
GLYCOSURIA	0 (0.0)	1 (0.4)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	0 (0.0)	1 (1.3)
HYPOGLYCAEMIA	1 (0.6)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

11JAN2002 09:53
SYSTEM USED: ARRON2.1(U)/asfua_aql

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GLUCOSE RELATED ANALYSIS

TABLE GAE.GA.DIAB GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND DIABETICS FOR SUBJ. WITH MED. HIST. INFO

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO
TRIAL DURATION: SHORT TERM
DIABETIC SUBJECT: YES

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	OTHER
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	31	50	35
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	3 (9.7)	4 (8.0)	1 (2.9)
METABOLIC AND NUTRITIONAL DISORDERS	3 (9.7)	4 (8.0)	1 (2.9)
HYPERGLYCAEMIA	3 (9.7)	4 (8.0)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	0 (0.0)	1 (2.9)
HYPOLYCAEMIA	1 (3.2)	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 30 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : ASD-5, INT-3, INT-24, INT-46, INT-5, INT-50, USA-102
LONG TERM : INT6, INT12, INT-23, INT-26

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GLUCOSE RELATED ANALYSIS

TABLE GAB.6A.DIAS GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND DIABETICS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO
TRIAL DURATION: SHORT TERM
DIABETIC SUBJECT: NO

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEDO	RISPERIDONE	OTHER
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	379	1793	531
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	3 (0.8)	5 (0.3)	2 (0.4)
METABOLIC AND NUTRITIONAL DISORDERS	3 (0.8)	5 (0.3)	2 (0.4)
HYPERGLYCAEMIA	1 (0.3)	4 (0.2)	2 (0.4)
GLYCOSURIA	0 (0.0)	1 (0.1)	0 (0.0)
DIABETES MELLITUS	1 (0.3)	0 (0.0)	0 (0.0)
HYPOGLYCAEMIA	1 (0.3)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

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GLUCOSE RELATED ANALYSIS

TABLE GAB.6A.DIAB GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND DIABETICS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO
TRIAL DURATION: LONG TERM
DIABETIC SUBJECT: YES

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	----- OTHER -----
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	38	2
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	3 (7.9)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	3 (7.9)	0 (0.0)
ACIDOSIS	1 (2.6)	0 (0.0)
DIABETES MELLITUS	1 (2.6)	0 (0.0)
HYPERGLYCAEMIA	1 (2.6)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

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GLUCOSE RELATED ANALYSIS

TABLE GAS.6A.DIAB GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND DIABETICS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO
TRIAL DURATION: LONG TERM
DIABETIC SUBJECT: NO

AE SYSTEM ORGYN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	----- OTHER -----
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	789	97
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.1)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.1)	0 (0.0)
HYPOGLYCAEMIA	1 (0.1)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

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SYSTEM USED: RPSYS01(0)/GLOCKON

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GLUCOSE RELATED ANALYSIS

DISPLAY SAP.1A GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION

POPULATION: ALL SUBJECTS
TRIAL DURATION: SHORT TERM

LABORATORY TEST	--- RISPERIDONE --- -- * INCIDENCE (%) --	--- PLACEBO --- -- * INCIDENCE (%) --	--- OTHER --- -- * INCIDENCE (%) --
GLUCOSE			
SUGGESTIVE OF DIABETIS	26/2676 (1.0)	8/575 (1.4)	4/611 (0.7)
SUGGESTIVE OF HYPERGLYCEMIA	56/2676 (2.1)	18/575 (3.1)	12/611 (2.0)

* NUMBER AND PERCENT OF SUBJECTS WHO HAVE RANDOM GLUCOSE LEVELS (≤ 7.8 mmol/l) AT BASELINE AND POST-BASELINE ASSESSMENT EXCEEDING THE RANGE LISTED BELOW
- SUGGESTIVE OF DIABETIS (≥ 11 mmol/l SOMEWHERE DURING TRIAL)
- SUGGESTIVE OF HYPERGLYCEMIA (≥ 8.9 mmol/l AND ≤ 11 mmol/l SOMEWHERE DURING TRIAL)

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SYSTEM USED: SPST01 (D) /GLUCR00

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GLUCOSE RELATED ANALYSIS

DISPLAY SAP.1A GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: LONG TERM

LABORATORY TEST	----- RISPERIDONE -----	----- OTHER -----
	-- * INCIDENCE (%) --	-- * INCIDENCE (%) --
GLUCOSE		
SUGGESTIVE OF DIABETIS	29/1182 (2.5)	7/230 (3.0)
SUGGESTIVE OF HYPERGLYCEMIA	54/1182 (4.6)	7/230 (3.0)

* NUMBER AND PERCENT OF SUBJECTS WHO HAVE RANDOM GLUCOSE LEVELS (≤ 7.8 mmol/l) AT BASELINE AND POST-BASELINE ASSESSMENT EXCEEDING THE RANGE LISTED BELOW
- SUGGESTIVE OF DIABETIS (≥ 11 mmol/l SOMEWHERE DURING TRIAL)
- SUGGESTIVE OF HYPERGLYCEMIA (≥ 8.9 mmol/l AND ≤ 11 mmol/l SOMEWHERE DURING TRIAL)

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SYSTEM USED: BPSYS03 (U)/GLUCR01

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GLUCOSE RELATED ANALYSIS

DISPLAY SAP.2A GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS

POPULATION: ALL SUBJECTS
TRIAL DURATION: SHORT TERM
AGE_CL: <18 years

LABORATORY TEST	---- RISPHERIDONE ----	----- OTHER -----
	-- * INCIDENCE (%) --	-- * INCIDENCE (%) --

GLUCOSE		
SUGGESTIVE OF DIABETIS	0/8 (0.0)	0/3 (0.0)
SUGGESTIVE OF HYPERGLYCEMIA	0/8 (0.0)	0/3 (0.0)

* NUMBER AND PERCENT OF SUBJECTS WHO HAVE RANDOM GLUCOSE LEVELS (<=7.8 mmol/l) AT BASELINE AND POST-BASELINE ASSESSMENT EXCEEDING THE RANGE LISTED BELOW
- SUGGESTIVE OF DIABETIS (>=11 mmol/l SOMEWHERE DURING TRIAL)
- SUGGESTIVE OF HYPERGLYCEMIA (>=9.9 mmol/l AND <11 mmol/l SOMEWHERE DURING TRIAL)

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SYSTEM USED: EPSY801(0)/GLUCRUM

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GLUCOSE RELATED ANALYSIS

DISPLAY SAF.2A GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: SHORT TERM
AGE_CL: 18-65 years

LABORATORY TEST	RISPERIDONE	PLACEBO	OTHER
	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)
GLUCOSE			
SUGGESTIVE OF DIABETIS	8/2092 (0.4)	1/257 (0.4)	1/464 (0.2)
SUGGESTIVE OF HYPERGLYCEMIA	15/2092 (0.7)	3/257 (1.2)	8/464 (1.7)

• NUMBER AND PERCENT OF SUBJECTS WHO HAVE RANDOM GLUCOSE LEVELS (≥ 7.8 mmol/l) AT BASELINE AND POST-BASELINE ASSESSMENT EXCEEDING THE RANGE LISTED BELOW
 - SUGGESTIVE OF DIABETIS (≥ 11 mmol/l SOMEWHERE DURING TRIAL)
 - SUGGESTIVE OF HYPERGLYCEMIA (≥ 8.9 mmol/l AND < 11 mmol/l SOMEWHERE DURING TRIAL)

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SYSTEM USED: EPSYS03 (D)/GLUCUR

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GLUCOSE RELATED ANALYSIS

DISPLAY SAP.2A GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: SHORT TERM
AGE_CL: >65 years

LABORATORY TEST	--- RISPERIDONE --- -- * INCIDENCE (%) --	--- PLACEBO --- -- * INCIDENCE (%) --	--- OTHER --- -- * INCIDENCE (%) --
GLUCOSE			
SUGGESTIVE OF DIABETIS	18/570 (3.2)	7/318 (2.2)	3/142 (2.1)
SUGGESTIVE OF HYPERGLYCEMIA	41/570 (7.2)	15/318 (4.7)	3/142 (2.1)

* NUMBER AND PERCENT OF SUBJECTS WHO HAVE RANDOM GLUCOSE LEVELS (≥ 7.8 mmol/l) AT BASELINE AND POST-BASELINE ASSESSMENT EXCEEDING THE RANGE LISTED BELOW
* SUGGESTIVE OF DIABETIS (≥ 11 mmol/l SOMEWHERE DURING TRIAL)
* SUGGESTIVE OF HYPERGLYCEMIA (≥ 8.9 mmol/l AND ≤ 11 mmol/l SOMEWHERE DURING TRIAL)

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SYSTEM USED: RPSYS03 (U)/GLUCR01

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GLUCOSE RELATED ANALYSIS

DISPLAY SAP.2A GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: SHORT TERM
AGE_CL: MISSING AGE

LABORATORY TEST	---- RISPERIDONE ----	----- OTHER -----
	-- * INCIDENCE (%) --	-- * INCIDENCE (%) --
GLUCOSE		
SUGGESTIVE OF DIABETIS	0/6 (0.0)	0/2 (0.0)
SUGGESTIVE OF HYPERGLYCEMIA	0/6 (0.0)	1/2 (50.0)

* NUMBER AND PERCENT OF SUBJECTS WHO HAVE RANDOM GLUCOSE LEVELS (≤ 7.8 mmol/l) AT BASELINE AND POST-BASELINE ASSESSMENT EXCEEDING THE RANGE LISTED BELOW
- SUGGESTIVE OF DIABETIS (≥ 11 mmol/l SOMEWHERE DURING TRIAL)
- SUGGESTIVE OF HYPERGLYCEMIA (≥ 8.9 mmol/l AND ≤ 11 mmol/l SOMEWHERE DURING TRIAL)

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SYSTEM USED: EPSYS01 (V) / GLUCRUM

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GLUCOSE RELATED ANALYSIS

DISPLAY SAF.2A GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: LONG TERM
XAGE_CL: <18 years

LABORATORY TEST	----- RISPERIDONE -----	
	-- * INCIDENCE (%) --	

GLUCOSE		

SUGGESTIVE OF DIABETIS	0/4	(0.0)
SUGGESTIVE OF HYPERGLYCEMIA	0/4	(0.0)

* NUMBER AND PERCENT OF SUBJECTS WHO HAVE RANDOM GLUCOSE LEVELS (≤ 7.8 mmol/l) AT BASELINE AND POST-BASELINE ASSESSMENT EXCEEDING THE RANGE LISTED BELOW
* SUGGESTIVE OF DIABETIS (≥ 11 mmol/l SOMEWHERE DURING TRIAL)
* SUGGESTIVE OF HYPERGLYCEMIA (≥ 9.9 mmol/l AND ≤ 11 mmol/l SOMEWHERE DURING TRIAL)

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SYSTEM USED: EPRYS03(U)/GLUCRUM

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GLUCOSE RELATED ANALYSIS

DISPLAY SAF.2A GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: LONG TERM
XAGE_CL: 18-65 years

LABORATORY TEST	--- RISPERIDONE ---		--- OTHER ---	
	-- * INCIDENCE (%) --		-- * INCIDENCE (%) --	
GLUCOSE				
SUGGESTIVE OF DIABETIS	17/900	(1.9)	7/230	(3.0)
SUGGESTIVE OF HYPERGLYCEMIA	20/900	(2.2)	7/230	(3.0)

* NUMBER AND PERCENT OF SUBJECTS WHO HAVE RANDOM GLUCOSE LEVELS (≤ 7.8 mmol/l) AT BASELINE AND POST-BASELINE ASSESSMENT EXCEEDING THE RANGE LISTED BELOW
- SUGGESTIVE OF DIABETIS (> 11 mmol/l SOMEWHERE DURING TRIAL)
- SUGGESTIVE OF HYPERGLYCEMIA (> 8.9 mmol/l AND < 11 mmol/l SOMEWHERE DURING TRIAL)

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SYSTEM USED: EPSYS03(U)/GLUCRON

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GLUCOSE RELATED ANALYSIS

DISPLAY SAP.2A GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: LONG TERM
AGE_CL: >65 years

LABORATORY TEST	--- RISPERIDONE --- -- * INCIDENCE (%) --

GLUCOSE	
SUGGESTIVE OF DIABETIS	12/276 (4.3)
SUGGESTIVE OF HYPERGLYCEMIA	34/276 (12.3)

* NUMBER AND PERCENT OF SUBJECTS WHO HAVE RANDOM GLUCOSE LEVELS (≥ 7.0 mmol/l) AT BASELINE AND POST-BASELINE ASSESSMENT EXCEEDING THE RANGE LISTED BELOW
- SUGGESTIVE OF DIABETIS (≥ 11 mmol/l SOMEWHERE DURING TRIAL)
- SUGGESTIVE OF HYPERGLYCEMIA (≥ 8.9 mmol/l AND < 11 mmol/l SOMEWHERE DURING TRIAL)

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GLUCOSE RELATED ANALYSIS

DISPLAY SAF.2A GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: LONG TERM
XAGE_CL: MISSING AGE

LABORATORY TEST	----- RISPERIDONE ----- -- * INCIDENCE (%) --

GLUCOSE	
SUGGESTIVE OF DIABETIS	0/2 (0.0)
SUGGESTIVE OF HYPERGLYCEMIA	0/2 (0.0)

* NUMBER AND PERCENT OF SUBJECTS WHO HAVE RANDOM GLUCOSE LEVELS (≥ 7.0 mmol/l) AT BASELINE AND POST-BASELINE ASSESSMENT EXCEEDING THE RANGE LISTED BELOW
- SUGGESTIVE OF DIABETIS (≥ 11 mmol/l SOMEWHERE DURING TRIAL)
- SUGGESTIVE OF HYPERGLYCEMIA (≥ 8.9 mmol/l AND < 11 mmol/l SOMEWHERE DURING TRIAL)

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GLUCOSE RELATED ANALYSIS

DISPLAY SAF. 5A GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND DIABETICS FOR SUBJECTS WITH MEDICAL HISTORY INFORMATION

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO
TRIAL DURATION: SHORT TERM
DIABETIC SUBJECT: YES

LABORATORY TEST	----- RISPERIDONE ----- -- * INCIDENCE (%) --	----- PLACEBO ----- -- * INCIDENCE (%) --	----- OTHER ----- -- * INCIDENCE (%) --
GLUCOSE			
SUGGESTIVE OF DIABETIS	2/22 (9.1)	1/16 (6.3)	3/16 (19.0)
SUGGESTIVE OF HYPERGLYCEMIA	6/22 (27.3)	3/16 (18.8)	2/16 (12.5)

* NUMBER AND PERCENT OF SUBJECTS WHO HAVE RANDOM GLUCOSE LEVELS (≤ 7.8 mmol/l) AT BASELINE AND POST-BASELINE ASSESSMENT EXCEEDING THE RANGE LISTED BELOW
- SUGGESTIVE OF DIABETIS (≥ 11 mmol/l SOMEWHERE DURING TRIAL)
- SUGGESTIVE OF HYPERGLYCEMIA (≥ 9.9 mmol/l AND < 11 mmol/l SOMEWHERE DURING TRIAL)

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SYSTEM USED: EPST503(U)/glucrun_sq1

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GLUCOSE RELATED ANALYSIS

DISPLAY SAF.SA GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND DIABETICS FOR SUBJECTS WITH MEDICAL HISTORY INFORMATION (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO
TRIAL DURATION: SHORT TERM
DIABETIC SUBJECT: NO

LABORATORY TEST	----- RISPERIDONE ----- -- * INCIDENCE (%) --	----- PLACEBO ----- -- * INCIDENCE (%) --	----- OTHER ----- -- * INCIDENCE (%) --
GLUCOSE			
SUGGESTIVE OF DIABETIS	6/1316 (0.5)	2/252 (0.8)	0/382 (0.0)
SUGGESTIVE OF HYPERGLYCEMIA	13/1316 (1.0)	8/252 (3.2)	3/382 (0.8)

* NUMBER AND PERCENT OF SUBJECTS WHO HAVE RANDOM GLUCOSE LEVELS (≤ 7.8 mmol/l) AT BASELINE AND POST-BASELINE ASSESSMENT EXCEEDING THE RANGE LISTED BELOW
- SUGGESTIVE OF DIABETIS (≥ 11 mmol/l SOMEWHERE DURING TRIAL)
- SUGGESTIVE OF HYPERGLYCEMIA (≥ 8.3 mmol/l AND ≤ 11 mmol/l SOMEWHERE DURING TRIAL)

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GLUCOSE RELATED ANALYSIS

DISPLAY SAP.5A GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND DIABETICS FOR SUBJECTS WITH MEDICAL HISTORY INFORMATION (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO
TRIAL DURATION: LONG TERM
DIABETIC SUBJECT: YES

LABORATORY TEST	--- RISPERIDONE ---	--- OTHER ---
	-- * INCIDENCE (%) --	-- * INCIDENCE (%) --
GLUCOSE		
SUGGESTIVE OF DIABETIS	1/5 (20.0)	0/2 (0.0)
SUGGESTIVE OF HYPERGLYCEMIA	1/5 (20.0)	1/2 (50.0)

* NUMBER AND PERCENT OF SUBJECTS WHO HAVE RANDOM GLUCOSE LEVELS (≥ 7.8 mmol/l) AT BASELINE AND POST-BASELINE ASSESSMENT EXCEEDING THE RANGE LISTED BELOW
- SUGGESTIVE OF DIABETIS (≥ 11 mmol/l SOMEWHERE DURING TRIAL)
- SUGGESTIVE OF HYPERGLYCEMIA (≥ 8.9 mmol/l AND < 11 mmol/l SOMEWHERE DURING TRIAL)

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GLUCOSE RELATED ANALYSIS

DISPLAY SAF.SA GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND DIABETICS FOR SUBJECTS WITH MEDICAL HISTORY INFORMATION (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO
TRIAL DURATION: LONG TERM
DIABETIC SUBJECT: NO

LABORATORY TEST	--- RISPERIDONE ---	--- OTHER ---
	-- * INCIDENCE (%) --	-- * INCIDENCE (%) --
GLUCOSE		
SUGGESTIVE OF DIABETIS	1/408 (0.2)	0/79 (0.0)
SUGGESTIVE OF HYPERGLYCEMIA	4/408 (1.0)	0/79 (0.0)

* NUMBER AND PERCENT OF SUBJECTS WHO HAVE RANDOM GLUCOSE LEVELS (≤ 7.0 mmol/l) AT BASELINE AND POST-BASELINE ASSESSMENT EXCEEDING THE RANGE LISTED BELOW
- SUGGESTIVE OF DIABETIS (≥ 11 mmol/l SOMEWHERE DURING TRIAL)
- SUGGESTIVE OF HYPERGLYCEMIA (≥ 8.9 mmol/l AND ≤ 11 mmol/l SOMEWHERE DURING TRIAL)

6.2 ANNEXES

Annex 1: Narratives

Cross-reference table of narratives for 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)					
INT-61 (Double-blind short-term)					
A30445 ^a	RIS oral	Hyperglycemia		X	
A30755	RIS oral	Diabetes mellitus		X	
USA-79 (Double-blind long-term)					
0054	RIS	Diabetes mellitus		X	
0601 ^a	RIS	Diabetes mellitus		X	
0084 ^a	HAL	Diabetes mellitus Hypoglycemia		X	
0302	HAL	Diabetes mellitus		X	
0349 ^a	HAL	Hyperglycemia	X	X	
INT-45 (Double-blind short-term)					
A30142 ^a	RIS	Hyperglycemia Hypoglycemia		X	
USA-102 (Double-blind short-term)					
A30030	PLA	Uncontrolled diabetes		X	
USA-6 (Open-label long-term)					
0254	RIS	Hypoglycemia		X ^b	
ELDERLY (>65 years)					
AUS-5 (Double-blind short-term)					
160	PLA	Hypoglycemia		X	
USA-63 (Double-blind short-term)					
0911 ^a	PLA	Hyperglycemia		X	
4113 ^{a,d}	PLA	Hyperglycemia	X	X	(X ^d)
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 long-term)					
A00118 ^a	RIS	Diabetes mellitus		X	
A00367	RIS	Hypoglycemia		X	(X ^d)
USA-70 (Open-label long-term)					
2916 ^a	RIS	Diabetes mellitus		X	
4118	RIS	Hyperglycemia	X	X	
4206	RIS	Hyperglycemia		X	
TOTAL			5^e	22	1^e

Risperidone: Integrated Clinical Report dp 329 safety - glucose

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

A patient narrative is provided in Annex 1 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 an endocrine disorder other than a glucose-related one.

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

c: Patient 0076 from trial USA-79 (HAL) was listed in the August 2000 report as having discontinued due to a glucose-related event, but is not included in this table as the discontinuation was due to other reasons. A narrative is provided.

d: This patient died but the cause of death was not due to a glucose-related adverse event. A narrative is provided in Annex 1 for completeness.

e: One patient is indicated because this 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.

Narratives from trials RIS-INT-61 and RIS-AUS-5 are located at the end of Annex 1.

Risperidone: Integrated Clinical Report dp 329 safety - glucose

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

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.

Risperidone: Integrated Clinical Report dp 329 safety - glucose

ECG data:

Date	Timepoint	Heart 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:	Dosage*	Start	End
Psychotropic medication:			
Haloperidol	10mg QD	15DEC92	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):	Severity	Relation to study med.	Start	End
Headache (intermittent)	mild	none	06SEP96	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:	Baseline	(Day 0)	Day 29	Day 190	Day 302	Day 365	Day 533
Laboratory test: Reference range							
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: Integrated Clinical Report dp 329 safety - glucose

Risperidone—RIS-USA-79 Serious Adverse Event Summary

Subject:	A30601/RED	Investigator:	Brammer, 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	Relation to study med	Start	End
Serious adverse event (verbatim):	Severity	none	26DEC97	31DEC97
Uncontrolled diabetes mellitus	moderate			

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 anteroapical 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 anteroapical 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

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.

Risperidone: Integrated Clinical Report dp 329 safety - glucose

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:	Dosage*	Start	End
Psychotropic medication:			
Chlorpromazine HCl	25mg TID	12NOV96	25AUG97
Other concomitant 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):	Severity	Relation to study med	Start	End
Gastritis	mild	none	27DEC97	31DEC97

Clinical laboratory tests:

Abnormal laboratory values:		(Day 0)					
Laboratory test:	Reference range	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: Integrated Clinical Report dp 329 safety - glucose

Risperidone—RIS-USA-79 Premature Discontinuation Summary

Subject:	A30076[REDACTED]	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			
Adverse event (verbatim):	Severity	Relation to study med	Start	End
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

Clinical narrative:

The patient, a 45-year-old man, began study medication treatment on July 18, 1996. On July 17, 1997, after approximately one year on study medication, the patient was referred to an internist secondary to abnormal laboratory results: his AST, ALT, alkaline phosphatase, GGT, glucose, and MCV were all mildly elevated (note: the patient was discontinued based on laboratory values other than those reported from standard blood draws for the study; the exact laboratory values were not available). These results were confirmed with a retest on August 1, 1997. On August 21, 1997, the patient saw an internist, who recommended he withdraw from the study. The patient contacted the site and was discontinued immediately; he completed final visit assessments on August 28,

1997. Physical examination results indicated tremor in both hands. The PANSS score was 47 (63 at baseline) and the CGI was "moderate" and unchanged relative to baseline. There were a couple of notable changes in the Extrapyramidal Symptom Rating Scale (ESRS). Expressive automatic movements (of the parkinsonism subscale) worsened from "very mild decrease in facial expressiveness" at baseline to "rare spontaneous smile, decreased blinking, voice slightly monotonous" at final visit, and tremors in both arms increased from "absent" to "moderate amplitude." The CGI subscale of the ESRS for dyskinesia remained "absent" throughout the study, and the parkinsonism CGI increased from "absent" to "mild" at study end. There is no further information concerning resolution of the abnormal laboratory values. The investigator considered all elevations in laboratory values to be possibly related to study medication.

Screening and Final Visit ECG results were reported by the site as within normal limits. Week 28 ECG results indicated non-specific T abnormality and borderline QTc. Week 52 ECG results reported borderline QT interval and Week 100 ECG results showed borderline QTc. All ECG abnormalities were judged by the site to be not clinically significant. This patient was discontinued from the study after 400 days at the recommendation of an internist because of liver function test abnormalities. Liver function abnormalities are expected with haloperidol. However, the underlying cause of the mild hepatic inflammation late in the course of the study (Day 365) is not clear from the provided information. The patient had liver function tests at 2 earlier assessments that were within normal limits while on the same dose of study medication (15 mg/day). Concomitant medications or conditions associated with liver dysfunction were not reported. Possible causes for mild hepatic inflammation include alcohol ingestion or use of over-the-counter medications such as NSAIDs or acetaminophen; the possibility of alcoholism is suggested by the increase in MCV. Arguing that haloperidol may have contributed is the improvement in laboratory values at Day 427. There was mild and intermittent monocytosis of unclear etiology. Monocytosis is not expected with haloperidol; common causes of monocytosis include infections and hematologic malignancies. Mild hyperglycemia was evident from Day 365 onward. Hyperglycemia is expected with haloperidol and it is possible that the study medication caused hyperglycemia in this patient, or the patient was in a non-fasting condition. There was borderline or mild prolongation of the QT on Days 196, 365, and 700. Many anti-psychotic medications lead to repolarization abnormalities as do a large number of other medications and metabolic abnormalities; such conditions and medications were not reported. Haloperidol may have contributed to the lengthened QT since it had increased after Screening; on the other hand, the QT remained prolonged at Week 100, long after study discontinuation, arguing that another factor may be contributing.

ECG data:

Date	Timepoint	Heart rate (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTc (ms)
11JUL96	SCREEN	85	154	72	344	409
31JAN97	WEEK 28	80	160	90	370	430
17JUL97	WEEK 52	73	140	70	420	460
28AUG97	WEEK 100	83	160	60	380	450

Concomitant medication:

Concomitant medication:	Dosage*	Start	End
Psychotropic medication:			
Haloperidol	10 mg q day	22AUG97	not specified
Other concurrent medication:			
None			

Other adverse events (verbatim):

Other adverse events (verbatim):	Severity	Relation to study med	Start	End
Hematuria	mild	possible	31JAN97	not specified
Intermittent L side tremor hand, arm & foot	mild	possible	01OCT96	19JUN97
Intermittent bilateral tremors of hand	moderate	possible	20JUN97	not specified
Intermittent rt side tremor in hand, arm	mild	possible	19NOV96	19JUN97

Clinical laboratory tests:

Abnormal laboratory values:

Laboratory test:	Reference range	Baseline	Day28	Day198	Day365	Day380	Day400+(7)*	Day427+(34)*
Monocytes	0 - 10%	11.3		11		13		
MCV	76 - 100 cu microns	94			104	103		106
Serum gluc	60 - 115 mg/dL	94			163	134	147	129
Uric acid	2 - 9 mg/dL	8.2	9.3			9.6		9.1
SGPT (ALT)	0 - 55 U/L	41				60	63	
SGOT (AST)	0 - 50 U/L	33				68	71	
GGT	0 - 65 U/L	45			69	69		

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

Risperidone: Integrated Clinical Report dp 329 safety - glucose

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			
Serious adverse event (verbatim):	Severity	Relation to study med	Start	End
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

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	Heart 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:

<u>Psychotropic medication:</u>	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

Risperidone: Integrated Clinical Report dp 329 safety - glucose

<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: Integrated Clinical Report dp 329 safety - glucose

Risperidone—RIS-USA-79 Serious Adverse Event Summary

Subject:	A30302RED	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	Relation to study med	Start	End
Serious adverse event (verbatim):	Severity	possible	19APR98	not specified
Onset of diabetes	severe	possible	19APR98	26APR98
Syncope	severe			

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.

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

Risperidone: Integrated Clinical Report dp 329 safety - glucose

<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>
Flightheaded & fell down	mild	none	11JUN98	11JUN98
Dizziness	severe	possible	19APR98	26APR98
Runny nose	mild	possible	20JAN98	25FEB98
<u>Clinical laboratory tests:</u>				
<u>Abnormal laboratory values:</u>		(Day 0)		
<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

Risperidone: Integrated Clinical Report dp 329 safety - glucose

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

Subject:	A30349RED	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.

Risperidone: Integrated Clinical Report dp 329 safety - glucose

<u>ECG data:</u>						
<u>Date:</u>	<u>Timepoint</u>	<u>Heart rate (bpm)</u>	<u>PR (ms)</u>	<u>QRS (ms)</u>	<u>QT (ms)</u>	<u>QTc (ms)</u>
15JUL97	SCREEN	101	150	100	352	457
<u>Concomitant medication:</u>		<u>Dosage*</u>	<u>Start</u>	<u>End</u>		
<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		
Beclo methasone 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.

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

<u>Clinical laboratory tests:</u>		
Abnormal laboratory values:		
	(Day 0)	
<u>Laboratory test:</u>	<u>Reference range</u>	<u>Baseline</u>
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

Risperidone: Integrated Clinical Report dp 329 safety - glucose

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

Subject: RED #A30142	Investigator: RIIHIKANGAS R., MD
Age: 50 years	Trial medication: RISPERIDONE
Race: Caucasian	Treatment duration: 49 days
Sex: male	Treatment start: August 13, 1998
Country: REDACTED	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: peylonefritis 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)

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

Risperidone: Integrated Clinical Report dp 329 safety - glucose

A30142 (cont.)

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
pentoxifyverine 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

Risperidone: Integrated Clinical Report dp 329 safety - glucose

CONCOMITANT MEDICATION (A30142 cont.)

Medication	Start	End
Dosage		
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+6 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.

Risperidone: Integrated Clinical Report dp 329 safety - glucose

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

Patient: RED #A30030	Investigator: Bénnner 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); furosemide (40mg); 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).

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).

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.

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).

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.

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.

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

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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 acetone 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.

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

COUNTRY:	USA
INVESTIGATOR:	I. 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.

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.

RISPERIDONE-RIS-USA-63
PREMATURE DISCONTINUATION SUMMARY

COUNTRY:	USA
INVESTIGATOR:	K. Sakauye, 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.

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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.

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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).

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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.

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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.

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RISPERIDONE -- RIS-INT-23

COUNTRY :	REDACTED
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.

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RISPERIDONE -- RIS-INT-23 DEATH SUMMARY	
COUNTRY:	USA
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

■ 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, tbc 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 03/11/95 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 70 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.

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- 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

RISPERIDONE-RIS-USA-70
SERIOUS ADVERSE EVENT/PREATURE 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.

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 DISCONTINUATION:	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), triamcinolone 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), Rocheffin (October 20, 1997-unknown), influenza vaccine (October 6, 1997), 5% dextrose/1/2 normal saline

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), alclometasoné 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.

RISPERIDONE-RIS-USA-70
SERIOUS ADVERSE EVENT/PREATURE 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).

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JRP--TRIAL RIS-AUS-005 SERIOUS ADVERSE EVENT SUMMARY

Subject: RED #160	Investigator: AMES, D., MD
Age: 90 years	Trial medication: PLACEBO
Race: Caucasian	Treatment duration: 83 days
Sex: male	Treatment start: July 14, 1999
Country: AUSTRALIA	Treatment stop: October 4, 1999

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
*hypoglycaemia (hypoglycemia)	severe	doubtful	05SEP99	06SEP99	treatment	54
*haematemesis (haematemesis)	severe	possibly	06SEP99	06SEP99	treatment	55

** days after start treatment

BASELINE SUBJECT DATA

- Vascular Dementia: uncomplicated
- Baseline Total AGGRESSION: 35.0
- Baseline MMSE Total: 11
- TIME FROM THE PREV. PSYCHIATRIC INSTIT.: 1
- Medical and surgical history: not significant
- Concomitant disorders: genito-urinary: urinary/faecal incontinence, prostatectomy 1984; other: occasional falls
- Physical examination: neurological: brisk reflexes, abnormal gait.
- Previous medications: temazepam (10 mg p/o nocte prn)

TREATMENT DATA:

Trt. Phase	Treatment	Start	Stop	Daily Dose (mg)	Duration
WASH OUT	PLACEBO	07JUL1999	13JUL1999	0	7
TREATMENT	PLACEBO	14JUL1999	17AUG1999	0	35
TREATMENT	PLACEBO	18AUG1999	18AUG1999	0	1
TREATMENT	PLACEBO	19AUG1999	05SEP1999	0	18
TREATMENT	PLACEBO	06SEP1999	06SEP1999	0	1
TREATMENT	PLACEBO	07SEP1999	09SEP1999	0	3
TREATMENT	PLACEBO	10SEP1999	10SEP1999	0	1
TREATMENT	PLACEBO	11SEP1999	03OCT1999	0	23
TREATMENT	PLACEBO	04OCT1999	04OCT1999	0	1

CLINICAL NARRATIVE

RED had uncomplicated vascular dementia. On September 5, 1999, 54 days after the start of double-blind treatment with placebo, he had hypoglycemia (1.6 mmol/L). On the following day, he experienced hematemesis and was hospitalized. Both of these serious adverse events were judged severe and possibly related to treatment with the study drug. They resolved on September 6, 1999. The subject returned to the nursing home on September 10, 1999.

The subject had no significant medical or surgical history. Concomitant medical conditions at baseline, abnormalities at baseline physical examination, previous medications, vital signs data, concomitant medications, other adverse events, and clinical laboratory test abnormalities are provided in the corresponding sections of this patient profile.

VITAL SIGNS DATA

Date	Phase Time	Weight (kg)	Pulse (b/min)	SBP (mmHg)	DBP (mmHg)	BMI
06JUL99	TREATSCREENING		76	150	70	
04OCT99	TREATWEEK 12		60			

Risperidone: Integrated Clinical Report dp 329 safety - glucose

CONCOMITANT MEDICATION

Medication	Start	End
Dosage		
amlodipine besilate	before trial	ongoing at end of trial
5 mg p/o mane		
chloramphenicol	before trial	16JUL1999
instil tds		
fosinopril sodium	before trial	ongoing at end of trial
10 mg p/o mane		
gliclazide	before trial	06SEP1999
160 mg p/o bd		
lacri-lube	before trial	ongoing at end of trial
apply topical bd		
lactulose	before trial	ongoing at end of trial
20 mls p/o mane		
paracetamol	before trial	04AUG1999
500mg-1g p/o nocte		
quinine sulfate	before trial	ongoing at end of trial
300 mg p/o nocte		
sorbolene cream with 10% glycerine	before trial	ongoing at end of trial
top dry limbs bd prn		
temazepam	before trial	ongoing at end of trial
10 mg p/o nocte prn		
paracetamol	04AUG1999	ongoing at end of trial
500mg-1gp/onocte prn		
oxazepam	21AUG1999	27AUG1999
15 mg p/o bd		
oxazepam	27AUG1999	ongoing at end of trial
30 mg p/o bd		
lomectil	03SEP1999	04SEP1999
2 tablets tds p/oprn		
dextrose and sodium chloride injection	06SEP1999	06SEP1999
1000ml ivi 8hourly		
furosemide	06SEP1999	06SEP1999
80 mg ivi stat		
gliclazide	06SEP1999	07SEP1999
80 mg p/o daily		
glucagon hydrochloride	06SEP1999	06SEP1999
1mg imi statum		
glucose	06SEP1999	06SEP1999
15 grammes p/o stat		
insulin	06SEP1999	06SEP1999
4 u/s s/c stat		
ranitidine	06SEP1999	ongoing at end of trial
150 mg p/o bd		
sodium chloride	06SEP1999	06SEP1999
1000ml ivi 12 hourly		
a.p.c.	07SEP1999	11SEP1999
150 mg p/o daily		
glucose	07SEP1999	07SEP1999
1000ml ivi 12 hourly		
coloxyl with senna	08SEP1999	ongoing at end of trial
2 tablets p/o bd		
gliclazide	08SEP1999	08SEP1999
80 mg p/o bd		
isosorbide mononitrate	08SEP1999	11SEP1999
30 mg p/o daily		
travad enema	08SEP1999	08SEP1999
130 ml p/r stat		
gliclazide	09SEP1999	ongoing at end of trial
40 mg p/o daily		
isosorbide mononitrate	11SEP1999	ongoing at end of trial
60 sr mg p/o daily		
trimethoprim	11SEP1999	17SEP1999
300 mg p/o daily		

Risperidone: Integrated Clinical Report dp 329 safety - glucose

CONCOMITANT MEDICATION

Medication	Start	End
oxazepam 30 mg p/o daily	12SEP1999	12SEP1999
oxazepam 15 mg p/o daily	13SEP1999	13SEP1999

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
sleep disorder (interrupted sleep pattern)	moderate	possibly	21JUL99		treatment	8
aggressive reaction (increasing aggression)	mild	not	21AUG99	27AUG99	treatment	39
aggressive reaction (increasing aggression)	mild	not	27AUG99		treatment	45
constipation (faecal impaction)	moderate	possibly	02SEP99	08SEP99	treatment	51
diarrhoea (diarrhoea)	moderate	doubtful	02SEP99	04SEP99	treatment	51
fall (fall)	mild	possibly	03SEP99	03SEP99	treatment	52
bronchitis (moist chest)	mild	doubtful	06SEP99	06SEP99	treatment	55
bronchospasm (wheezy chest)	mild	doubtful	06SEP99	06SEP99	treatment	55
extrasystoles (irregular pulse)	moderate	possibly	06SEP99	06SEP99	treatment	55
pallor (pale colour)	moderate	possibly	06SEP99	06SEP99	treatment	55
pulmonary congestion (mild pulmonary venous congestion)	mild	not	06SEP99	06SEP99	treatment	55
urinary retention (urinary retention)	moderate	doubtful	06SEP99	09SEP99	treatment	55
urinary tract infection (urinary tract infection)	mild	not	07SEP99	17SEP99	treatment	56
somnolence (drowsiness)	mild	possibly	11SEP99	13SEP99	treatment	60
fall (fall)	mild	possibly	29SEP99	29SEP99	treatment	78
fall (fall)	mild	possibly	30SEP99	30SEP99	treatment	79
injury (black eyes)	moderate	not	30SEP99		treatment	79
somnolence (drowsiness)	moderate	possibly	03OCT99		treatment	82

** days after start treatment

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)
calcium (2.1-2.6 mmol/l)
2.08 at screening
vitamin b12 (0-200 pg/ml)
327 at screening

Risperidone: Integrated Clinical Report dp 329 safety - glucose

JRF--TRIAL RIS-INT-61
SERIOUS ADVERSE EVENT SUMMARY

PATIENT #A30445

Subject: RED #A30445	Investigator: Thumilla u., MD
Age: 50 years	Trial medication: RIS 6 MG ORAL
Race: Caucasian	Run-in duration: 56 days
Sex: female	Depot duration: 72 days
Country: RED	Treatment start: April 3, 2000
Diagnosis: 13 years	Treatment stop: June 26, 2000
Trial term: June 26, 2000	Term type: Completed

Trial termination reason:
treatment1=depot/oral(1), treatment2=depot/oral(2)
oral(1)=risperidone
oral(2)=risperidone for oral treatment group, placebo for depot treatment group

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbatim) Days**	Severity	Related	Start	End	Phase	
*hyperglycaemia (hyperglycaemia)	severe	not	14APR00	14APR00	treatment1	12
*hypertension aggravated (hypertension crisis)	severe	not	14APR00	14APR00	treatment1	12

** days after start treatment1

BASELINE SUBJECT DATA

- Diagnosis: schizophrenia(paranoid)
- Medical and surgical history: genito-urinary: uterus myomatosis
- Concomitant disorders: cardiovascular: hypertension under control by medication;
endocrine: diabetes mell. under control by medication; genito-urinary: urinary infection
; other: hyperuricaemia, liver increase (ggt)
- Physical examination: no abnormalities
- Previous medications: haloperidol decanoate (3 ml qmo)

TREATMENT DATA:

Trt. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
RUN-IN	RIS ORAL		07FEB2000	20FEB2000	6	14
RUN-IN	RIS ORAL		21FEB2000	06MAR2000	6	15
RUN-IN	RIS ORAL		07MAR2000	02APR2000	6	27
TREATMENT1	PLA DEPOT/RIS ORAL 1		03APR2000	16APR2000	0/6	14
TREATMENT1	PLA DEPOT/RIS ORAL 2		17APR2000	23APR2000	0/6	7
TREATMENT2	PLA DEPOT/RIS ORAL		24APR2000	01MAY2000	0/6	8
TREATMENT2	PLA DEPOT/RIS ORAL 3		02MAY2000	14MAY2000	0/6	13
TREATMENT2	PLA DEPOT/RIS ORAL 4		15MAY2000	28MAY2000	0/6	14
TREATMENT2	PLA DEPOT/RIS ORAL 5		29MAY2000	12JUN2000	0/6	15
TREATMENT2	PLA DEPOT/RIS ORAL 6		13JUN2000	26JUN2000	0/6	14

CLINICAL NARRATIVE

RED (CIRF ID A30445) was a white female with a 13-year history of paranoid schizophrenia. She was 50-years old at the time of trial entry. She entered the run-in period of clinical trial RIS-INT-61 on 7 February 2000 and completed run-in 2 April 2000. During run-in, she received risperidone 6 mg/day for 56 days. On 3 April, she was randomized to receive double blind treatment. She received oral risperidone 6 mg/day and placebo depot injection biweekly. Oral risperidone 6 mg/day was given until 26 June. She completed the trial on 26 June 2000.

On 14 April, she was hospitalized for the serious adverse events "hyperglycemia" and "hypertension crisis". During the trial, she also experienced the adverse events "headache" and "hypertension crisis".

Her medical history and concomitant medications are provided in the narrative profile. Concomitant disorders were significant for urinary tract infection and hyperuricemia as well as hypertension and diabetes that were both controlled by medication. Physical examination at baseline was normal. On 7 February, blood pressure at screening was 180/110, at baseline on 3 April, blood pressure was 145/100, on 2 May, it was 150/95 and on 26 June, was 160/105. ECG findings and clinical laboratory values are provided in the narrative profile.

The serious adverse events "hyperglycemia" and "hypertension crisis" resolved on 14 April. The investigator considered the "hyperglycemia" and "hypertension crisis" severe and not related to study treatment.

Both hypertension and diabetes were pre-existing conditions, controlled by medication. The study medication was not interrupted because of the events and the patient completed the trial. The sponsor considered a relationship with the use of risperidone unlikely.

ECG DATA

Date	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcF (ms)	QTcL (ms)
07FEB2000	TRT	SCREENING	72	170	100	400	438	425	426
03APR2000	TRT	BASELINE	80	170	80	400	462 BL	440	439
02MAY2000	TRT	WEEK 4	73	150	90	370	408	395	397
26JUN2000	TRT	WEEK 12	72	170	90	360	394	383	386

(A=Above normal B=Below normal *-Abnormal BL=Borderline PL=Prolonged)

VITAL SIGNS DATA

Date	Phase	Time	Weight (kg)	BMI	Stand/Supine Pulse (b/min)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
07FEB2000	TRT	SCREENING	90	31	85 / 80	180 / 180	110 / 110
03APR2000	TRT	BASELINE	90	31	108 / 100	145 / 140	100 / 95
02MAY2000	TRT	WEEK 4			100 / 96	150 / 150	95 / 95
26JUN2000	TRT	WEEK 12	93	32	88 / 80	160 / 155	105 / 105

Risperidone: Integrated Clinical Report dp 329 safety - glucose

CONCOMITANT MEDICATION

Medication	Start	End
Dosage		
amlodipine besilate		
5 mg od po	before trial	ongoing at end of trial
dyazide		
1 x od po	before trial	ongoing at end of trial
enalapril		
20 mg od po	before trial	ongoing at end of trial
glimepiride		
3 mg od po	before trial	ongoing at end of trial
metformin hydrochloride		
850 mg od po	before trial	ongoing at end of trial
panadeine co		
1 x po	13FEB2000	13FEB2000
glyceryl trinitrate		
1 x 0.8 mg sl	18FEB2000	18FEB2000
insulin		
8ie od sc	14APR2000	14APR2000
nifedipine		
20 mg od po	14APR2000	14APR2000

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
headache	moderate	not	13FEB00	13FEB00	run-in	-50
(headache)						
hypertension aggravated	moderate	not	18FEB00	18FEB00	run-in	-45
(hypertension crisis)						

** days after start treatment1

CLINICAL LABORATORY TESTS

The following laboratory tests had results outside of normal limits during the trial:

Test (laboratory limits, unit)		
alt (sgpt) (1-30 U/L)		
41 at screening	54 at baseline	37 at week 12
ast (sgot) (1-32 U/L)		
25 at screening	42 at baseline	23 at week 12
chloride (96-110 meq/l)		
97 at screening	95 at baseline	93 at week 12
creatinine (0.4-1.5 mg/dl)		
1.48 at screening	1.59 at baseline	1.59 at week 12
ggt (6-32 U/L)		
44 at screening	40 at baseline	39 at week 12
lymphocytes (25-45 %)		
11 at screening	17 at baseline	31 at week 12
monocytes (2-10 %)		
1 at screening	2 at baseline	4 at week 12
neutrophils (50-65 %)		
87 at screening	80 at baseline	65 at week 12
prolactin (2-23 ng/ml)		
52.5 at baseline	17.3 at week 12	
sodium (136-148 meq/l)		
134 at screening	131 at baseline	131 at week 12
urea (20-50 mg/dl)		
51 at screening	54 at baseline	83 at week 12
uric acid (2.5-6 mg/dl)		
7.6 at screening	8.4 at baseline	9.4 at week 12

Risperidone: Integrated Clinical Report dp 329 safety - glucose

PLASMA CONCENTRATIONS

Date	RIS, ng/ml	9-OH-RIS, ng/ml	ACTIVE MOIETY, ng/ml
03APR2000	1.18	28.1	29.3
17APR2000	NQ	1.66	1.7
02MAY2000	NQ	4.74	4.7
13JUN2000	NQ	2.11	2.1
15JUN2000	0.16	15.6	15.8
19JUN2000	46.5	63.6	110.1
26JUN2000	NQ	3.5	3.5

NQ=Not quantifiable (LOQ=0.1 ng/ml) NR=No Result

CGI

Date	Phase	Time	CGI
03APR2000	TRT	BASELINE	MODERATE
06MAY2000	TRT	RUN-IN	MODERATE
07FEE2000	TRT	SCREENING	MODERATE
13JUN2000	TRT	WEEK 10	MODERATE
26JUN2000	TRT	WEEK 12	MODERATE
17APR2000	TRT	WEEK 2	MODERATE
02MAY2000	TRT	WEEK 4	MODERATE
15MAY2000	TRT	WEEK 6	MODERATE
29MAY2000	TRT	WEEK 8	MODERATE

Risperidone: Integrated Clinical Report dp 329 safety - glucose

JRP--TRIAL RIS-INT-61
SERIOUS ADVERSE EVENT SUMMARY

PATIENT #A30755

Subject: REC #A30755	Investigator: David a., MD
Age: 54 years	Trial medication: RIS 2 MG ORAL
Race: Caucasian	Run-in duration: 64 days
Sex: male	Depot duration: 71 days
Country: REDACTED	Treatment start: July 13, 2000
Diagnosis: 28 years	Treatment stop: October 4, 2000
Trial term: October 5, 2000	Term.type: Completed

Trial termination reason:
treatment1=depot/oral(1), treatment2=depot/oral(2)
oral(1)=risperidone
oral(2)=risperidone for oral treatment group, placebo for depot treatment group

SERIOUS ADVERSE EVENTS: see * in table below

Adverse event (verbatim) Days**	Severity	Related	Start	End	Phase	
*diabetes mellitus (non insulin dependant diabetes mellitus)	moderate	doubtful	13JUL00		treatment1	1

** days after start treatment1

BASELINE SUBJECT DATA

- Diagnosis: schizophrenia(undifferentiated)
- Medical and surgical history: not significant
- Concomitant disorders: dermatological: psoriasis pathes on both legs; eyes: impaired acuity- needs mild bifacals; musculoskeletal: some occasional (legs) aches + pains w exercise
- Physical examination: breasts: some gynaecomastic; skin: 11 campbell de morgan's spots-trunk/ psoriasis pathes both legs, mild
- Previous medications: fluphenazine decanoate (10mg 4/52)

TREATMENT DATA:

Trt. Phase	Treatment	Inj.	Start	Stop	Dose (mg)	Duration
RUN-IN	RIS ORAL		10MAY2000	17MAY2000	0	8
RUN-IN	RIS ORAL		18MAY2000	31MAY2000	2	14
RUN-IN	RIS ORAL		01JUN2000	14JUN2000	2	14
RUN-IN	RIS ORAL		15JUN2000	12JUL2000	2	28
TREATMENT1	PLA DEPOT/RIS ORAL 1		13JUL2000	26JUL2000	0/2	14
TREATMENT1	PLA DEPOT/RIS ORAL 2		27JUL2000	02AUG2000	0/2	7
TREATMENT2	PLA DEPOT/RIS ORAL		03AUG2000	09AUG2000	0/2	7
TREATMENT2	PLA DEPOT/RIS ORAL 3		10AUG2000	23AUG2000	0/2	14
TREATMENT2	PLA DEPOT/RIS ORAL 4		24AUG2000	06SEP2000	0/2	14
TREATMENT2	PLA DEPOT/RIS ORAL 5		07SEP2000	20SEP2000	0/2	14
TREATMENT2	PLA DEPOT/RIS ORAL 6		21SEP2000	04OCT2000	0/2	14

CLINICAL NARRATIVE

RED (CRF ID A30755) was a white male with a 28-year history of undifferentiated schizophrenia. He was 54-years old at the time of trial entry. He entered the run-in period of clinical trial RIS-INT-61 on 10 May 2000 and completed the run-in on 12 July 2000. During the run-in, he received risperidone oral 0-2 mg/day for 64 days. On 13 July, he was randomized to receive double-blind treatment. He received oral risperidone 2 mg/day and placebo depot injections biweekly. Oral risperidone 2 mg/day was given until 4 October. He completed the trial on 5 October 2000.

On 13 July, the serious adverse event "non-insulin-dependent diabetes mellitus" occurred. On 15 May, at screening, glycosuria was detected on laboratory tests and on 13 July he was diagnosed with non-insulin dependent diabetes mellitus (NIDDM). He was asymptomatic during this event. He also experienced the adverse events "heartburn", "lingering taste of tablets", "morning unsteady on feet", "morning drowsiness", and "URI (cold)", "tight chest", "constipation" three times, and "headache" during the trial.

Prior medical history was not remarkable. Concomitant disorders and concomitant medications are listed in the narrative profile. Physical examination at baseline was unremarkable. Vital signs, ECG findings, and clinical laboratory values were not related to the serious adverse event.

The serious adverse event of "non-insulin-dependent diabetes mellitus" did not resolve. The investigator considered the adverse event moderately severe and doubtfully related to study treatment.

The NIDDM was pre-existing before the trial. The patient was randomized and completed the trial as planned. The sponsor considered a relationship with the use of risperidone highly unlikely.

ECG DATA

Date	Phase	Time	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcP (ms)	QTcL (ms)
10MAY2000	TRT	SCREENING	60	190	90	430	430 BL	430 BL	430 BL
13JUL2000	TRT	BASELINE	60	180	90	420	420	420	420
10AUG2000	TRT	WEEK 4	65	190	100	390	406	401	402
05OCT2000	TRT	WEEK 12	69	190	100	380	408	398	400

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

VITAL SIGNS DATA

Date	Phase	Time	Weight (kg)	BMI	Stand/Supine Pulse (b/min)	Stand/Supine SBP (mmHg)	Stand/Supine DBP (mmHg)
10MAY2000	TRT	SCREENING	91	33	/ 69	116 / 120	80 / 80
13JUL2000	TRT	BASELINE	89	32	66 / 64	120 / 99	81 / 57
10AUG2000	TRT	WEEK 4			/	134 / 113	76 / 62
04OCT2000	TRT	WEEK 12	86	31	95 / 65	114 / 96	74 / 50

Risperidone: Integrated Clinical Report dp 329 safety - glucose

CONCOMITANT MEDICATION

Medication	Start	End
Dosage		
acetylsalicylic acid		
(7150mg) 1 tablet	29MAY2000	30MAY2000
paracetamol		
500mg	30MAY2000	31MAY2000
paracetamol		
500mg	06JUN2000	07JUN2000
magnesium sulfate		
5mg	26SEP2000	26SEP2000
senna fruit		
2tablets	27SEP2000	27SEP2000
senna fruit		
2tablets	02OCT2000	02OCT2000
paracetamol		
250mg	03OCT2000	03OCT2000

OTHER ADVERSE EVENTS

Adverse event (verbatim)	Severity	Related	Start	End	Phase	Days**
dyspepsia	mild	possibly	18MAY00	16JUN00	run-in	-56
(heartburn)						
taste perversion	mild	probable	18MAY00	16JUN00	run-in	-56
(lingering taste of tablets)						
gait abnormal	mild	possibly	19MAY00	06JUL00	run-in	-55
(morning unsteady on feet)						
somnolence	mild	possibly	19MAY00	06JUL00	run-in	-55
(morning drowsiness)						
upper resp tract infection	mild	not	28MAY00	31JUL00	run-in	-46
(urti(cold))						
chest pain	mild	doubtful	25JUL00	26JUL00	treatment1	13
(tight chest)						
constipation	mild	doubtful	23SEP00	24SEP00	treatment2	73
(constipation)						
constipation	mild	doubtful	26SEP00	27SEP00	treatment2	76
(constipation)						
constipation	mild	doubtful	02OCT00	03OCT00	treatment2	82
(constipation)						
headache	mild	doubtful	03OCT00	03OCT00	treatment2	83
(headache)						

** days after start treatment1

CLINICAL LABORATORY TESTS

The following laboratory tests had results outside of normal limits during the trial:

Test (laboratory limits, unit)		
alkaline phosphatase (31-121 U/L)		
140 at screening	131 at baseline	109 at week 12
calcium (4-5.5 meq/l)		
5.4 at screening	5.6 at baseline	5.6 at week 12
ggt (10-49 U/L)		
76 at screening	49 at baseline	28 at week 12
lymphocytes (25-45 %)		
19.9 at screening	13.1 at baseline	17.5 at week 12
neutrophils (50-65 %)		
68.4 at screening	78.3 at baseline	72.1 at week 12

Risperidone: Integrated Clinical Report dp 329 safety - glucose

PLASMA CONCENTRATIONS

Date	RIS, ng/ml	9-OH-RIS, ng/ml	ACTIVE MOIETY, ng/ml
13JUL2000	1.98	11.5	13.5
27JUL2000	1.17	10.6	11.8
10AUG2000	2.08	12.3	14.4
21SEP2000	1.62	14.5	16.1
26SEP2000	1.25	11.5	12.8
28SEP2000	0.98	6.56	7.5
05OCT2000	1.14	10.8	11.9

NQ=Not quantifiable (LOQ=0.1 ng/ml) NR=No Result

CGI

Date	Phase	Time	CGI
13JUL2000	TRT	BASELINE	MILD
15JUN2000	TRT	RUN-IN	MILD
10MAY2000	TRT	SCREENING	MILD
21SEP2000	TRT	WEEK 10	MILD
04OCT2000	TRT	WEEK 12	MILD
27JUL2000	TRT	WEEK 2	MILD
10AUG2000	TRT	WEEK 4	MILD
24AUG2000	TRT	WEEK 6	MILD
07SEP2000	TRT	WEEK 8	MILD



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

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920 U.S. Highway 202
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Raritan, NJ 08869

RE: NDA # 20-272; 20-588
Risperdal (risperidone)
MACMIS # 12195

Dear Ms. Ohye:

This letter responds to Johnson & Johnson Pharmaceutical Research and Development, L.L.C.'s, (J&JPRD) letters on behalf of Janssen Pharmaceutica Products L.P. (Janssen) dated July 26, June 28, June 8, May 24, April 28, and April 19, 2004. These letters are regarding corrective actions taken in response to the Division of Drug Marketing, Advertising, and Communications' (DDMAC) serious concerns, voiced in its Warning Letter of April 19, 2004 regarding Janssen's dissemination of a Dear Healthcare Provider (DHCP) letter for Risperdal (risperidone). In addition, reference is made to DDMAC's May 27 and June 16, 2004 supplemental correspondences.

DDMAC reviewed Janssen's DHCP Letter, dated November 10, 2003, and concluded that it was false or misleading in violation of the Federal Food, Drug, and Cosmetic Act (Act). In its correspondence, J&JPRD indicated that it had discontinued all promotional materials for Risperdal containing same or similar claims, issued a corrective DHCP letter (Important Correction Of Drug Information Letter) to 754,000 healthcare providers, and issued an alternative DHCP letter that was posted on FDA's MedWatch website.

In light of the aforementioned actions taken by J&JPRD regarding Risperdal's promotional materials, DDMAC considers this matter closed.

JJRP 00509137
Confidential/Produced in Litigation Pursuant to Protective Order

Donna Ohye
J&JPRD
NDA 20-272/20-588 MACMIS 12195

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If you have any questions, please contact me by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 8B-45; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds you that only written communications are considered official. In all future correspondence regarding this matter, please refer to MACMIS # 12195 and the NDA numbers.

Sincerely,

{See appended electronic signature page}

Michael Brony, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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/s/

Michael Brony
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STATE OF SOUTH CAROLINA	)	IN THE COURT OF COMMON PLEAS
	)	
COUNTY OF SPARTANBURG	)	FOR THE SEVENTH JUDICIAL CIRCUIT
	)	
STATE OF SOUTH CAROLINA,	)	
ex rel. HENRY McMASTER, in his	)	
capacity as Attorney General of the State	)	
of South Carolina,	)	
	)	
PLAINTIFF,	)	Case No.: 2007-CP-42-1438
	)	
VERSUS	)	
	)	
JANSSEN PHARMACEUTICA, INC., et al.	)	
	)	
DEFENDANTS.	)	
_____	)	

EXPERT REPORT OF WILLIAM E. WECKER, PH.D.

DECEMBER 3, 2010

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1. My name is William E. Wecker. I am a statistician and applied mathematician. I received the Bachelor of Science degree (Basic Sciences) from the United States Air Force Academy in 1963. I received both the Master of Science degree (Operations Research, 1970) and Doctor of Philosophy degree (Statistics and Management Science, 1972) from the University of Michigan. I have served on the faculties of the University of Chicago, the University of California, Davis, and Stanford University where I taught statistics and applied mathematics at the graduate level. I have performed research in statistical theory, statistical methods, and applied mathematics since 1972. I am currently President of William E. Wecker Associates, Inc., an applied mathematics consulting firm located in Novato, California. I am a member of the American Statistical Association, the Institute of Mathematical Statistics, and the Society for Risk Analysis. I have served as associate editor of the *Journal of the American Statistical Association* for four years and of the *Journal of Business and Economic Statistics* for eighteen years. These qualifications and a list of my professional publications are shown in my curriculum vitae, which is appended to this report as Exhibit 1.

2. A list of all cases in which I have testified as an expert at trial or by deposition since January 1, 2006, is appended to this report as Exhibit 2. The billing rate for my time working on this matter is \$650 per hour.

3. My report consists of three primary sections that follow this introduction. First, in Section I, I identify and cite some of the primary allegations made by plaintiff of purportedly unlawful conduct by Janssen. Also in Section I, I identify the central questions that plaintiff's allegations raise for my expert analysis in this case and the data sources that are available for statistical analysis and evaluation of plaintiff's allegations. The available data include statistical surveys of South Carolina doctors, patient claims data produced by the

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plaintiff, and peer-reviewed epidemiological and experimental studies. The results of my statistical survey of South Carolina doctors and analysis of patient claims data are presented in Section II. In Section III, I review and analyze the eight peer-reviewed epidemiological studies existing as of November 2003 that compared the risk of diabetes in patients treated with Risperdal to the risk in untreated schizophrenia patients, patients treated with conventional antipsychotics, or patients treated with other second generation antipsychotics. Also in Section III, I discuss the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study.

4. In forming my opinions, I have considered the documents listed on Exhibit 3 and the data and electronic files provided to the plaintiff in conjunction with this report. It is my understanding that plaintiff has thus far provided reports from only two of the three experts it intends to present at trial in this case: Dr. Laura Plunkett and Dr. William Wirshing. I reserve the right to conduct further analysis of plaintiff's allegations and the work of plaintiff's experts, and further reserve the right to review and offer opinions on additional material as it becomes available.

5. I am providing electronic files that document my work and are a part of this report.

**I. Plaintiff's Allegations and Available Data Sources
for Analysis of Plaintiff's Allegations**

6. In plaintiff's Second Amended Complaint ("2d Am. Compl."), plaintiff alleges that Janssen made misrepresentations about Risperdal's safety and effectiveness and marketed Risperdal for off-label uses. In particular, plaintiff alleges:

a. Defendants made "false and misleading misrepresentations of fact regarding Risperdal's risk profile, including but not limited to misrepresenting the likelihood and severity of the side effects associated with Risperdal, including diabetes, stroke, high blood pressure, weight gain, and other serious and potentially life-threatening conditions." (2d Am. Compl. ¶ 57(a).)

b. Defendants "misrepresent[ed] that Risperdal is safer and more effective than less expensive first generation 'typical' antipsychotics." (2d Am. Compl. ¶ 57(c).)

c. Defendants "heavily marketed Risperdal for multiple non-approved purposes." (2d Am. Compl. ¶ 23.)

d. A November 10, 2003 mailing from defendant Janssen to health care providers misled doctors concerning the risk of diabetes with Risperdal. (2d Am. Compl. ¶ 46.)

e. "[T]he CATIE study proved what Defendants knew since launching Risperdal: (1) that Risperdal is no more effective in treating schizophrenia; (2) that Risperdal is no safer; and (3) that Risperdal has intolerable side effects making it no more desirable than the less expensive atypical antipsychotics." (2d Am. Compl. ¶ 52.)

7. Plaintiff's allegations raise several questions for my analysis. At a broad level, the question for analysis is whether the allegations of wrongful conduct by Janssen are valid. On a more specific level, plaintiff's allegations raise the questions of how Risperdal's safety and efficacy compare to first generation antipsychotics and other second generation antipsychotics, how Janssen marketed Risperdal to doctors in South Carolina, and how South Carolina patients responded when treated with Risperdal, as compared to alternative medications. Plaintiff's allegations concerning Janssen's November 10, 2003 mailing to health

care providers raise the question of whether data and literature—in the form of South Carolina patient claims data and the eight peer-reviewed epidemiological studies cited by Janssen—support the statements Janssen made in the cover letter that accompanied the revised Risperdal package insert that Janssen sent to South Carolina doctors. Finally, plaintiff's allegations regarding the CATIE study raise the question of whether the conclusions reached by the study or those that plaintiff attempts to draw from it are valid.

8. I have identified three primary, available data sources that provide information related to the fundamental questions raised by plaintiff's allegations:

a. Documented South Carolina physician experience, such as may be found from South Carolina doctors who treat patients with Risperdal, including the doctors' experience with Risperdal's efficacy, experience with the potential side effects of antipsychotic medications, the circumstances in which off-label use is regarded by the physician as appropriate, and Janssen promotional practices.

b. Observational data, such as the claims data produced by plaintiff from the State Fee-for-Service ("FFS") and State Health Plan ("SHP") benefits programs.

c. Published experimental and epidemiological studies.

9. My analysis of physician experience and observational data is explained in Section II, below. I address published experimental and epidemiological studies in Section III. The explanations provided here are supplemented by the presentation of results in the tables and charts at the end of this report and in the electronic files that are being produced with this report and are a part of my expert work in this case.

II. Statistical Analysis of Plaintiff's Allegations

A. Documented Physician Experience

10. Given the size of the relevant prescriber population, it would be prohibitively time-consuming and expensive to interview each prescriber of Risperdal in South

Carolina concerning his or her experience with Risperdal and other antipsychotic medications. However, a properly representative sample of South Carolina doctors provides an economically feasible, reasonably accurate approximation of the same information. It is generally accepted among professional statisticians as well as scientists and scholars in related fields that statistical sampling is the only generally applicable, scientifically valid method for creating a representative sample from a universe that is too large to process exhaustively. By means of statistical sampling it is possible to produce unbiased, reasonably accurate approximations, having a known degree of potential error, to questions whose exact answers would be impracticably expensive or burdensome to obtain. I therefore obtained information about the experience of South Carolina doctors from legal depositions of randomly identified doctors who treated FFS and SHP beneficiaries in the State.

11. The theory and practice of statistical sampling, including sample surveys of human subjects, has been a fundamental topic within the science of statistics at least since the early twentieth century. During the decades of my education and career as a professional statistician in academia and consulting, I have acquired extensive experience with numerous aspects of sampling theory, sample and survey design, sample and survey implementation, and the analysis of sample and survey data.

12. Richard Johnson and Gouri Bhattacharyya recognized the importance of statistical sampling in their text *Statistics Principles and Methods*: "The subject of statistics provides the methodology to make inferences about the population from the collection and

analysis of sample data. These methods enable one to derive plausible generalizations and then assess the extent of uncertainty underlying these generalizations.”¹

13. Leading statistician William Cochran has also recognized the importance of statistical sampling for decision-makers in his book *Sampling Techniques*.²

14. Johnson and Bhattacharyya emphasize that “[s]tatistical concepts are also essential during the planning stage of an investigation when decisions must be made as to the mode and extent of the sampling process,” thus the “design of the sampling process is an important step” and “[a] good design for the process of data collection permits efficient inferences, often with a straightforward analysis.”³

15. In this case, the population sampled consists of doctors who prescribed antipsychotic drugs for South Carolina patients in the Fee-for-Service (FFS) or State Health Plan (SHP) claims databases.

16. Generally speaking, physicians who prescribed antipsychotic drugs to greater numbers of patients can be expected to have more experience regarding the efficacy of Risperdal and more experience regarding marketing and promotional activities of Janssen than physicians with fewer such patients. Because the Court limited Janssen to surveying 20 doctors through deposition, my survey sample was randomly identified from the 101 doctors who prescribed antipsychotics most frequently.⁴

¹ Richard Johnson and Gouri Bhattacharyya, *Statistics Principles and Methods*, John Wiley & Sons, 3rd edition, 1996, 14.

² Cochran, William G., *Sampling Techniques*, John Wiley & Sons, New York, 1977.

³ Johnson and Bhattacharyya, *op. cit.*, 14.

⁴ The population to be sampled was the top 100 prescribers. Two doctors tied for 100th place, so the sample was drawn from a population of 101 prescribers.

17. From the 101 most frequent prescribers, I selected, at random, with equal probability of selection, a sample of 20.⁵ I used a random process—a sequence of random numbers generated by a computer—to identify the final sample members from a list of all doctors eligible for selection.⁶ This random selection procedure guarantees a statistically representative sample because it rules out any purposive or inadvertent selection bias that could skew the composition of the sample towards any favored subgroup of doctors. Random sampling of this kind is a standard procedure in scientific survey research.

18. Counsel for Janssen endeavored to contact the selected doctors in the deposition sample to arrange for and conduct their depositions. Certain of the selected doctors were not available for deposition.⁷ In each of those instances, the next member in the random selection sequence was designated as a replacement.

19. The specific questions posed to the 20 doctors who were deposed are set forth in Exhibit 4 together with the doctors' responses. Exhibit 4 also shows the percent of doctor-deponents answering "yes" or "probably yes" to each question.

20. The questions to doctors in deposition asked doctors about their experience with Risperdal and other antipsychotic medications and their specific exposure to Janssen promotional activity and communications. I sought fact-based answers from doctors in response to questions about whether Janssen had marketed Risperdal to them for off-label uses,

⁵ "Equal probability samples" are also called "simple random samples."

⁶ I employed the following standard procedure for selecting the sample. Let N denote the population size, and n the designated sample size. I used the SAS statistical software package to assign independently to each of the N population members a decimal-fraction random number between zero and one, equally likely to fall within either of any given pair of subintervals of equal length within the overall interval from zero to one. I then sorted the list of N population members in order of these assigned random numbers, and selected the first n members of the sorted list as the sample.

⁷ One doctor was unavailable due to terminal illness; one had moved to California; one refused to be deposed; and three could not be located. See Wecker electronic file "sample list.xls".

whether they had received specific correspondence from Janssen, and how their patients fared while taking Risperdal and other antipsychotics.

21. As noted, the methodology I employed is a well-established one that allows statisticians to reach conclusions about a population from the collection and analysis of sample data. Exhibit 5 shows the conclusions that can be derived from the responses of 20 doctor-deponents about the entire population of the 101 most frequent prescribers. In aggregate, those 101 doctors wrote 33 percent of the antipsychotic prescriptions paid for through the FFS and SHP programs.⁸

22. The depositions regarding the actual experience of South Carolina doctors prescribing Risperdal and other antipsychotics yield results that contradict the plaintiff's allegations. For example, the great majority of physicians affirmed the following statements based on their experience: Risperdal is generally effective for treating the positive symptoms of schizophrenia; Risperdal is generally effective for treating the negative symptoms of schizophrenia; Risperdal typically has a more moderate side effect profile than first generation antipsychotics; both efficacy and tolerability increase the likelihood that a patient will take an antipsychotic medication consistently; and patients who consistently take their antipsychotic medications are less likely to require costly follow-up treatment, such as in-patient psychiatric care, than patients who do not consistently take their medications.

23. Plaintiff's allegations are also contradicted by the result that no doctors affirmed that: any Janssen sales representative ever promoted to them any off-label use of Risperdal in children or geriatric patients; or that any Janssen sales representative ever promoted to them any off-label use of Risperdal at all. No Janssen sales representative ever represented

⁸ See Wecker electronic file "ffs_top_101.apd_pct.lst".

anything inconsistent with the warnings about Risperdal that are provided on the FDA-approved package insert, and no Janssen sales representative ever misrepresented information about the potential side effects associated with Risperdal use to a deposed doctor.

24. Only a small number of physicians recall seeing Janssen's November 10, 2003 mailing to health care professionals. Of those, almost none changed their choice of antipsychotic medication based on the mailing. These responses are consistent with the history of the frequency with which doctors prescribed Risperdal, discussed below, which showed almost no change in Risperdal sales as a percentage of overall antipsychotic prescriptions after the mailing was sent to South Carolina doctors.

25. The commonly-used and accepted statistical tools that allow me to draw conclusions about the entire population of frequent South Carolina prescribers to FFS and SHP patients based on the answers provided in the survey show that the experience of South Carolina doctors contradicts plaintiff's allegations. The sample size of 20 allows me to reach reliable population estimates for the 101 most frequent prescribers, as shown in Exhibit 5.

B. Observational Data

26. Claims data produced by the plaintiff from South Carolina State databases is also useful for analyzing plaintiff's allegations.⁹ I performed three different analyses. First, I was able to utilize claims data produced by the State to compare the incidence of side effects alleged by plaintiff to be risks from Risperdal use to the incidence of the same side effects in untreated patients suffering from psychotic disorders; patients treated with first generation (conventional) antipsychotics; and patients treated with other second generation (atypical)

⁹ For my analyses of plaintiff's claims data, I combined HMO claims data with the FFS claims data. The two programs use a common patient identification code and some patients had claims records in both data bases.

antipsychotics. Second, I was able to utilize claims data to compare time to discontinuation—the primary measure of efficacy of the CATIE study—in Risperdal patients to patients using first generation antipsychotics. Third, I was able to determine Risperdal use as a percentage of all antipsychotic use by patients in the FFS or SHP programs over time.

B.1. Incidence of Alleged Side Effects

27. I analyzed the claims data to calculate the incidence of side effects that plaintiff alleges are caused by Risperdal, and to compare the incidence of those side effects in patients receiving Risperdal to the incidence of those side effects in untreated patients suffering from psychotic disorders; patients treated with first generation (conventional) antipsychotics; and patients treated with other second generation (atypical) antipsychotics.

28. In order to perform this analysis, I first identified patients who, based on their FFS or SHP claims, were receiving only Risperdal, only first generation antipsychotics, or only other second generation antipsychotics. I then examined all claims in the 36 months after their first antipsychotic drug prescription for diagnoses indicating an alleged side effect. To attempt to ensure that the first antipsychotic drug prescription recorded in the State claims data was a patient's first use of the drug, I required a minimum of 12 months of uninterrupted eligibility prior to the first antipsychotic drug prescription. To attempt to ensure that I was comparing patients with similar histories with respect to each side effect, I required that there be no diagnosis indicating the side effect prior to the first antipsychotic drug prescription. To analyze untreated patients, I separately identified patients with uninterrupted eligibility for a period of at least 36 months prior to their first antipsychotic drug prescription and no diagnosis indicating the side effect prior to the 36 month period. I then examined all claims in that 36 month period for diagnoses indicating an alleged side effect. I analyzed two time periods: the

full claims data base, providing data for 1994–2007 and the period limited to claims on or before November 10, 2003.¹⁰

29. The results of a direct comparison of the side effects reported in the claims database, for patients treated with different antipsychotic drugs, is shown in Exhibits 6 and 7. The percents of South Carolina patients with first alleged side effect diagnosis during the 36 months after their first antipsychotic drug prescription (treated patients) or before their first antipsychotic drug prescription reflect elevated side effect rates compared to Risperdal. Statistically significant differences from Risperdal are indicated by asterisks.

30. My analysis shows that:

a. Diabetes. Patients treated with conventional antipsychotics, patients treated with other atypical antipsychotics, and untreated patients had a statistically significantly elevated risk of diabetes compared to patients treated with Risperdal, whether measured based on analysis of all data or data existing as of November 10, 2003.

b. Metabolic adverse events.¹¹ Patients treated with conventional antipsychotics, patients treated with other atypical antipsychotics, and untreated patients had a statistically significantly elevated risk of metabolic adverse events compared to patients treated with Risperdal based on analysis of all data. Patients treated with other atypical antipsychotics had a statistically significantly elevated risk of metabolic adverse events compared to patients treated with Risperdal based on analysis of data existing as of November 10, 2003.

c. Increased prolactin secretion. Patients treated with conventional antipsychotics, patients treated with other atypical antipsychotics, and

¹⁰ I do not believe it is proper to limit analysis to data existing as of November 10, 2003 when seeking to determine whether the South Carolina claims data supports statements made by Janssen about Risperdal in the November 10, 2003 mailing. Instead, statisticians and other scientists should look at all available evidence, regardless of when it became available, to evaluate whether Janssen's statements were true or false. I have nevertheless included analysis of data as of November 10, 2003, in case plaintiff or any of its experts take the position that the truth or falsity of Janssen's communications should be evaluated without reference to anything that occurred after Janssen sent the November 10, 2003 mailing.

¹¹ Includes diabetes mellitus, secondary diabetes mellitus, abnormal glucose, abnormal weight gain, obesity, and other hyperalimentation.

untreated patients had a statistically significantly elevated risk of increased prolactin secretion compared to patients treated with Risperdal based on analysis of all data.¹²

31. The data for South Carolina patients contradicts the opinion of plaintiff's expert Dr. William Wirshing that "risperidone elevates prolactin more than any marketed antipsychotic except the more recently marketed Janssen product paliperidone, a metabolite of risperidone." (Wirshing Report, p. 7). Dr. Wirshing's criticism of Janssen for "believ[ing] that the FDA mandated class labeling change and to a slightly lesser extent the consensus guidelines painted all of the medications with the same toxic brush" (Wirshing Report, p. 8) is similarly contradicted by the experience of South Carolina patients, because patient experience demonstrates differences in risk for Risperdal compared to other antipsychotics.

B.2. Time to Discontinuation

32. Plaintiff alleges in its Petition that the authors of the CATIE study "concluded that Risperdal is no more effective than the first generation, 'typical' antipsychotic, perphenazine, in treating schizophrenia. In addition, the time to discontinuation because of intolerable side effects, including movement disorders, were similar among all groups." (2d Am. Compl., ¶ 52.)

33. The CATIE study used "all-cause discontinuation" as the primary outcome measure of efficacy, meaning that the "failure" of a drug was attributed to the patient's discontinuation of the drug for any reason. The longer a patient took a drug in the CATIE trial, the more effective it was deemed to be by the study authors. I will return to the question of what the CATIE study shows, or does not show, about "all-cause discontinuation" times. But first, I

¹² The November 10, 2003 mailing did not discuss increased prolactin secretion.

will describe my analysis of all-cause discontinuation times in the South Carolina population of State beneficiaries.

34. I have performed a statistical analysis of claims contained in the FFS and SHP data to determine all-cause discontinuation times in the South Carolina population of State beneficiaries. Using the claims data, I analyzed the comparative time to discontinuation for South Carolina patients treated with different antipsychotics. In order to be confident that I was measuring the first use of a drug, or first use after a substantial period of time in which the patient had not taken the drug for which I was measuring time to discontinuation, I identified those claims that were preceded by a minimum of 12 months of uninterrupted eligibility with no claims for the drug in question.

35. I then measured time to discontinuation following the first prescription by tracking patient claims histories for 18 months, as the CATIE study does. To determine discontinuation, I looked for periods of time without refills that followed the expiration of a patient's last prescription for the drug using three different, alternative time periods without refills to define discontinuation: 15 days, 30 days and 60 days. For example, if a patient received a prescription for a 30-day supply of Risperdal on April 1, but did not obtain another prescription until May 28, the patient would be deemed to have discontinued Risperdal use under the 15 days period, but not the 30 day or 60 day periods, because there was a 28 day period without a Risperdal refill prescription following the expiration of the 30 days supply prescribed on April 1. There is support in the medical literature for each of the time periods I use to define discontinuation: 15 days,¹³ 30 days,¹⁴ and 60 days.¹⁵

¹³ Mullins, C. Daniel, *et al.*, *Risk of discontinuation of atypical antipsychotic agents in the treatment of schizophrenia*, Schizophrenia Research, Vol. 98 (2008), § 2.3.1.1 p. 9; Ren, X. S., *et al.*, *An alternative approach to*

36. My results show that Risperdal has a longer time to discontinuation compared to first generation antipsychotics in the FFS and SHP population under each of the three definitions of time to discontinuation. The complete results are set out in Exhibit 8. My analysis shows that:

a. Defining discontinuation as a 60-day period. Average time to discontinuation was 211 days for Risperdal, 133 days for perphenazine, 130 days for Haldol, and 58 days for all other first generation antipsychotics considered as a group.

b. Defining discontinuation as a 30-day period. Average time to discontinuation was 166 days for Risperdal, 107 days for perphenazine, 99 days for Haldol, and 44 days for all other first generation antipsychotics considered as a group.

c. Defining discontinuation as a 15-day period. Average time to discontinuation was 126 days for Risperdal, 83 days for perphenazine, 78 days for Haldol, and 35 days for all other first generation antipsychotics considered as a group.

B.3. Risperdal Use Over Time

37. Using the claims data, I was also able to analyze Risperdal prescriptions as a percentage of all antipsychotic prescriptions paid for by the State through the FFS or SHP benefits programs and determine whether the comparative frequency of Risperdal prescriptions changed following events that plaintiff cites in its Complaint: the November 10, 2003 and July 21, 2004 mailings from Janssen to health care providers; the April 2005 FDA advisory and

measuring treatment persistence with antipsychotic agents among patients with schizophrenia in the Veterans Health Administration, Neuropsychiatric Disease and Treatment, Vol. 3, No. 2 (2007), p. 279; Ren, X. S., et al., Treatment persistence: a comparison among patients with schizophrenia who were initiated on atypical antipsychotic agents, J. Clin. Pharm. and Therap., Vol. 31 (2006), p. 59.

¹⁴ Ren, X. S., et al., *An alternative approach to measuring treatment persistence with antipsychotic agents among patients with schizophrenia in the Veterans Health Administration, Neuropsychiatric Disease and Treatment, Vol. 3, No. 2 (2007), p. 279.*

¹⁵ Kilzieh, Nael, et al., *Time to Discontinuation and Self-Discontinuation of Olanzapine and Risperidone in Patients With Schizophrenia in a Naturalistic Outpatient Setting, J. Clin. Psychopharmacol., Vol 28, No. 1 (Feb. 2008), p. 75; Zhu, Baojin, et al., Time to Discontinuation of Depot and Oral First-Generation Antipsychotics in the Usual Care of Schizophrenia, Psychiatric Services, Vol. 59, No. 3 (Mar. 2008), p. 316.*

subsequent black box warning for geriatric use; or the publication of the CATIE trial results in September 2005.

38. In order to determine the percentage of all antipsychotic prescriptions that Risperdal accounts for, I first eliminated claims that were reversed and duplicate claims within the database, so that each prescription for an antipsychotic medication would be counted only once. I then counted Risperdal prescriptions for each month from January 2003–December 2005. I separately counted all antipsychotic prescriptions in the same months. It was then straightforward to determine the number of Risperdal prescriptions as a percentage of all antipsychotic prescriptions paid for by the State through the FFS and SHP programs.

39. The results of my analysis are presented numerically and graphically in Exhibit 9. As the graph in Exhibit 9 shows, I was able to specifically analyze whether the events cited in the Complaint were followed by any change in the frequency with which South Carolina doctors prescribed Risperdal to patients in the FFS or SHP programs, as compared to all antipsychotic prescriptions.

40. In particular, I found no change in Risperdal prescribing frequency following Janssen's November 10, 2003 mailing to health care providers. If, as plaintiff contends, Janssen misled doctors about Risperdal's safety compared to other antipsychotics, I would expect to see an increase in the frequency with which doctors prescribed Risperdal compared to other antipsychotics. There was no such increase.

41. There was likewise no change in Risperdal prescribing frequency following July 2004, when Janssen sent its "correction" letter to South Carolina doctors at the request of the DDMAC division of FDA. The data also demonstrates that Risperdal use did not decline after the FDA issued its April 2005 advisory and subsequently required a black box

warning for risk of death in geriatric patients or in the time period following the publication of the CATIE study results in September 2005. If, as plaintiff contends, these events mark times when doctors were exposed to information previously withheld or when “the public perception of Risperdal created by Defendants was dealt a crushing blow” (2d Am. Compl. ¶ 50), I would expect to see a decline in the frequency with which doctors prescribed Risperdal compared to other antipsychotics. That did not occur.

III. Analysis of Peer-Reviewed Literature

A. The Eight Studies Cited by Janssen in Its November 10, 2003 Mailing

42. Plaintiff alleges that a November 10, 2003 mailing from Janssen to doctors in South Carolina contained misleading information about the risk of diabetes in patients taking Risperdal. As shown in Exhibits 4–7 and addressed above, the experience of South Carolina doctors and South Carolina patients supports the statements that Janssen made in the mailing:

Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiological research¹⁻³ suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

Janssen’s statements are also supported by the eight then-existing peer-reviewed epidemiological studies addressing the risk of diabetes in patients taking Risperdal compared to untreated patients, patients taking conventional antipsychotics and patients taking other atypical antipsychotics.

43. The eight studies cited by Janssen, which collectively analyze data from 6 million patients,¹⁶ are:

¹⁶ See Wecker electronic file “eight studies patient counts.xls”.

- a. Buse JB, Cavazonni P, Hornbuckle K et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiology* 2003; 56: 164-170.
- b. Caro JJ, Ward A, Levinton C and Robinson K. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry* 2002; 63:1135-1139.
- c. Fuller MA, Shermock KM, Secic M and Grogg AL. Comparative study of the development of diabetes mellitus in patients taking risperidone and olanzapine. *Pharmacotherapy* 2003; 23(8): 1037-1043.
- d. Gianfrancesco F, White R, Wang RH and Nasrallah HA. Antipsychotic-induced type 2 diabetes: evidence from a large health plan database. *J Clin Psychopharmacol* 2003; 23(4): 328-335 ("Gianfrancesco 1").
- e. Gianfrancesco F, Grogg AL, Mahmoud RA et al. Differential effects of antipsychotic agents on the risk of development of type 2 diabetes mellitus in patients with mood disorders. *Clin Therapeutics* 2003; 25(4): 1150-1171 ("Gianfrancesco 2").
- f. Gianfrancesco F, Grogg AL, Mahmoud RA et al. Differential effect of risperidone, olanzapine, clozapine and conventional antipsychotics on type II diabetes: Findings from a large health plan database. *J Clin Psychiatry* 2002; 63: 920-930 ("Gianfrancesco 3").
- g. Koro CE, Fedder DO, L'Italien GJ et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 2002; 325: 243-245.
- h. Sernyak MJ, Leslie DL, Alarcon RD et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry* 2002; 159: 561-566.

44. I have reviewed and analyzed the statistical conclusions presented in the eight studies. Four of the eight studies contain results comparing patients treated with Risperdal to untreated patients: Gianfrancesco 1, Gianfrancesco 2, Gianfrancesco 3 and Koro. All four of these studies find "that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients"

45. Six of the eight studies contain results comparing patients treated with Risperdal to patients treated with conventional antipsychotics: Buse, Gianfrancesco 1, Gianfrancesco 2, Gianfrancesco 3, Koro and Sernyak. All six of these studies find “that RISPERDAL is not associated with an increased risk of diabetes when compared to ... patients treated with conventional antipsychotics.”

46. Buse warrants additional attention. Buse found overall that the incidence of diabetes mellitus for patients treated with Risperdal was lower than for patients treated with conventional antipsychotics. The hazard ratio for Risperdal was also lower than the hazard ratio for conventional antipsychotics.¹⁷ Buse separately reported results for a subgroup analysis that compared each of the four atypical antipsychotics, including Risperdal, to the haloperidol cohort.¹⁸ As a part of his subgroup analysis, Buse calculated that Risperdal’s hazard ratio compared to haloperidol was 1.23, with a 95% confidence interval of 1.01–1.50 and a p-value of 0.040. A p-value of 0.040 would indicate a statistically significant result for a primary endpoint of a study, but it does not indicate a statistically significant result for a secondary, subgroup analysis. Subgroup p-values need to be interpreted based on the number of comparisons made in subgroups that are analyzed—at least four in this case.¹⁹ Properly interpreted, the p-value of 0.040, which is part of the haloperidol subgroup analysis is not a statistically significant result.²⁰

¹⁷ Buse at 168, Table 3.

¹⁸ Buse at 168, Table 4.

¹⁹ Walsh, Bruce. *Multiple Comparisons: Bonferroni Corrections and False Discovery Rates*, Lecture notes for EEB 581, 2004.

²⁰ There are several formulaic ways to assess statistical significance for a subgroup analysis. The most common and easiest method to apply is the method of Bonferroni. (See Walsh, *op. cit.*) In the case of the haloperidol subgroup analysis and the p-value of 0.040, which is a part of that analysis, the Bonferroni p-value is 0.16 ($= 4 \times 0.040$) which is not a statistically significant result.

47. All eight studies contain results comparing patients treated with Risperdal to patients treated with another atypical antipsychotic, and four of those eight found statistically significant results: Ward, Fuller, Gianfrancesco 2, and Gianfrancesco 3. All four of these studies find “that RISPERDAL is associated with a [statistically significantly] lower risk of diabetes than some other studied atypical antipsychotics.”

48. Taken together, the results of the eight studies, like the experience of South Carolina doctors and patients, contradict the contention of plaintiff’s expert Laura Plunkett, that “the language of the November 2003 ‘Dear Health Care Provider’ letter was not an accurate reflection of the risks posed by Risperdal.” (Plunkett Report, ¶ 50.) Contrary to Dr. Plunkett’s opinion, Janssen’s statement in the mailing was an accurate reflection of the risks posed by Risperdal, whether judged by the then-existing body of published peer-reviewed epidemiological literature or the data from South Carolina doctors and patients.

B. The CATIE Study

49. As described above, the experience of South Carolina doctors with Risperdal and other antipsychotic medications contradicts plaintiff’s interpretation of the CATIE study:

[T]he CATIE study proved what Defendants knew since launching Risperdal: (1) that Risperdal is no more effective in treating schizophrenia; (2) that Risperdal is no safer; and (3) that Risperdal has intolerable side effects making it no more desirable than the less expensive atypical antipsychotics. (2d Am. Compl. ¶ 52.)

In the experience of South Carolina doctors, Risperdal is more effective; has a more moderate side effect profile; and is better tolerated than first generation antipsychotics.

50. The experience of South Carolina patients also contradicts plaintiff’s interpretation of the CATIE study. Time to discontinuation of Risperdal, for South Carolina

patients, is longer than time to discontinuation of perphenazine, Haldol, or other first generation antipsychotics.

51. It takes no deep statistical analysis to show that the CATIE study itself demonstrates that Risperdal is more effective than and safer than perphenazine, the first generation drug included in the CATIE study. The study protocol states that perphenazine is “contraindicated” for patients with a prior history of tardive dyskinesia.²¹ This contraindication alone is sufficient to show that Risperdal is more effective than and safer than perphenazine for at least this large segment of the patient population.

52. Any direct comparisons of results from the perphenazine group to other treatment groups in the CATIE study will produce only ambiguous results, because the perphenazine group excluded patients with tardive dyskinesia while the other groups did not. Thus, the perphenazine group differs from the other groups in two ways: a difference in treatment and a difference in the patients treated. Because the perphenazine group differs from the other groups in more than one way, it is not valid to claim that any difference in outcomes for the perphenazine group versus any of the other treatment groups is due to the difference in treatment alone.

53. In an apparent attempt to cure the problem caused by the difference in patients treated with perphenazine compared to patients who received other treatments, the CATIE study chose to ignore results from patients with a prior history of tardive dyskinesia when making certain comparisons between treatment groups. But ignoring patients with a prior history of tardive dyskinesia is not a cure, because perphenazine, which is contraindicated for such patients, can be expected to have a differential and less satisfactory outcome for such

²¹ Protocol, Comparative Effectiveness of Antipsychotic Medications in Patients with Schizophrenia, 26-27.

patients. Ignoring outcomes for patients for whom perphenazine is expected to be ineffective or harmful amounts to ignoring an important difference in treatment results that will occur in the general population, which makes such comparisons inapplicable to the general population.

IV. Conclusion

54. In summary, for the reasons I have explained, statistical analysis of the primary data sources that provide information related to the central questions at issue refutes plaintiff's allegations.

December 3, 2010

A handwritten signature in black ink, appearing to read 'W. Wecker', with a horizontal line drawn underneath it.

William E. Wecker

December 2010

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EDUCATION

B.S. Basic Science, U.S. Air Force Academy (1963)
M.S. Operations Research, University of Michigan (1970)
Ph.D. Statistics and Management Science, University of Michigan (1972)

EMPLOYMENT

1963-1967 Fighter pilot, U.S. Air Force
1968-1969 Chief of Protocol, U.S. Air Force, Berlin, Germany
1970-1972 Graduate Student, University of Michigan
1973-1976 Assistant Professor, Graduate School of Business, University of Chicago
1977-1983 Associate Professor, Graduate School of Business, University of Chicago
1984-1985 Associate Professor, Graduate School of Management, University of California, Davis
1985-1989 Professor, Graduate School of Management, University of California, Davis
1994-1998 Consulting Professor of Law, School of Law, Stanford University
1990- President, William E. Wecker Associates, Inc.

ACTIVITIES

1977-1981 Associate Editor (Theory and Methods), Journal of the American Statistical Association
1981-1999 Associate Editor, Journal of Business and Economic Statistics
1990-1992 Management Committee, Journal of Business and Economic Statistics
1976-1994 Seminar Leader, NSF/NBER Seminar on Time Series Analysis
1993-1994 National Advisory Council on Environmental Policy and Technology
(Lead Subcommittee)

Member of: American Association for the Advancement of Science
American Statistical Association
Institute of Mathematical Statistics
Society for Risk Analysis

PUBLICATIONS

- "A Nonparametric Approach to the Construction of Prediction Intervals for Time Series Forecasts" (with W. A. Spivey), Proceedings of the Business and Economic Statistics Section—American Statistical Association, 1972.
- "Regional Economic Forecasting: Concepts and Methodology" (with W. A. Spivey), The Regional Science Association Papers, Vol. 28, 1972, pp. 257-276.
- "On the Weighted Average Cost of Capital" (with R. R. Reilly), Journal of Financial and Quantitative Analysis, January 1973, Vol. VIII, pp. 123-126.
- "On Random Walks with Absorbing Barriers" (with Thomas E. Morton), Proceedings of the Business and Economic Statistics Section—American Statistical Association, 1973.
- "Prediction Methods for Censored Time Series," Proceedings of the Business and Economic Statistics Section—American Statistical Association, 1974.
- "More on the Weighted Average Cost of Capital: Reply" (with R. R. Reilly), Journal of Financial and Quantitative Method, June 1975.
- "Predicting Mail Order Demand for Style Goods," Proceedings of the Business and Economic Statistics Section—American Statistical Association, 1975.
- "The Prediction of Turning Points," Proceedings of the Business and Economic Statistics Section—American Statistical Association, 1976.
- "Bounds on Absorption Probabilities for the m-Dimensional Random Walk" (with T. Morton), Journal of the American Statistical Association, March 1977.
- "Discounting, Ergodicity and Convergence of Markov Decision Processes" (with T. Morton), Management Science, April 1977.
- "Comments on 'Forecasting with Econometric Methods: Folklore versus Fact'," Journal of Business, 1978, pp. 585-586.
- "Comment on 'Seasonal Adjustment When Both Deterministic and Stochastic Seasonality Are Present'," Proceedings of the NBER-CENSUS Conference on "Seasonal Analysis of Economic Time Series", U.S. Government Printing Office, Washington, D.C., 1978, pp. 274-280.
- "Predicting Demand from Sales Data in the Presence of Stockouts," Management Science, 1978, Vol. 34, No. 10, pp. 1043-1054.
- "The Time Series Which Is the Product of Two Stationary Time Series," Stochastic Processes and Their Application, 1978, pp. 153-157.
- "Predicting the Turning Points of a Time Series," Journal of Business, January 1979, Vol. 52, pp. 35-50.

- "A New Approach to Seasonal Adjustment," Proceedings of the Business and Economic Statistics Section--American Statistical Association, 1979.**
- "Linear and Nonlinear Regression Viewed as a Signal Extraction Problem" (with C. Ansley), Proceedings of the Business and Economic Statistics Section-- American Statistical Association, 1980.**
- "Asymmetric Time Series," Journal of the American Statistical Association, March 1981.**
- "Predicting a Multitude of Time Series" (with R. A. Thisted), Journal of the American Statistical Association, September 1981.**
- "Applications of the Signal Extraction Approach to Regression" (with C. Ansley), Proceedings of the Business and Economic Statistics Section--American Statistical Association, 1981.**
- "Nonparametric Multiple Regression by Projection Iteration" (with C. Ansley), Proceedings of the Business and Economic Statistics Section--American Statistical Association, 1982.**
- "The Signal Extraction Approach to Nonlinear Regression and Spline Smoothing" (with C. Ansley), Journal of the American Statistical Association, March 1983.**
- "Extensions and Examples of the Signal Extraction Approach to Regression" (with C. Ansley), Applied Time Series Analysis of Economic Data, A. Zellner (ed.), Washington, D.C.: Bureau of the Census/ASA, 1983.**
- "The Signal Extraction Approach to Estimating Income and Price Elasticities: A Data Example" (with C. Ansley), Proceedings of the Business and Economic Statistics Section--American Statistical Association, 1983.**
- "A Nonparametric Bayesian Approach to the Calibration Problem," (with C. Ansley), Proceedings of the Business and Economic Statistics Section--American Statistical Association, 1984.**
- "On Dips in the Spectrum of a Seasonally Adjusted Time Series" (with C. Ansley), Journal of Business and Economic Statistics, October 1984.**
- "Estimating Damages in a Class Action Litigation" (with E. George), Journal of Business and Economic Statistics, April 1985.**
- "Statistics in Accounting, Marketing, Finance and Production" (with R. Hamada, J. Patell, R. Staelin), Proceedings of the Business and Economic Statistics Section--American Statistical Association, 1986.**
- "The Role of Statistics in Accounting, Marketing, Finance and Production" (with R. Hamada, J. Patell, R. Staelin), Journal of Business and Economic Statistics, 1988.**
- "Assessing the Accuracy of Time Series Model Forecasts of Count Observations," Journal of Business and Economic Statistics, October 1989.**

"Impact of the Soviet Grain Embargo; A Comparison of Methods" (with A. Webb, et al), Journal of Policy Modeling, pp. 361-389, 1989.

"Modeling Daily Milk Yield in Holstein Cows Using Time Series Analysis" (with H. Deluyker, et al.), Journal of Dairy Science, pp. 539 - 548, 1990.

"Controlling Emissions from Motor Vehicles: A Benefit-Cost Analysis of Vehicle Emission Control Alternatives" (with L. Lave, et al.), Environmental Science & Technology, August 1990.

"Statistical Estimation of Incremental Cost from Accounting Data" (with R. Weil), Handbook of Litigation Services for Accountants and Lawyers, John Wiley & Sons, 1990.

"Correcting for Omitted-Variables and Measurement-Error Bias in Regression with an Application to the Effect of Lead on IQ" (with M. L. Marais), Journal of the American Statistical Association, June 1998.

Exhibit 2

**William E. Wecker
Deposition and Trial Testimony
January 1, 2006 – December 3, 2010**

1. **Carla P. Cox v. Ford Motor Company and Mullinax Ford South, Inc. Circuit Court, Broward County, Florida, No. 02012391.**
2. **Cook, et al., v. Rockwell International Corp., et al. USDC, Denver, Colorado, No. 90-K-181.**
3. **Misty Arias, et al. v. Award Homes, Inc., et al. Superior Court, Monterey County, California, No. M54183.**
4. **Marjorie Rosenthal, et al. v. Ford Motor Company, et al. USDC, Connecticut, No. 3:05-cv-478(JCH).**
5. **Karen Jean Hubbard, et al. v. Ford Motor Company, et al. Superior Court, Macon County, Georgia, No. 2003CV-283-P.**
6. **Ronene J. Bracken, et al. v. Ford Motor Company, et al. USDC, Nevada, No. CV-S-04-1543-RLH(RJJ).**
7. **Thelma Byrd, et al. v. Ford Motor Company, et al. Circuit Court, Copiah County, Mississippi, No. 2002-0446.**
8. **Yolanda Adams v. Ford Motor Company. District Court of the Virgin Islands, Division of St. Croix.**
9. **Ford Explorer Cases, Coordination Proceeding (Gray; Tompkins; Katz; Montoya and McLachlan v. Ford Motor Company). Superior Court, Sacramento County, California, JCCP Nos. 4226 and 4270.**
10. **State of California ex rel. Barakat Consulting Incorporated and Samir F. Barakat v. Los Angeles Department of Water and Power. Superior Court, San Bernardino County, California, No. SCVSS 100293.**
11. **Holmbaum, et al. v. Brinker Restaurant Corporation, et al. Superior Court, San Diego County, California, No. GIC834348.**
12. **Leslie J. Whiteley and Leonard Whiteley v. Raybestos-Manhattan, Inc., et al. Superior Court, San Francisco, California, No. 303184.**

13. Dallas R. Maxwell and Angela J. Maxwell v. U-Haul International, Inc., Ford Motor Company, et al. Circuit Court, Jackson County, Missouri, No. 04CV226516.
14. Lindsay Rae Burnett, et al. v. Pirelli North America, Inc., Ford Motor Company, et al. District Court, Clark County, Nevada, No. A476187.
15. Rodrigo Ibarra, et al. v. Goodyear Tire and Rubber Company, Ford Motor Company, et al. District Court, Clark County, Nevada, No. A485304.
16. National Economic Research Associates, Inc. and Marsh & McLennan Companies, Inc. v. David S. Evans, LECG Corporation and LECG, LLC. Superior Court Department of the Trial Court, Suffolk, Massachusetts, No. 04-2618.
17. Michael Gutzler, et al. vs. General Motors Corporation. Circuit Court, Jackson County, Missouri, No. 03CV208786.
18. Self-Insurers' Security Fund v. Gallagher Bassett Services, Inc. USDC, Northern District of California, San Francisco Division, No. C 06-02828 JSW/JCS.
19. Autry Petroleum Company and McDonald Oil Company v. BP Products North America, Inc. USDC, Middle District of Georgia, Columbus Division, No. 4:05-CV-113 (CDL).
20. Wyeth v. Impax Laboratories, Inc. USDC, Delaware, No. C.A. 06-222 (JJF).
21. Discover Financial Services, DFS Services LLC, and Discover Bank v. Visa, U.S.A. Inc., Visa International Services Association, Mastercard Incorporated and Mastercard International Incorporated. USDC, Southern District of New York, No. 04-CV-7844 (BSJ).
22. In re: New Motor Vehicles Canadian Export Antitrust Litigation. USDC, Maine, MDL No. 03-md-1532.
23. Lyle Verry and Carla Verry v. General Motors Corporation. USDC, Eastern District of California, No. 2:06-CV-01566-LKK-PAN.
24. Equal Employment Opportunity Commission v. University of Phoenix, Inc. and Apollo Group, Inc. USDC, Arizona, No. CV06-2303-PHX-MHM.
25. Charles Foti, Attorney General *ex rel*, State of Louisiana v. Janssen Pharmaceutica, Inc. et al. Judicial District Court, Parish of St. Landry, Louisiana, No. 04-C-3967-D.
26. Sabrina Black Manuel v. Ford Motor Company, et al. Beverly Barber-Crouse v. Ford Motor Company, et al. Eugene Manuel, Jr. v. Ford Motor Company, et al. USDC, North District of Illinois, Eastern District, Nos. 07C5320, 07C5324, 07C5325.

27. **i4i Limited Partnership v. Microsoft Corporation.** USDC, Eastern District of Texas, Tyler Division, No. 6:07-CV-113-LED.
28. **Wyeth v. Apotex Inc. and Apotex, Corp.** USDC, Southern District of Florida, No. 1:2008cv22308.
29. **Steven Wirsz v. Nissan North America, Inc., et al.** Superior Court, Los Angeles County, California, No. BC 377417.
30. **L-3 Communications Integrated Systems, LP v. Lockheed Martin Corporation.** USDC, Northern District of Texas, Dallas Division, No. 3-07CV0341-B.
31. **Zurn PEX Plumbing Products Liability Litigation.** USDC Minnesota, MDL 08-MD-1958.
32. **Network-1 Security Solutions, Inc. v. Cisco Systems, Inc.** USDC, Eastern Division of Texas, Tyler Division, No. 6:08cv030-LED.
33. **In Re Payment Card Interchange Fee and Merchant Discount Antitrust Litigation.** USDC, Eastern District of New York, No. 1:05-MD-1720 (JG)(JO).
34. **In Re: Tobacco Litigation (Individual Personal Injury Cases).** Circuit Court, Ohio County, West Virginia, No. 00-C-5000.
35. **City of St. Louis, et al. v. American Tobacco Company, et al.** Circuit Court, City of St. Louis, Missouri, No. 982-9652.

Exhibit 3

List of Materials Considered

Datasets and Electronic Files:

South Carolina Fee For Service, State Health Plan, and HMO claims data produced by plaintiff (including eligibility data).

Cover letters, data dictionaries, correspondence between plaintiff and defense counsel regarding data production.

Depositions:

Millard Clinton Trott
Delfin Valite
Eugene F. Smith
Andrew W. Hedgepath
Balbir Coshal
William H. Bragdon
Rosen J. Lawsin
Glenn Hooker
Anil Juneja
James Frank Riddle
Lori W. Barwick
Laurel A. Weston
Sallie Amanda Carter
Kathy Marie Waggett
Kenneth G. Kassebaum
Ricardo J. Fermo
Evan L. Vogel
Michael J. Wood
Paul P. Lowe
James L. Elmore

Books, Articles and Papers:

Richard Johnson and Gouri Bhattacharyya, *Statistics Principles and Methods*, John Wiley & Sons, 3rd edition, 1996.

Cochran, William G., *Sampling Techniques*, John Wiley & Sons, New York, 1977.

Mullins, C. Daniel, *et al.*, *Risk of discontinuation of atypical antipsychotic agents in the treatment of schizophrenia*, Schizophrenia Research, Vol. 98 (2008).

Ren, X. S., *et al.*, *An alternative approach to measuring treatment persistence with antipsychotic agents among patients with schizophrenia in the Veterans Health Administration*, Neuropsychiatric Disease and Treatment, Vol. 3, No. 2 (2007).

Ren, X. S., *et al.*, *Treatment persistence: a comparison among patients with schizophrenia who were initiated on atypical antipsychotic agents*, J. Clin. Pharm. and Therap., Vol. 31 (2006).

Kilzieh, Nael, *et al.*, *Time to Discontinuation and Self-Discontinuation of Olanzapine and Risperidone in Patients With Schizophrenia in a Naturalistic Outpatient Setting*, J. Clin. Psychopharmacol., Vol 28, No. 1 (Feb. 2008).

Zhu, Baojin, *et al.*, *Time to Discontinuation of Depot and Oral First-Generation Antipsychotics in the Usual Care of Schizophrenia*, Psychiatric Services, Vol. 59, No. 3 (Mar. 2008).

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

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

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

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

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

Gianfrancesco F, Grogg AL, Mahmoud RA *et al.*, *Differential effect of risperidone, olanzapine, clozapine and conventional antipsychotics on type II diabetes: Findings from a large health plan database*, J. Clin. Psychiatry 2002, 63:920-930.

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

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

Lieberman, J., et al., *Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia (CATIE)*, New Eng. J. Med., 353(12) (Sept. 2005).

Rosenheck, R., et al., *Cost Effectiveness of Second-Generation Antipsychotics and Perphenazine in a Randomized Trial of Treatment for Chronic Schizophrenia*, Am. J. of Psych., 163(12) (2006).

Rosenheck RA, *et al.* (2006), Supplemental table A, Patient characteristics at the time of random assignment by initial treatment, available at <http://ajp.psychiatryonline.org/>.

Walsh, Bruce, *Multiple Comparisons: Bonferroni Corrections and False Discovery Rates*, Lecture notes for EEB 581, 2004.

Pleadings, Court Filings and Discovery:

Second Amended Complaint.

July 1, 2009 Order (a ruling on Janssen's request to take doctor depositions).

Expert Reports of William E. Wirshing, M.D., July 10, 2009.

Expert Report of Laura M. Plunkett, Ph.D., DABT, July 7, 2009.

Declaration of Lon S. Schneider, M.D., July 10, 2009,

Expert Report of John Abramson, M.D., July 10, 2009.

Supplemental Expert Report of Laura M. Plunkett, Ph.D., DABT; August 4, 2010.

Other documents:

Janssen November 10, 2003 mailing to health care providers.

Risperdal package inserts and drug labels.

Protocol, Comparative Effectiveness of Antipsychotic Medications in Patients with Schizophrenia (Rev. Oct. 15, 2001).

Exhibit 4

Deposition Questions and Responses of 20 Doctors

Question:	Yes	Probably Yes	No	Probably No	Refills Only	Don't Recall	Don't Know	It Depends	First Generation Antipsychotic	Second Generation Antipsychotic	More Effective	Safer	Other Answers	Not Asked	Total	Percent Responding "Yes" or "Probably Yes"
Have you ever treated pediatric patients, meaning patients 0 through 12 years old?	19		1												20	95%
Have you ever treated adolescent patients, meaning patients 13 through 17 years old?	20														20	100%
Have you ever treated non-geriatric adult patients, meaning patients 18 through 64 years old.	20														20	100%
Have you ever treated geriatric patients, meaning patients 65 or older?	19		1												20	95%
Have you ever prescribed Risperdal® for any of your patients?	20														20	100%
Have you ever prescribed Risperdal® for a pediatric patient?	14		2		1	3									20	70%
For an adolescent patient?	14		2			4									20	70%
For a non-geriatric adult patient?	20														20	100%
For a geriatric patient?	16	1	2			1									20	85%
For a South Carolina Medicaid patient?	20														20	100%
For a South Carolina State Health Plan patient?	8	3	2			2	5								20	55%
Have you ever prescribed antipsychotic medications other than Risperdal® for any of your patients?	20														20	100%
Have you ever prescribed antipsychotic medications other than Risperdal® for a pediatric patient?	14	2	2		1	1									20	80%
For an adolescent patient?	17	1	1			1									20	90%
For a non-geriatric adult patient?	20														20	100%
For a geriatric patient?	17	2	1												20	95%
Have you ever prescribed first generation antipsychotics for any of your patients?	20														20	100%
Have you ever prescribed second generation antipsychotics other than Risperdal® for any of your patients?	19													1	20	95%
In your experience, is Risperdal® generally effective for treating the positive symptoms of schizophrenia?	20														20	100%
In your experience, is Risperdal® generally effective for treating the negative symptoms of schizophrenia?	13	1	1				2						3		20	70%

Exhibit 4

Deposition Questions and Responses of 20 Doctors

Question	Yes	Probably Yes	No	Probably No	Refills Only	Don't Recall	Don't Know	It Depends	First Generation Antipsychotic	Second Generation Antipsychotic	More Effective	Safer	Other Answer	Not Asked	Total	Percent Responding "Yes" or "Probably Yes"
In your experience, do patients who take Risperdal® have better overall outcomes more frequently than patients who take a first generation antipsychotic?	12	1	3				1	2					1		20	65%
In your practice, for patients requiring antipsychotic medications, do you generally prefer to use first generation antipsychotics, or, second generation antipsychotics? [Percent shown is for "second generation".]								1	1	14			4		20	70%
In your experience, are patients who take first generation antipsychotics, such as Haldol and Thorazine, more likely to experience extrapyramidal and anticholinergic side effects than patients who take second generation antipsychotics?	20														20	100%
In your experience, are patients who take first generation antipsychotics, such as Haldol and Thorazine, more likely to experience tardive dyskinesia than patients who take second generation antipsychotics?	18						2								20	90%
In your experience, does Risperdal® typically have a more moderate side effect profile than first generation antipsychotics?	14						1	4					1		20	70%
In your experience, is Risperdal® typically better tolerated than first generation antipsychotics?	17							1					2		20	85%
In your experience with antipsychotic medications, are both efficacy and tolerability important considerations in the choice of which antipsychotic to prescribe?	19												1		20	95%
In your experience, do both efficacy and tolerability increase the likelihood that a patient will take an antipsychotic medication consistently?	19													1	20	95%
In your experience, are patients who consistently take their antipsychotic medications less likely to require costly follow-up treatment, such as in-patient psychiatric care, than patients who do not?	19						1								20	95%
In your experience, are patients who consistently take their antipsychotic medications less likely, to require costly follow-up treatment, such as emergency room care, than patients who do not?	17						1							2	20	85%
In your experience, does increased patient compliance with antipsychotic prescriptions result in overall conservation, as opposed to consumption, of healthcare resources?	17		1				2								20	85%
In your experience, does the use of Risperdal® typically conserve healthcare resources as compared to first generation antipsychotics?	9		1				4	2					4		20	45%
In your experience, does increased patient compliance with antipsychotic prescriptions typically decrease the human consequences of psychiatric illnesses?	20														20	100%
In your experience, does compliance taking antipsychotic medications typically make patients less likely to experience recurrence of	20														20	100%
Less likely to be violent?	17	1					2								20	90%

Exhibit 4

Deposition Questions and Responses of 20 Doctors

Question	Yes	Probably Yes	No	Probably No	Refills Only	Don't Recall	Don't Know	It Depends	First Generation Antipsychotic	Second Generation Antipsychotic	More Effective	Safer	Other Answer	Not Asked	Total	Percent Responding "Yes" or "Probably Yes"
Less likely to be an extreme burden on family members?	20														20	100%
Less likely to experience worsening of their conditions?	19						1								20	95%
Overall, in your experience, is Risperdal® a reasonably safe and effective medication for treating schizophrenia and other psychotic disorders?	19												1		20	95%
Overall, in your experience, is Risperdal® a safer and more effective medication for treating schizophrenia and other psychotic disorders than the first generation medications?	11		1				3	2			1	2			20	55%
In your experience, are there circumstances when the off-label use of medications is appropriate?	20														20	100%
In your experience, is it fair to say that off-label use of medications is not an uncommon practice?	18												2		20	90%
In your experience, are there circumstances when the off-label use of antipsychotic medications is appropriate?	18			1									1		20	90%
In your experience, is it fair to say that off-label use of antipsychotic medications is not an uncommon practice?	18						1						1		20	90%
Have you ever prescribed a medication for off-label use?	19					1									20	95%
In those circumstances, did you expect your patients to benefit from the off-label use of the medication?	19													1	20	95%
Have you ever prescribed an antipsychotic medication for off-label use?	18		1			1									20	90%
Have you ever prescribed Risperdal® for off-label use?	16	2	1			1									20	90%
Did you expect your patients to benefit from the off-label use of Risperdal®?	18													2	20	90%
Has any Janssen sales representative ever promoted to you any off-label use of Risperdal® in children?			19			1									20	0%
Has any Janssen sales representative ever promoted to you any off-label use of Risperdal® in geriatric patients?			19										1		20	0%
Has any Janssen sales representative ever promoted to you any off-label use of Risperdal® at all?			19										1		20	0%
Have you ever received or seen any communication from Janssen promoting the off-label use of Risperdal®?			20												20	0%
Based on your training and experience, is it common for medications to have both benefits and risks?	20														20	100%

Exhibit 4

Deposition Questions and Responses of 20 Doctors

Question	Yes	Probably Yes	No	Probably No	Refills Only	Don't Recall	Don't Know	It Depends	First Generation Antipsychotic	Second Generation Antipsychotic	More Effective	Safer	Other Answers	Not Asked	Total	Percent Responding "Yes" or "Probably Yes"
Based on your training and experience, is it your understanding that all antipsychotic medications – both first generation and second generation - have potential side effects?	20														20	100%
Are you aware of an association between antipsychotic medications and weight gain?	20														20	100%
Are you aware of an association between antipsychotic medications and risk of diabetes?	19													1	20	95%
When you prescribe antipsychotic medications, including Risperdal®, do you monitor your patients for weight gain?	20														20	100%
If you see or learn of rapid weight gain in a patient after the patient begins taking antipsychotics, do you typically consider changing the dosage and medication?	12		2					6							20	60%
If you see or learn of a change in blood glucose level in a patient after the patient begins taking antipsychotics, do you typically consider changing the dosage and medication?	12		2					6							20	60%
Would you agree that the 1993 package insert for Risperdal® advised of an association between Risperdal® and weight gain?	20														20	100%
Would you agree that the 1993 package insert for Risperdal® advised of an association between Risperdal® and diabetes?	20														20	100%
Would you agree that the 2004 package insert for Risperdal® incorporated a class warning of hyperglycemia and diabetes?	20														20	100%
Were you aware of an association between second generation antipsychotics, and weight gain or a risk of diabetes, prior to the 2004 revision to the package insert for Risperdal®?	16					2	2								20	80%
Did the change to the package insert for Risperdal® in 2004 cause you to change the circumstances in which you prescribe Risperdal® for patients?	2	1	15				1						1		20	15%
Has any Janssen sales representative ever represented to you anything inconsistent with the warnings about Risperdal® that are provided on the package insert?			19			1									20	0%
Has any Janssen sales representative ever represented to you that there is no association between Risperdal® and increased mortality in the elderly?			20												20	0%
Has any Janssen sales representative ever misrepresented to you information about the potential side effects associated with Risperdal® use?			19											1	20	0%
Have you ever seen this letter before? [November 10, 2003]	1	3	2			10	4								20	20%
Did this letter cause you to change the circumstances in which you prescribe antipsychotics to your patients?	1		4			1	1							13	20	5%

Exhibit 4

Deposition Questions and Responses of 20 Doctors

Question:	Yes	Probably Yes	No	Probably No	Refills Only	Don't Recall	Don't Know	It Depends	First Generation Antipsychotic	Second Generation Antipsychotic	More Effective	Safer	Other Answer	Not Asked	Total	Percent Responding "Yes" or "Probably Yes"
Did it cause you to change your choice of which antipsychotic to prescribe?		1	4										1	14	20	5%
Did it cause you to change your method for monitoring for side effects in your patients on antipsychotic medications?	1		4			1								14	20	5%
Prior to the deposition today, have you had any communications with any of the attorneys for the Plaintiff in this case?	3		15											2	20	15%

See Wecker electronic file summary.depos.xls.

Exhibit 5

Population Estimates from Responses to Deposition Questions

Question	Estimated Percent Responding "Yes" or "Probably Yes"	95% Confidence Limits
Have you ever treated pediatric patients, meaning patients 0 through 12 years old?	95.0%	(77.2% , 99.0%)
Have you ever treated adolescent patients, meaning patients 13 through 17 years old?	100.0%	(85.1% , 100.0%)
Have you ever treated non-geriatric adult patients, meaning patients 18 through 64 years old.	100.0%	(85.1% , 100.0%)
Have you ever treated geriatric patients, meaning patients 65 or older?	95.0%	(77.2% , 99.0%)
Have you ever prescribed Risperdal® for any of your patients?	100.0%	(85.1% , 100.0%)
Have you ever prescribed Risperdal® for a pediatric patient?	70.0%	(48.5% , 86.1%)
For an adolescent patient?	70.0%	(48.5% , 86.1%)
For a non-geriatric adult patient?	100.0%	(85.1% , 100.0%)
For a geriatric patient?	85.0%	(64.4% , 95.0%)
For a South Carolina Medicaid patient?	100.0%	(85.1% , 100.0%)
For a South Carolina State Health Plan patient?	55.0%	(33.7% , 74.3%)
Have you ever prescribed antipsychotic medications other than Risperdal® for any of your patients?	100.0%	(85.1% , 100.0%)
Have you ever prescribed antipsychotic medications other than Risperdal® for a pediatric patient?	80.0%	(59.4% , 93.1%)
For an adolescent patient?	90.0%	(71.3% , 98.0%)
For a non-geriatric adult patient?	100.0%	(85.1% , 100.0%)
For a geriatric patient?	95.0%	(77.2% , 99.0%)
Have you ever prescribed first generation antipsychotics for any of your patients?	100.0%	(85.1% , 100.0%)
Have you ever prescribed second generation antipsychotics other than Risperdal® for any of your patients?	95.0%	(77.2% , 99.0%)

Exhibit 5

Population Estimates from Responses to Deposition Questions

Question	Estimated Percent Responding "Yes" or "Probably Yes"	95% Confidence Limits
In your experience, is Risperdal® generally effective for treating the positive symptoms of schizophrenia?	100.0%	(85.1% , 100.0%)
In your experience, is Risperdal® generally effective for treating the negative symptoms of schizophrenia?	70.0%	(48.5% , 86.1%)
In your experience, do patients who take Risperdal® have better overall outcomes more frequently than patients who take a first generation antipsychotic?	65.0%	(43.6% , 82.2%)
In your practice, for patients requiring antipsychotic medications, do you generally prefer to use first generation antipsychotics, or, second generation antipsychotics? [Percent shown is for "second generation".]	70.0%	(48.5% , 86.1%)
In your experience, are patients who take first generation antipsychotics, such as Haldol and Thorazine, more likely to experience extrapyramidal and anticholinergic side effects than patients who take second generation antipsychotics?	100.0%	(85.1% , 100.0%)
In your experience, are patients who take first generation antipsychotics, such as Haldol and Thorazine, more likely to experience Tardive Dyskinesia than patients who take second generation antipsychotics?	90.0%	(71.3% , 98.0%)
In your experience, does Risperdal® typically have a more moderate side effect profile than first generation antipsychotics?	70.0%	(48.5% , 86.1%)
In your experience, is Risperdal® typically better tolerated than first generation antipsychotics?	85.0%	(64.4% , 95.0%)
In your experience with antipsychotic medications, are both efficacy and tolerability important considerations in the choice of which antipsychotic to prescribe?	95.0%	(77.2% , 99.0%)
In your experience, do both efficacy and tolerability increase the likelihood that a patient will take an antipsychotic medication consistently?	95.0%	(77.2% , 99.0%)
In your experience, are patients who consistently take their antipsychotic medications less likely to require costly follow-up treatment, such as in-patient psychiatric care, than patients who do not consistently take their medications?	95.0%	(77.2% , 99.0%)
In your experience, are patients who consistently take their antipsychotic medications less likely, to require costly follow-up treatment, such as emergency room care, than patients who do not consistently take their medications?	85.0%	(64.4% , 95.0%)
In your experience, does increased patient compliance with antipsychotic prescriptions result in overall conservation, as opposed to consumption, of healthcare resources?	85.0%	(64.4% , 95.0%)
In your experience, does the use of Risperdal® typically conserve healthcare resources as compared to first generation antipsychotics?	45.0%	(25.7% , 66.3%)

Exhibit 5

Population Estimates from Responses to Deposition Questions

Question	Estimated Percent Responding "Yes" or "Probably Yes"	95% Confidence Limits
In your experience, does increased patient compliance with antipsychotic prescriptions typically decrease the human consequences of psychiatric illnesses?	100.0%	(85.1% , 100.0%)
In your experience, does compliance taking antipsychotic medications typically make patients less likely to experience recurrence of psychosis?	100.0%	(85.1% , 100.0%)
Less likely to be violent?	90.0%	(71.3% , 98.0%)
Less likely to be an extreme burden on family members?	100.0%	(85.1% , 100.0%)
Less likely to experience worsening of their conditions?	95.0%	(77.2% , 99.0%)
Overall, in your experience, is Risperdal® a reasonably safe and effective medication for treating schizophrenia and other psychotic disorders?	95.0%	(77.2% , 99.0%)
Overall, in your experience, is Risperdal® a safer and more effective medication for treating schizophrenia and other psychotic disorders than the first generation medications?	55.0%	(33.7% , 74.3%)
In your experience, are there circumstances when the off-label use of medications is appropriate?	100.0%	(85.1% , 100.0%)
In your experience, is it fair to say that off-label use of medications is not an uncommon practice?	90.0%	(71.3% , 98.0%)
In your experience, are there circumstances when the off-label use of antipsychotic medications is appropriate?	90.0%	(71.3% , 98.0%)
In your experience, is it fair to say that off-label use of antipsychotic medications is not an uncommon practice?	90.0%	(71.3% , 98.0%)
Have you ever prescribed a medication for off-label use?	95.0%	(77.2% , 99.0%)
In those circumstances, did you expect your patients to benefit from the off-label use of the medication?	95.0%	(77.2% , 99.0%)
Have you ever prescribed an antipsychotic medication for off-label use?	90.0%	(71.3% , 98.0%)
Have you ever prescribed Risperdal® for off-label use?	90.0%	(71.3% , 98.0%)
Did you expect your patients to benefit from the off-label use of Risperdal®?	90.0%	(71.3% , 98.0%)

Exhibit 5

Population Estimates from Responses to Deposition Questions

Question	Estimated Percent Responding "Yes" or "Probably Yes"	95% Confidence Limits
Has any Janssen sales representative ever promoted to you any off-label use of Risperdal® in children?	0.0%	(0.0% , 11.9%)
Has any Janssen sales representative ever promoted to you any off-label use of Risperdal® in geriatric patients?	0.0%	(0.0% , 11.9%)
Has any Janssen sales representative ever promoted to you any off-label use of Risperdal® at all?	0.0%	(0.0% , 11.9%)
Have you ever received or seen any communication from Janssen promoting the off-label use of Risperdal®?	0.0%	(0.0% , 11.9%)
Based on your training and experience, is it common for medications to have both benefits and risks?	100.0%	(85.1% , 100.0%)
Based on your training and experience, is it your understanding that all antipsychotic medications – both first generation and second generation – have potential side effects?	100.0%	(85.1% , 100.0%)
Are you aware of an association between antipsychotic medications and weight gain?	100.0%	(85.1% , 100.0%)
Are you aware of an association between antipsychotic medications and risk of diabetes?	95.0%	(77.2% , 99.0%)
When you prescribe antipsychotic medications, including Risperdal®, do you monitor your patients for weight gain?	100.0%	(85.1% , 100.0%)
If you see or learn of rapid weight gain in a patient after the patient begins taking antipsychotics, do you typically consider changing the dosage and medication?	60.0%	(38.6% , 78.2%)
If you see or learn of a change in blood glucose level in a patient after the patient begins taking antipsychotics, do you typically consider changing the dosage and medication?	60.0%	(38.6% , 78.2%)
Would you agree that the 1993 package insert for Risperdal® advised of an association between Risperdal® and weight gain?	100.0%	(85.1% , 100.0%)
Would you agree that the 1993 package insert for Risperdal® advised of an association between Risperdal® and diabetes?	100.0%	(85.1% , 100.0%)
Would you agree that the 2004 package insert for Risperdal® incorporated a class warning of hyperglycemia and diabetes?	100.0%	(85.1% , 100.0%)
Were you aware of an association between second generation antipsychotics, and weight gain or a risk of diabetes, prior to the 2004 revision to the package insert for Risperdal®?	80.0%	(59.4% , 93.1%)
Did the change to the package insert for Risperdal® in 2004 cause you to change the circumstances in which you prescribe Risperdal® for patients?	15.0%	(5.0% , 35.6%)

Exhibit 5

Population Estimates from Responses to Deposition Questions

Question	Estimated Percent Responding "Yes" or "Probably Yes"	95% Confidence Limits
Has any Janssen sales representative ever represented to you anything inconsistent with the warnings about Risperdal® that are provided on the package insert?	0.0%	(0.0% , 11.9%)
Has any Janssen sales representative ever represented to you that there is no association between Risperdal® and increased mortality in the elderly?	0.0%	(0.0% , 11.9%)
Has any Janssen sales representative ever misrepresented to you information about the potential side effects associated with Risperdal® use?	0.0%	(0.0% , 11.9%)
Have you ever seen this letter before? [November 10, 2003]	20.0%	(6.9% , 40.6%)
Did this letter cause you to change the circumstances in which you prescribe antipsychotics to your patients?	5.0%	(1.0% , 22.8%)
Did it cause you to change your choice of which antipsychotic to prescribe?	5.0%	(1.0% , 22.8%)
Did it cause you to change your methods for monitoring for side effects in your patients on antipsychotic medications?	5.0%	(1.0% , 22.8%)
Prior to the deposition today, have you had any communications with any of the attorneys for the Plaintiff in this case?	15.0%	(5.0% , 35.6%)

See Wecker electronic file, confidence_limits.nb.

Exhibit 6

Analysis of South Carolina Fee for Service, State Health Plan, and HMO Claims
Antipsychotic Drugs and Alleged Side Effects

Excess Side Effect Risk
Relative to Risperdal

		Alleged Side Effect		
		Diabetes	Metabolic Adverse Events	Increased Prolactin Secretion
Antipsychotic Drug Prescribed:	1st Generation	1.62% (*)	1.46% (*)	3.64% (*)
	Other 2nd Generation	2.33% (*)	4.47% (*)	1.82% (*)
	Untreated	1.29% (*)	0.99% (*)	2.22% (*)

Notes: 1. Percent of Patients with First Alleged Side Effect Diagnosis within 36 Months from First Antipsychotic Drug Prescription.

2. Treated patients excluded if prescribed more than one type of antipsychotic drug; if less than 12 months of uninterrupted eligibility prior to their first antipsychotic drug prescription; if diagnosis of alleged side effect occurs prior to their first antipsychotic drug prescription; or if less than 36 months of uninterrupted eligibility following their first antipsychotic drug prescription.

3. Untreated patients excluded if less than 48 months of uninterrupted eligibility prior to their first antipsychotic drug prescription; or if diagnosis of alleged side effect occurs prior to 36 months before their first antipsychotic drug prescription.

4. Asterisk (*) indicates value is statistically significantly different from Risperdal value at 95% confidence level.

See Wecker electronic files side.effect.diab.lst, side.effect.mae.lst, and side.effect.prlc.lst.

Exhibit 7

Analysis of South Carolina Fee for Service, State Health Plan, and HMO Claims
Antipsychotic Drugs and Alleged Side Effects
Data as of November 10, 2003

Excess Side Effect Risk
Relative to Risperdal

		Alleged Side Effect	
		Diabetes	Metabolic Adverse Events
Antipsychotic Drug Prescribed:	1st Generation	1.17% (*)	0.65%
	Other 2nd Generation	1.84% (*)	3.02% (*)
	Untreated	1.32% (*)	0.78%

Notes: 1. Percent of Patients with First Alleged Side Effect Diagnosis within 36 Months from First Antipsychotic Drug Prescription.

2. Treated patients excluded if prescribed more than one type of antipsychotic drug; if less than 12 months of uninterrupted eligibility prior to their first antipsychotic drug prescription; if diagnosis of alleged side effect occurs prior to their first antipsychotic drug prescription; or if less than 36 months of uninterrupted eligibility following their first antipsychotic drug prescription.

3. Untreated patients excluded if less than 48 months of uninterrupted eligibility prior to their first antipsychotic drug prescription; or if diagnosis of alleged side effect occurs prior to 36 months before their first antipsychotic drug prescription.

4. Asterisk (*) indicates value is statistically significantly different from Risperdal value at 95% confidence level.

5. The November 10, 2003 mailing did not discuss increased prolactin secretion.

See Wecker electronic files side.effect.diab.lst, side.effect.mae.lst, and side.effect.prlc.lst.

Exhibit 8

Analysis of South Carolina Fee for Service, State Health Plan, and HMO Claims
Antipsychotic Drugs and Time to Discontinuation

Average Days to Discontinuation

Antipsychotic Drug Prescribed:		Patient Count	"Treatment Discontinuation" Defined as X or More Days without Drug Supply		
			X=15 Days	X=30 Days	X=60 Days
	Risperdal	27,197	125.59	166.00	211.23
	Perphenazine	976	82.70 (*)	106.50 (*)	132.84 (*)
	Haldol	7,071	77.86 (*)	98.96 (*)	130.43 (*)
	Other 1st Generation	18,531	34.81 (*)	44.40 (*)	58.14 (*)

(*) Value is statistically significantly different from Risperdal value at 95% confidence level.

Notes: Patients are followed up for 18 months.

Patients excluded if less than 12 months of uninterrupted eligibility prior to start of treatment, or
less than 18 months of uninterrupted eligibility after start of treatment.

See Wecker electronic file time_to_discontinuation.lst.

Exhibit 9

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

Month and Year	Risperdal	First Generation Antipsychotics	Other Second Generation Antipsychotics	Total	Percent Risperdal
Jan 2003	6,945	3,798	13,034	23,777	29.21%
Feb 2003	6,518	3,503	12,415	22,436	29.05%
Mar 2003	7,068	3,606	13,569	24,243	29.15%
Apr 2003	7,254	3,696	13,742	24,692	29.38%
May 2003	7,199	3,601	14,082	24,882	28.93%
Jun 2003	6,906	3,464	13,916	24,286	28.44%
Jul 2003	7,179	3,669	14,593	25,441	28.22%
Aug 2003	7,111	3,564	14,341	25,016	28.43%
Sep 2003	7,131	3,490	14,820	25,441	28.03%
Oct 2003	7,603	3,558	15,278	26,439	28.76%
Nov 2003	6,809	3,230	14,067	24,106	28.25%
Dec 2003	7,648	3,644	15,918	27,210	28.11%
Jan 2004	7,073	3,272	14,546	24,891	28.42%
Feb 2004	6,954	3,107	14,254	24,315	28.60%
Mar 2004	7,811	3,505	16,540	27,856	28.04%
Apr 2004	7,653	3,336	15,607	26,596	28.78%
May 2004	7,429	3,177	15,276	25,882	28.70%
Jun 2004	7,884	3,345	16,177	27,406	28.77%
Jul 2004	7,721	3,266	15,901	26,888	28.72%
Aug 2004	7,886	3,273	16,447	27,606	28.57%
Sep 2004	7,764	3,234	16,312	27,310	28.43%
Oct 2004	7,809	3,233	16,184	27,226	28.68%
Nov 2004	8,047	3,314	16,852	28,213	28.52%
Dec 2004	8,090	3,373	17,011	28,474	28.41%
Jan 2005	7,460	3,094	16,041	26,595	28.05%
Feb 2005	7,199	2,947	15,516	25,662	28.05%
Mar 2005	7,975	3,266	17,410	28,651	27.83%
Apr 2005	7,748	3,152	16,995	27,895	27.78%
May 2005	7,970	3,175	17,483	28,628	27.84%
Jun 2005	7,918	3,300	17,641	28,859	27.44%
Jul 2005	7,549	2,970	16,632	27,151	27.80%
Aug 2005	8,625	3,296	18,350	30,271	28.49%
Sep 2005	8,204	3,294	17,616	29,114	28.18%
Oct 2005	8,336	3,246	17,614	29,196	28.55%
Nov 2005	8,471	3,221	18,037	29,729	28.49%
Dec 2005	8,227	3,108	17,102	28,437	28.93%

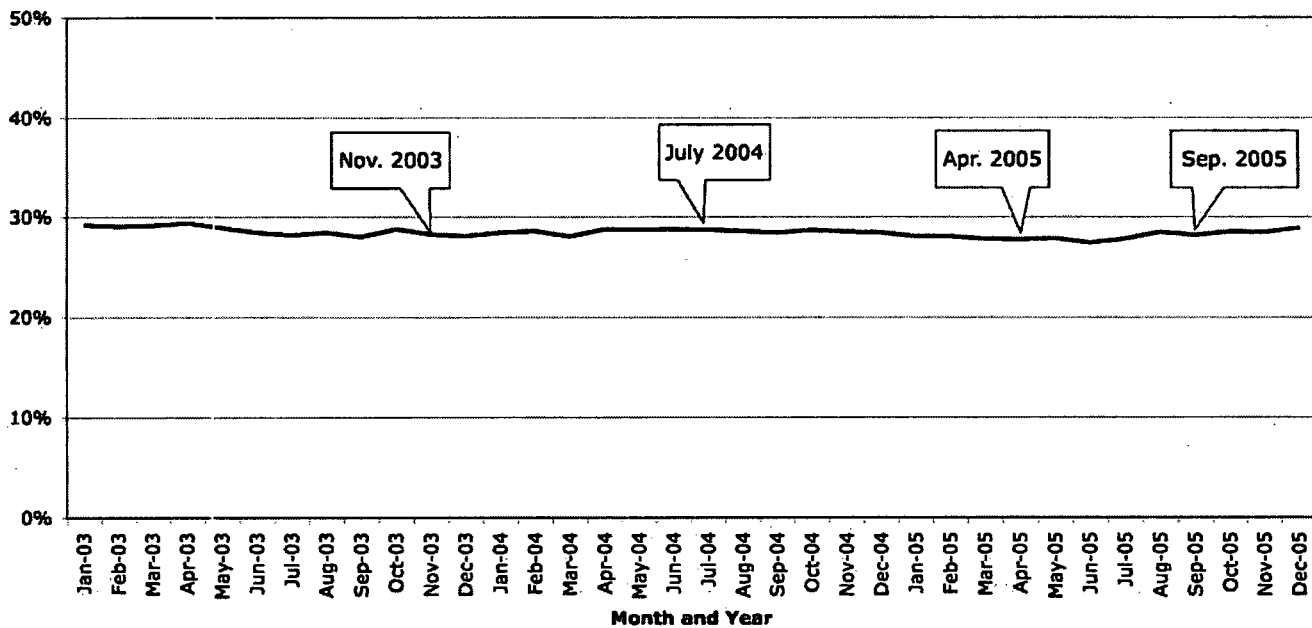
Notes: 1. Percent=Risperdal/Total x 100

2. Claims counts are net of reversals.

See Wecker electronic file risp.percent.lst.

Exhibit 9 (cont.)

South Carolina Fee for Service, State Health Plan, and HMO Claims Data
Percent Risperdal Prescriptions by Month



Notes: Percent = $\text{Risperdal} / (\text{Antipsychotic Prescriptions Total}) \times 100$

November 2003: Janssen's November 10, 2003 mailing to health care providers.

July 2004: Janssen's "correction" letter.

April 2005: FDA advisory.

September 2005: publication of the CATIE trial results in N Engl J Med.

See Wecker electronic file risp.percent.lst.

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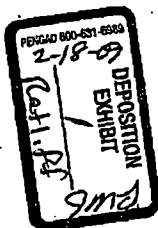
South Carolina Department Of Health And Human Services
Drug Utilization Review Program
Patient Drug History Profile

9/19/2002

Case Number: 259

HIID-SC 229

Date of Service	RX Number	Drug Description	Strength	Qty	Days Supply	Pharmacy Number	Prescriber Number
07/16/02	4001578	TEMASEPAM	30MG	30	30	761274	005408
07/10/02	6646749	POTASSIUM CHLORIDE	20MEQ	14	14	736224	00000195
07/10/02	6646748	SEROQUEL	25MG	60	30	736224	019546
07/10/02	6646752	LOTREL	5-20MG	30	30	736224	00000195
07/10/02	6646750	SUCRALFATE	1G	90	30	736224	00000195
07/01/02	6644894	FLUOXETINE HCL	20MG	90	30	736224	000565
07/01/02	4406332	CHLORDIAZEPOXIDE HCL	10MG	90	30	736224	000565
07/01/02	6642090	ACIPHEX	20MG	34	34	736224	005408
06/25/02	6646289	SYNTHROID	25MCG	30	30	736224	014752
06/25/02	6646288	LITHOBID	300MG	30	15	736224	014752
06/07/02	6644895	WELLBUTRIN SR	150MG	60	30	736224	000565
06/07/02	4406332	CHLORDIAZEPOXIDE HCL	10MG	90	30	736224	000565
06/07/02	6644894	FLUOXETINE HCL	20MG	90	30	736224	000565
05/29/02	6645602	SUCRALFATE	1G	100	33	736224	005408



Health
Information
Designs, Inc.

South Carolina Department Of Health And Human Services
Drug Utilization Review Program
Patient Drug History Profile

9/19/2002

Case Number: 259

Date of Service	RX Number	Drug Description	Strength	Qty	Days Supply	Pharmacy Number	Prescriber Number
05/23/02	6645212	PENICILLIN V POTASSIUM	500MG	14	7	736224	DEN00011
05/19/02	4406389	ACETAMINOPHEN W/CODEINE	30-300MG	12	2	736224	DEN00011
05/15/02	6645212	VEETIDS 500	500MG	14	7	736224	DEN00011
05/02/02	6644899	WELLBUTRIN SR	150MG	60	30	736224	000565
05/02/02	6644894	FLUOXETINE HCL	20MG	90	30	736224	000565
04/30/02	6642090	ACIPHEX	20MG	34	34	736224	005408
04/24/02	4405967	CHLORDIAZEPOXIDE HCL	25MG	120	30	736224	005408
04/23/02	6644964	DOXYCYCLINE HYCLATE	100MG	20	10	736224	005408
04/01/02	6641662	WELLBUTRIN SR	150MG	60	30	736224	000565
03/29/02	6642090	ACIPHEX	20MG	34	34	736224	005408
03/29/02	6641663	FLUOXETINE HCL	20MG	90	30	736224	000565
03/29/02	4406203	HYDROCODONE/ACETAMINOPHEN	5-500MG	15	2	736224	013613
03/01/02	6642090	ACIPHEX	20MG	34	34	736224	005408
02/25/02	4405967	CHLORDIAZEPOXIDE HCL	25MG	120	30	736224	005408
02/19/02	6641663	FLUOXETINE HCL	20MG	90	30	736224	LL3226
02/04/02	6642091	PROMETHAZINE HCL	25MG	100	25	736224	005408
02/01/02	6642090	ACIPHEX	20MG	34	34	736224	005408
01/27/02	4405913	CHLORDIAZEPOXIDE HCL	10MG	90	30	736224	LL3226
01/21/02	6641663	FLUOXETINE HCL	20MG	90	30	736224	LL3226
01/21/02	6641662	WELLBUTRIN SR	150MG	60	30	736224	LL3226
01/09/02	6641287	RANITIDINE HCL	150MG	60	30	736224	005408
01/02/02	4001185	CHLORDIAZEPOXIDE HCL	10MG	90	30	761274	020292
01/02/02	6001513	ACIPHEX	20MG	31	31	761274	005408
12/18/01	6640720	WELLBUTRIN SR	150MG	60	30	736224	020292
12/18/01	6640719	FLUOXETINE HCL	40MG	30	30	736224	020292
12/05/01	6640340	ACIPHEX	20MG	30	30	736224	005408
12/01/01	4405288	CHLORDIAZEPOXIDE HCL	10MG	90	30	736224	LL3226
12/01/01	6640177	HYOSCYAMINE SULFATE	0.125MG	100	33	736224	005408
11/05/01	6001851	HYOSCYAMINE SULFATE	0.125MG	100	33	761274	005408
11/02/01	6001817	PROZAC	40MG	30	30	761274	005408

HID-SC 230

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South Carolina Department Of Health And Human Services
Drug Utilization Review Program
Patient Drug History Profile

8/19/2002

Case Number: 259

Date of Service	ICD Number	Drug Description	Strength	Qty	Days Supply	Pharmacy Number	Prescriber Number
11/01/01	6001513	ACIPHEX	20MG	31	31	761274	005408
11/01/01	4001050	CHLORDIAZEPOXIDE HCL	25MG	100	25	761274	005408
10/14/01	6001631	WELLBUTRIN SR	150MG	60	30	761274	000565
10/08/01	6001595	PROZAC	40MG	30	30	761274	000565
10/01/01	6001513	ACIPHEX	20MG	31	31	761274	005408
10/01/01	4001050	CHLORDIAZEPOXIDE HCL	25MG	100	25	761274	005408
09/01/01	6636842	PROZAC	40MG	30	30	736224	LL3226
09/01/01	4405288	CHLORDIAZEPOXIDE HCL	10MG	90	30	736224	LL3226
09/01/01	6636638	ACIPHEX	20MG	30	30	736224	005408
09/01/01	6636843	WELLBUTRIN SR	150MG	60	30	736224	LL3226
08/05/01	4405288	CHLORDIAZEPOXIDE HCL	10MG	90	30	736224	LL3226
08/05/01	6636638	ACIPHEX	20MG	30	30	736224	005408
08/05/01	6636842	PROZAC	40MG	30	30	736224	LL3226
07/22/01	6634489	WELLBUTRIN SR	150MG	60	30	736224	LL3226
07/22/01	4404919	CHLORDIAZEPOXIDE HCL	10MG	60	30	736224	LL3226

HID-SC 231

Current Date of Service	ICD Code	Diagnosis Description	Reference Date	Number of Occurrences Since Reference Date
05/02/02	29635	MAJOR DEPRESSIVE AFFECTIVE DISORDER RECURRENT EPISODE IN PARTIAL OR UNSPECIFIED REMISSION	07/26/01	6



**SOUTH CAROLINA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
DRUG UTILIZATION REVIEW PROGRAM**

September 19, 2002

ENGLES, TODD H
105 BELFAIR RD
IRMO, SC 29063

DEAR PRESCRIBER ENGLES:

In compliance with the OBRA '90 federal legislation, state Medicaid agencies are mandated to institute Retrospective Drug Utilization Review Programs (retroDUR). The program's goal is to ensure that Medicaid patients receive optimal drug therapy at the lowest reasonable cost. One way to achieve this goal is to identify potential drug therapy problems that may place patients at risk, particularly if multiple providers are identified. This retroDUR program is informational in nature and allows you to incorporate the information provided into your continuing assessment of the patient's drug therapy requirements.

During a recent review of the enclosed drug history profile, it was noted that your patient, [REDACTED], is receiving SEROQUEL. *The use of clozapine, olanzapine, risperidone or quetiapine may increase the risk of developing type II diabetes mellitus or impaired glucose tolerance. Patients with a family history of diabetes or with pre-existing diabetes may need to have blood sugar monitored closely or changed to an alternative medication.* In presenting this information to you, we recognize that the management of each patient's drug therapy depends upon an assessment of the patient's entire clinical situation about which we are not fully aware.

The success of the DUR program is enhanced by effective two-way exchange of information. Therefore, at your convenience, we would appreciate learning of your assessment of this information and of any action taken in response to this notice. Although your participation in this program is voluntary, we find your feedback helpful in adjusting our program to address clinically important problems. Please use the enclosed response to note your comments and return it in the enclosed envelope or fax it to the number below.

At the bottom of this letter are the specific prescriptions attributed to you by the dispensing pharmacy. In addition, if multiple prescribers are involved in the therapy identified above, each will receive this information. Thank you for your professional consideration.

RX #(s): 6646748

Sincerely,

W. Murray Yarbrough, M.D.

W. Murray Yarbrough, M.D.
Medical Director
Health Information Designs, Inc.

Case#: 259
Enclosures

Administered by Health Information Designs, Inc.
1550 Pumphrey Ave.
Auburn, AL 36832-9956
(800)225-6998 x 37 Fax(800)748-0016HID-SC 232

SC Criteria List

Criteria 454-- During a recent review of the enclosed drug history profile, it was noted that your patient, [t1d0-recipefst-nm] [t1d0-recipefst-nm], has received and is apparently taking similar and/or potentially conflicting drugs prescribed by multiple physicians ([drug_a_name]).

Criteria 561-- During a recent review of the enclosed drug history profile, it was noted that your patient, [t1d0-recipefst-nm] [t1d0-recipefst-nm], is apparently taking the following drugs which have the same or similar therapeutic effects: [drug_a_name] and [drug_b_name].

Criteria 586-- During a recent review of the enclosed drug history profile, it was noted that your patient, [t1d0-recipefst-nm] [t1d0-recipefst-nm], is receiving [drug_a_name]. The use of atypical antipsychotics may increase the risk of developing type II diabetes mellitus or impaired glucose tolerance. Patients with a family history of diabetes or with pre-existing diabetes may need to have blood sugar monitored closely or changed to an alternative medication.

Criteria 667-- During a recent review of the enclosed drug history profile, it was noted that your patient, [t1d0-recipefst-nm] [t1d0-recipefst-nm], is receiving [drug_a_name] and [drug_b_name]. The concurrent use of tizanidine and CNS depressant medications may result in additive sedation.

Criteria 1572-- During a recent review of the enclosed drug history profile, it was noted that your patient, [t1d0-recipefst-nm] [t1d0-recipefst-nm], is apparently underutilizing the drug(s) [drug_a_name]. Quetiapine (Seroquel/Seroquel XR) may be under-utilized.

Icer Date	Case Num	Physician Name	Alert Date	Criteria
8/18/2002	1	SLOAN, ALLEN L	9/13/2002	HID667
8/18/2002	17	SHAH, JAGDISH V	9/13/2002	HID586
8/18/2002	42	GEER, ANDREW E	9/13/2002	HID667
8/18/2002	42	SMITH, ARTHUR R	9/13/2002	HID667
8/18/2002	56	DARTON, JOHNTA L	9/13/2002	HID586
8/18/2002	57	PRUITT, ARMSTEAD B	9/13/2002	HID667
8/18/2002	57	DAWSON, WILLIAM T	9/13/2002	HID667
8/18/2002	66	BROWN, FRANKLIN B	9/13/2002	HID586
8/18/2002	120	WEISS, EDGAR J	9/13/2002	HID586
8/18/2002	132	MCNAMARA, KATHLEEN L	9/13/2002	HID586
8/18/2002	147	RYDER-COOK, ALLAN S	9/13/2002	HID586
8/18/2002	148	SLATER, VICTOR L	9/13/2002	HID586
8/18/2002	166	CUSTER, JOHN V	9/13/2002	HID454
8/18/2002	166	LEWIS, DEQUINCY A	9/13/2002	HID454
8/18/2002	167	MOSELEY, WILLIE B	9/13/2002	HID586
8/18/2002	175	KHAN, FAZAL M	9/13/2002	HID586
8/18/2002	190	HOTCHKISS, ROBERT K	9/13/2002	HID561
8/18/2002	190	MOZINGO, ELLIE B	9/13/2002	HID561
8/18/2002	218	KING, WILLIAM A	9/13/2002	HID586
8/18/2002	246	LAMM, RENEE R	9/16/2002	HID586
8/18/2002	254	JEWELL, JAMES L	9/16/2002	HID561
8/18/2002	259	ENGLES, TODD H	9/16/2002	HID586
8/18/2002	281	CATHCART, JOHN H	9/16/2002	HID586
8/18/2002	284	MAZGAJ, JAMES P	9/16/2002	HID586
8/18/2002	332	GAY, WALTER C	9/16/2002	HID586
8/18/2002	403	MYERS, BARNWELL R	9/16/2002	HID586
8/18/2002	424	TROUCHE, PERRY E	9/16/2002	HID586
8/18/2002	439	DUNLAP, JOHN C	9/16/2002	HID586
8/18/2002	470	HIPPENSTEAL, ALAN R	9/16/2002	HID667
8/18/2002	470	CAMPANARO, KELLEY A	9/16/2002	HID667
8/18/2002	470	JACOBS, DAVID C	9/16/2002	HID667
8/18/2002	488	GAMMON, DAVID B	9/16/2002	HID561
8/18/2002	488	COX, ROBERT D	9/16/2002	HID561
8/18/2002	537	SMITH, EUGENE F	9/16/2002	HID586
8/18/2002	550	HODGES, ELBERT R	9/16/2002	HID586
8/18/2002	563	WOOLERY, JANET D	9/16/2002	HID586
8/18/2002	565	GILL, AHMAD N	9/16/2002	HID561
8/18/2002	635	MAZGAJ, JAMES P	9/16/2002	HID586
9/24/2002	646	KATZ, BARRY S	10/10/2002	HID561
9/24/2002	646	DEBERRY, SKYE N	10/10/2002	HID561
9/24/2002	648	PAOLONE, TIMOTHY J	10/10/2002	HID586
9/24/2002	648	GUNTHER, JENNIFER S	10/10/2002	HID586
9/24/2002	650	MAZGAJ, JAMES P	10/10/2002	HID561
9/24/2002	650	WOOLERY, JANET D	10/10/2002	HID561
9/24/2002	672	WALLACE, FURMAN T	10/10/2002	HID586
9/24/2002	674	FORD, JAMES E	10/10/2002	HID586

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12/13/2003	4041 GODWIN, WINSTON	1/7/2004 HID454
12/13/2003	4042 GIBBS, GARY	1/7/2004 HID454
12/13/2003	4043 LAWSON, JULIUS	1/7/2004 HID454
12/13/2003	4047 SELLERS, CHRISTINE	1/9/2004 HID454
12/13/2003	4047 IGAMA, JULIET	1/9/2004 HID454
12/13/2003	4047 WOOD, MICHAEL	1/9/2004 HID454
12/13/2003	4048 BANK, ROBERT	1/9/2004 HID454
12/13/2003	4048 COSHAL, BALBIR	1/9/2004 HID454
12/13/2003	4049 KENDALL, EDWARD	1/9/2004 HID454
12/13/2003	4050 WISCHHUSEN, USA	1/9/2004 HID454
12/13/2003	4051 WRIGHT, TARA	1/9/2004 HID454
12/13/2003	4054 HERMIDA, ADRIANA	1/9/2004 HID454
12/13/2003	4054 HOBGOOD, KELLY	1/9/2004 HID454
12/13/2003	4055 BELMAR, PAULA	1/9/2004 HID454
12/13/2003	4055 ALDRICH, WILLIAM	1/9/2004 HID454
12/13/2003	4056 ESTEFANO, ALFONSO	1/9/2004 HID454
12/13/2003	4058 KENDALL, DOROTHY	1/9/2004 HID454
12/13/2003	4061 GAMMON, DAVID	1/9/2004 HID454
12/13/2003	4061 CASTRIOTTA, RALPH	1/9/2004 HID454
1/16/2004	4064 NORTHWALL, KARL	2/6/2004 HID454
1/16/2004	4065 BANK, ROBERT	2/6/2004 HID454
1/16/2004	4067 NNADI, NGOZI	2/6/2004 HID454
1/16/2004	4069 HO, BENG	2/6/2004 HID454
1/16/2004	4069 WOOD, VANESSA	2/6/2004 HID454
1/16/2004	4074 KAZAGLIS, JON	2/6/2004 HID454
1/16/2004	4074 COX, ROBERT	2/6/2004 HID454
1/16/2004	4080 MEETZE, DANIEL	2/6/2004 HID454
1/16/2004	4080 MARTIN, MARK	2/6/2004 HID454
1/16/2004	4081 BLANTON, EDWIN	2/6/2004 HID454
1/16/2004	4082 DODDS, CHERYL	2/6/2004 HID454
1/16/2004	4082 KAUP, MICHAEL	2/6/2004 HID454
1/16/2004	4085 SHARAWY, EMAN	2/6/2004 HID454
1/16/2004	4087 BLOCH, SILVIA MARGIT	2/6/2004 HID454
1/16/2004	4087 SHAH, JAGDISH	2/6/2004 HID454
1/16/2004	4088 SCHARSTEIN, JEFFERY	2/6/2004 HID454
1/16/2004	4088 MAZGAJ, JAMES	2/6/2004 HID454
1/16/2004	4092 OGUNFOWORA, AYODELE	2/6/2004 HID454
1/16/2004	4093 LOWE, PAUL	2/6/2004 HID454
1/16/2004	4093 DEMOS, DEBRA	2/6/2004 HID454
1/16/2004	4096 KHAN, FAZAL	2/6/2004 HID454
1/16/2004	4096 HARLEY, AL	2/6/2004 HID454
1/16/2004	4097 KREISER, CATHERINE	2/6/2004 HID454
1/16/2004	4097 WILKENFELD, BYRON	2/6/2004 HID454
1/16/2004	4098 SMITH, GREGORY	2/6/2004 HID454
1/16/2004	4098 PAOLINI, RONALD	2/6/2004 HID454
1/16/2004	4099 HAJJAR, IHAB	2/6/2004 HID454
1/16/2004	4099 CHAVEZ, JOSE	2/6/2004 HID454

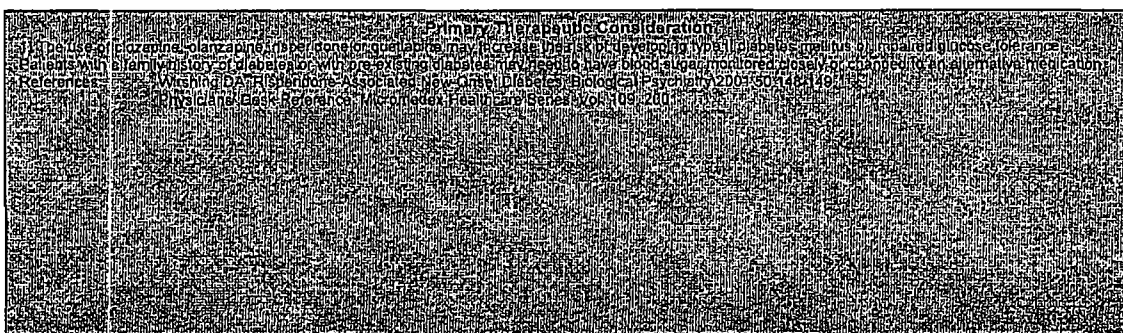
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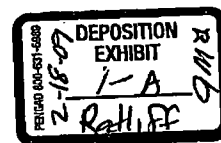
South Carolina Department Of Health And Human Services
Drug Utilization Review Program
Patient Drug History Profile

9/19/2002

Case Number: 259



Date of Service	RX Number	Drug Description	Strength	Qty	Days Supply	Pharmacy Number	Prescriber Number
07/16/02	4001578	TEMAZEPAM	30MG	30	30	761274	005408
07/10/02	6646749	POTASSIUM CHLORIDE	20MEQ	14	14	736224	00000195
07/10/02	6646748	SEROQUEL	25MG	60	30	736224	019546
07/10/02	6646752	LOTREL	5-20MG	30	30	736224	00000195
07/10/02	6646750	SUCRALFATE	1G	90	30	736224	00000195
07/01/02	6644894	FLUOXETINE HCL	20MG	90	30	736224	000565
07/01/02	4406332	CHLORDIAZEPOXIDE HCL	10MG	90	30	736224	000565
07/01/02	6642090	ACIPHEX	20MG	34	34	736224	005408
06/25/02	6646289	SYNTHROID	25MCG	30	30	736224	014752
06/25/02	6646288	LITHOBID	300MG	30	15	736224	014752
06/07/02	6644895	WELLBUTRIN SR	150MG	60	30	736224	000565
06/07/02	4406332	CHLORDIAZEPOXIDE HCL	10MG	90	30	736224	000565
06/07/02	6644894	FLUOXETINE HCL	20MG	90	30	736224	000565
05/29/02	6645602	SUCRALFATE	1G	100	33	736224	005408



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Diabetes Care

FEBRUARY 2004 PAGES 596-601

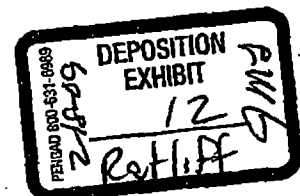
WWW.DIABETES.ORG/DIABETES CARE

Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

AMERICAN DIABETES ASSOCIATION
AMERICAN PSYCHIATRIC ASSOCIATION

AMERICAN ASSOCIATION OF CLINICAL
ENDOCRINOLOGISTS
NORTH AMERICAN ASSOCIATION FOR THE
STUDY OF OBESITY

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Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

AMERICAN DIABETES ASSOCIATION
AMERICAN PSYCHIATRIC ASSOCIATION

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ENDOCRINOLOGISTS
NORTH AMERICAN ASSOCIATION FOR THE
STUDY OF OBESITY

Antipsychotic medications are an important component in the medical management of many psychotic conditions. With the introduction of the second-generation antipsychotics (SGAs) over the last decade, the use of these medications has soared. Although the SGAs have many notable benefits compared with their earlier counterparts, their use has been associated with reports of dramatic weight gain, diabetes (even acute metabolic decompensation, e.g., diabetic ketoacidosis [DKA]), and an atherogenic lipid profile (increased LDL cholesterol and triglyceride levels and decreased HDL cholesterol).

Because of the close associations between obesity, diabetes, and dyslipidemia and cardiovascular disease (CVD), there is heightened interest in the relationship between the SGAs and the development of these major CVD risk factors. To gain a better understanding of this relationship, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity convened a consensus development conference 19–21 November 2003 on the subject of antipsychotic drugs and diabetes. An eight-member panel heard presentations from 14 experts drawn from the areas of psychiatry, obesity, and diabetes. Presentations were also made by a representative from the U.S. Food and Drug Administration (FDA) and by representatives from the AstraZeneca, Bristol-Myers Squibb,

Janssen, Lilly, and Pfizer pharmaceutical companies. In addition, before the conference, the consensus panel was given copies of most of the known peer-reviewed, English language clinical studies published in this area, as well as additional articles from animal studies; other papers and abstracts were reviewed at the conference.

With this information, the panel developed a consensus position on the following questions:

1. What is the current use of antipsychotic drugs?
2. What is the prevalence of obesity, pre-diabetes, and type 2 diabetes in the populations in which the SGAs are used?
3. What is the relationship between the use of these drugs and the incidence of obesity or diabetes?
4. Given the above risks, how should patients be monitored for the development of significant weight gain, dyslipidemia, and diabetes, and how should they be treated if diabetes develops?
5. What research is needed to better understand the relationship between these drugs and significant weight gain, dyslipidemia, and diabetes?

1. WHAT IS THE CURRENT USE OF ANTIPSYCHOTIC DRUGS? — Antipsychotic medications (Table 1) are the mainstay of treat-

ment for psychotic illnesses and are also widely used in many other psychiatric conditions. Introduced ~50 years ago, these medications have helped millions of people manage their symptoms. For people who respond well, antipsychotics can mean the difference between leading an engaged, fulfilling community life and being severely disabled.

The first-generation antipsychotics (FGAs) are still widely available and are effective at treating positive symptoms of psychosis, such as hallucinations and delusions. FGAs do not, however, adequately alleviate many other common and important aspects of psychotic illness, such as negative symptoms (e.g., withdrawal, apathy, poverty of speech), cognitive impairment, and affective symptoms. In addition, all FGAs can produce significant extrapyramidal side effects at clinically effective doses. These side effects, which include dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia, can make treatment intolerable for some people, leading to subjective distress, diminished function, stigma, and nonadherence.

The effort to find more effective medications with fewer and less-severe side effects led to the development of the SGAs, often referred to as the "atypical antipsychotics." SGAs have fewer or no extrapyramidal side effects at clinically effective doses. Many of these newer medications are also more effective than the older agents at treating the negative, cognitive, and affective symptoms of psychotic illnesses.

The six currently available SGAs vary in their efficacy, formulation, biochemistry, receptor binding, and side effect profiles. One of them, clozapine, is clearly the most effective antipsychotic. However, clozapine is only indicated after other medications have failed or in patients at high risk for suicidal behavior, largely because it can cause agranulocytosis.

In general, SGAs are better tolerated and more effective than the FGAs. Aside from clozapine, they have become the first-line agents for their indicated use and

From the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity.

Address correspondence to Nathaniel G. Clark, MD, American Diabetes Association, 1701 N. Beauregard St., Alexandria, VA 22311. E-mail: nclark@diabetes.org.

Abbreviations: CVD, cardiovascular disease; DKA, diabetic ketoacidosis; FDA, Food and Drug Administration; FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics.

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SC DMH : 05118

Table 1—Antipsychotic medications

	Generic name	Trade name	Year approved
Commonly used FGAs	Chlorpromazine	Thorazine	—
	Perphenazine	Trilafon	—
	Trifluoperazine	Stelazine	—
	Thiothixene	Navane	—
	Haloperidol	Haldol	—
	Fluphenazine	Prolixin	—
SGAs	Clozapine	Clozaril	1989
	Risperidone	Risperdal	1993
	Olanzapine	Zyprexa	1996
	Quetiapine	Seroquel	1997
	Ziprasidone	Geodon	2001
	Aripiprazole	Abilify	2002

are increasingly being used off-label. In current practice, people who are likely to be treated with an SGA include those with schizophrenia spectrum disorders, bipolar disorder, dementia, psychotic depression, autism, and developmental disorders and, to a lesser extent, individuals with conditions such as delirium, aggressive behavior, personality disorders, and posttraumatic stress disorder. These psychiatric conditions are common and often require lifelong treatment. In the U.S., the prevalence of schizophrenia and related conditions is ~1%, the prevalence of bipolar disorders is ~2%, and the prevalence of major depression is ~8%. The SGAs are therefore widely used medications, and their use has important public health ramifications.

2. WHAT IS THE PREVALENCE OF OBESITY, PRE-DIABETES, AND TYPE 2 DIABETES IN THE POPULATIONS IN WHICH THE SGAs ARE USED? —

It is difficult to determine whether the prevalence of these metabolic disorders is increased in these psychiatric populations independent of drug treatment. Most of the available data are derived from studies of individuals with schizophrenia, and even in this condition, the evidence is very limited. Data from most studies suggest that the prevalence of both diabetes and obesity among individuals with schizophrenia and affective disorders is ~1.5–2.0 times higher than in the general population. Many characteristics of people with schizophrenia, such as sedentary

behavior, may contribute to the apparently higher prevalence of metabolic abnormalities. However, none of these studies controlled for all of the major diabetes risk factors. For example, BMI and family history of diabetes were rarely determined, nor were the control populations appropriately matched for these and other variables. Thus, it is unclear whether psychiatric conditions per se, independent of other known diabetes risk factors, account for the increased prevalence.

There are limited data evaluating the metabolic profile and diabetes risk of drug-naïve subjects with schizophrenia. In a small cohort of adults with schizophrenia untreated with medications, visceral fat content (which is correlated with insulin resistance) was threefold higher than in age- and BMI-matched control subjects. In another study, the same investigators found that drug-naïve patients presenting with their first episode of schizophrenia had an increased prevalence of impaired fasting glucose, were more insulin resistant, and had higher plasma levels of glucose, insulin, and cortisol than did matched control subjects.

Overall, the limited amount of epidemiological data suggest an increased prevalence of obesity, impaired glucose tolerance, and type 2 diabetes in people with psychiatric illness. Whether this is a function of the illness itself versus its treatment is unknown. Studies using the proper diagnoses of glucose intolerance and more complete risk factor characterization are necessary in order to resolve this issue.

3. WHAT IS THE RELATIONSHIP BETWEEN THE USE OF THESE DRUGS AND THE INCIDENCE OF OBESITY OR DIABETES? —

Recognition of an association between SGAs and diabetes was first derived from case reports of severe, sometimes fatal, acute diabetic decompensation, including DKA. Subsequent drug surveillance and retrospective database analyses suggest there is an association between specific SGAs and both diabetes and obesity. This potential relationship is of considerable clinical concern because obesity and diabetes are important risk factors for CVD, and the relative risk of CVD mortality is significantly greater in people with psychiatric disorders than in the general population. High rates of smoking and physical inactivity may also contribute to the excess mortality. Therefore, if SGA therapy further increases the risk for obesity and type 2 diabetes, this should be of major clinical concern.

Although there are significant shortcomings in many of the studies examining the relationships between the SGAs and obesity or diabetes, clear-cut trends can be identified.

Obesity

There is considerable evidence, particularly in patients with schizophrenia, that treatment with SGAs can cause a rapid increase in body weight in the first few months of therapy that may not reach a plateau even after 1 year of treatment. There is, however, considerable variability in weight gain among the various SGAs (Table 2). At 10 weeks of therapy, estimated average weight gain with drug treatment compared with placebo varies from ~0.5 to 5.0 kg. Limited data suggest that in humans, most of the weight gained

Table 2—SGA's and metabolic abnormalities

Drug	Weight gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/-	-	-
Ziprasidone*	+/-	-	-

± = increase effect; - = no effect; D = discrepant results. *Newer drugs with limited long-term data.

is fat. Data derived from a canine model indicated that certain SGAs increase total visceral fat mass and intrahepatic lipid content.

The mechanism(s) responsible for weight gain associated with SGA therapy are unknown. Weight gain occurs when more energy is ingested than is expended. Therefore, weight gain is due to increased energy intake, decreased energy expenditure, or both. Even a small, chronic imbalance between energy intake and expenditure can lead to large changes in body weight over time. For example, ingestion of ~500 kcal/day more than is expended can account for the largest average weight gain reported with SGA therapy (4.5 kg at 10 weeks). This amount of daily increase in energy intake represents the calories in a normal-size candy bar plus a soda or in an ice cream dessert. Hunger and satiety may be altered in people taking SGAs because of the known binding affinities of these drugs to serotonin, norepinephrine, dopamine, and particularly histamine-H1 receptors. All of these receptors have been implicated in the control of body weight.

Weight gain and changes in body composition may account for many of the purported metabolic complications associated with SGA therapy, e.g., insulin resistance, pre-diabetes, diabetes, and dyslipidemia. A possible direct effect of SGAs on β -cell function and insulin action in liver and muscle tissue could also be involved, as discussed below.

Diabetes

Numerous case reports have documented the onset or exacerbation of diabetes, including the occurrence of hyperglycemic crises, following initiation of therapy with many of the SGAs.

Several of these events occurred within a few weeks of initiating drug treatment. In some, but not all cases, hyperglycemia promptly resolved after the medication was discontinued. Several reports documented recurrent hyperglycemia after another challenge with the same drug. Additional cases of diabetes or hyperglycemia have been reported through MedWatch into the FDA's Adverse Event Reporting System.

Large retrospective cohort studies have been reported that estimate the prevalence of diabetes in patients using SGAs. These reports relied on a variety of methods for determining the diagnosis of dia-

betes, such as ICD-9 codes and data on prescriptions for diabetes medications. In addition, several cross-sectional studies of patients taking different SGAs, "switch studies" of patients changed from one medication to another, and one prospective randomized controlled trial evaluating SGA therapy on parameters of insulin sensitivity and glycemic control have been conducted. Despite limitations in study design, the data consistently show an increased risk for diabetes in patients treated with clozapine or olanzapine compared with patients not receiving treatment with FGAs or with other SGAs. The risk in patients taking risperidone and quetiapine is less clear; some studies show an increased risk for diabetes, while others do not. The two most recently approved SGAs, aripiprazole and ziprasidone, have relatively limited epidemiological data, but available clinical trial experience with these drugs has not shown an increased risk for diabetes (Table 2).

One possible mechanism for hyperglycemia is impairment of insulin action (i.e., insulin resistance). Drug-induced insulin resistance may occur because of weight gain or a change in body fat distribution or by a direct effect on insulin-sensitive target tissues. Patients treated with olanzapine and clozapine have higher fasting and postprandial insulin levels than patients treated with FGAs, even after adjusting for body weight. To date, studies in humans have not shown adverse effects of any antipsychotic medication on β -cell function, but this issue has not been adequately studied in individuals with psychiatric illnesses.

Dyslipidemia

An additional related consequence of SGA use is their effect on serum lipids. Although the data are limited, the available evidence suggests that changes in serum lipids are concordant with changes in body weight. Clozapine and olanzapine, which produce the greatest weight gain, are associated with the greatest increases in total cholesterol, LDL cholesterol, and triglycerides and with decreased HDL cholesterol. Aripiprazole and ziprasidone, which are associated with the least amount of weight gain, do not seem to be associated with a worsening of serum lipids. Risperidone and quetiapine appear to have intermediate effects on lipids (Table 2).

Risk-benefit assessment

Despite the adverse effects cited above, a number of factors should be considered when choosing among the antipsychotic medications. These include the nature of the patient's psychiatric condition, specific target signs and symptoms, past history of drug response (both therapeutic and adverse), patient preference, history of treatment adherence, medication effectiveness, psychiatric and medical comorbidities, availability of appropriate formulations (e.g., fast-dissolving oral, short- or long-acting intramuscular), need for special monitoring, and cost of and access to medications. Nonetheless, the risks of obesity, diabetes, and dyslipidemia have considerable clinical implications in this patient population and should also influence drug choice.

Even for those medications associated with an increased risk of metabolic side effects, the benefit to specific patients could outweigh the potential risks. For example, clozapine has unique benefits for treatment-refractory patients and those at significant risk for suicidal behavior. Since treatment response in many psychiatric conditions is heterogeneous and unpredictable, physicians and patients can benefit from the availability of a broad array of different therapeutic agents.

4. GIVEN THE ABOVE RISKS, HOW SHOULD PATIENTS BE MONITORED FOR THE DEVELOPMENT OF SIGNIFICANT WEIGHT GAIN, DYSLIPIDEMIA, AND DIABETES, AND HOW SHOULD THEY BE TREATED IF DIABETES DEVELOPS? —

Given the serious health risks, patients taking SGAs should receive appropriate baseline screening and ongoing monitoring. Clinicians who prescribe SGAs for patients with psychiatric illnesses should have the capability of determining a patient's height and weight (BMI) and waist circumference. These values should be recorded and tracked for the duration of treatment. Clinicians should also encourage patients to monitor and chart their own weight. It is particularly important to monitor any alteration in weight following a medication change. The patients' psychiatric illness should not discourage clinicians from addressing the metabolic

Table 3—Monitoring protocol for patients on SGAs*

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

*More frequent assessments may be warranted based on clinical status

complications for which these patients are at increased risk.

Baseline monitoring

The panel recommends that baseline screening measures be obtained before, or as soon as clinically feasible after, the initiation of any antipsychotic medication (Table 3). These include

- Personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease
- Weight and height (so that BMI can be calculated)
- Waist circumference (at the level of the umbilicus)
- Blood pressure
- Fasting plasma glucose
- Fasting lipid profile

These assessments can determine if the patient is overweight (BMI 25.0–29.9) or obese (BMI ≥30), has pre-diabetes (fasting plasma glucose 100–125 mg/dl) or diabetes (fasting plasma glucose ≥126 mg/dl), hypertension (blood pressure >140/90 mmHg), or dyslipidemia. If any of these conditions are identified, appropriate treatment should be initiated. Psychiatrists should not hesitate to refer the patient to the appropriate health care professional or specialist knowledgeable about these disorders.

The panel recommends that nutrition and physical activity counseling be provided for all patients who are overweight

or obese, particularly if they are starting treatment with an SGA that is associated with significant weight gain. Referral to a health care professional or program with expertise in weight management may also be appropriate.

Health professionals, patients, family members, and caregivers should be aware of the signs and symptoms of diabetes and especially those associated with the acute decompensation of diabetes such as DKA (Table 4). The latter is a life-threatening condition and always requires immediate treatment. Patients, family members, and caregivers also need to know that treatment with some SGAs may be associated with significant weight gain and a heightened risk of developing diabetes and dyslipidemia. For patients with, or at higher risk for, diabetes and in those treated with other medications that may increase these risks (e.g., valproate, lithium, Depo-Provera), it may be preferable to initiate treatment with an SGA that appears to have a lower propensity for weight gain and glucose intolerance (Table 2). Potential for weight gain should also be considered in the choice of other psychiatric and nonpsychiatric medications.

Follow-up monitoring

The patient's weight should be reassessed at 4, 8, and 12 weeks after initiating or changing SGA therapy and quarterly thereafter at the time of routine visits (Table 3). If a patient gains ≥5% of his or her initial weight at any time during therapy, one should consider switching the SGA. In such a situation, the panel recommends cross-titration to be the safest approach; abrupt discontinuation of an antipsychotic drug should generally be avoided. When switching from one antipsychotic drug to another, it is preferable to discontinue the current medication in a gradual fashion. The profile of the subsequent drug will determine the initial dose

and escalation strategy. Particular consideration should be given before discontinuing clozapine because of the potential for serious psychiatric sequelae.

Fasting plasma glucose, lipid level, and blood pressure should also be assessed 3 months after initiation of antipsychotic medications. Thereafter, blood pressure and plasma glucose values should be obtained annually or more frequently in those who have a higher baseline risk for the development of diabetes or hypertension. In those with a normal lipid profile, repeat testing should be performed at 5-year intervals or more frequently if clinically indicated.

Although limited data are available in children and adolescents regarding the risks of diabetes when SGAs are given, these patients should have their height, in addition to weight, measured at regular intervals and their BMI calculated. BMI percentile adjusted for age and sex should be used to determine if excessive weight gain has occurred, and if present, a change in therapy should be considered.

For people who develop worsening glycemia or dyslipidemia while on antipsychotic therapy, the panel recommends considering switching to an SGA that has not been associated with significant weight gain or diabetes (Table 2). All patients with diabetes should be referred to an American Diabetes Association-recognized diabetes self-management education program, if available. Referral to a clinician with experience treating people with diabetes is recommended. These patients should carry diabetes identification.

Immediate care or consultation is required for patients with symptomatic or severe hyperglycemia (glucose values ≥300 mg/dl), symptomatic hypoglycemia, or glucose levels ≤60 mg/dl, even in the absence of symptoms. The presence of

Table 4—DKA clinical presentation

Rapid onset of:

- Polyuria, polydipsia
- Weight loss
- Nausea, vomiting
- Dehydration
- Rapid respiration
- Clouding of sensorium, even coma

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symptoms of DKA (Table 4), requires immediate evaluation and treatment.

Blood pressure, lipid, and glycemic goals of therapy for people with diabetes apply equally to those who also have psychiatric disorders. However, all goals need to be individualized. The benefits and risks of different therapeutic agents used in the treatment of diabetes and its comorbidities should be considered in the context of the patient's psychiatric condition and treatment.

In summary, the panel recommends the following:

- Consideration of metabolic risks when starting SGAs
- Patient, family, and care giver education
- Baseline screening
- Regular monitoring
- Referral to specialized services, when appropriate

5. WHAT RESEARCH IS NEEDED TO BETTER UNDERSTAND THE RELATIONSHIP BETWEEN THESE DRUGS AND SIGNIFICANT WEIGHT GAIN, DYSLIPIDEMIA, AND DIABETES?

Evidence for weight gain and abnormalities of glucose and lipid metabolism in patients taking SGAs is in part derived from case-control studies, pharmacovigilance (e.g., through MedWatch), and database reviews. Many of these studies suffer from their retrospective nature, heterogeneity of methodology, selection or ascertainment bias, and absence of appropriate or well-characterized control subjects. Comparison studies among SGAs are also limited by relatively short periods of study, by failure to control for a possible treatment sequence bias in "switchover" studies, and by not always using clinically equivalent dosages of the medications.

Trials with SGAs should be randomized and controlled, preferably using drug-naïve subjects. Weight gain and measures of glucose and lipid metabolism should be thoroughly evaluated. Study subjects should be well-characterized in terms of their baseline risk factors for diabetes, obesity, and lipid disorders and their degree of baseline impairment in insulin sensitivity and β -cell function. The duration of exposure to the various SGAs should be carefully controlled. Future re-

search studies should focus on the following:

- Baseline body composition in untreated patients with psychiatric disorders and changes that occur during treatment with SGAs need to be better characterized. This would include measures of fat versus fat-free mass and visceral and subcutaneous adipose stores, using valid methods to measure body fat (e.g., magnetic resonance imaging, computed tomography, dual-energy X-ray absorptiometry).
- The contribution of altered neuroendocrine function (e.g., hypothalamic-pituitary-adrenal axis activation) to alterations in body composition and abnormalities in glucose and lipid metabolism needs further study to distinguish the acute effects of stress from the underlying disease process.
- Studies are needed that examine glucose and lipid metabolism as they relate to alterations in insulin sensitivity in peripheral and hepatic tissues (e.g., euglycemic-hyperinsulinemic clamp with labeled glucose infusions), alterations in β -cell function (hyperglycemic clamp or frequently sampled intravenous glucose tolerance test), and alterations in lipid metabolism (using tracer infusions).
- Large prospective studies should be conducted to identify baseline and early treatment factors that predict the later occurrence of abnormalities in body weight and composition and disorders of glucose and lipid metabolism during treatment with these drugs.
- Additional studies are needed to identify whether there are baseline characteristics that predict acute, life-threatening complications (e.g., DKA, pancreatitis).
- Additional data are needed to determine whether the risks of therapy are increased in certain ethnic groups (e.g., African Americans).
- Studies determining the effect of SGAs in various psychiatric disorders are needed to clarify the disease-related risk for the development of weight gain and metabolic disturbances.
- Alterations in energy intake and expenditure as contributors to weight gain in the psychiatric population and how these processes are altered by treatment with SGAs should be studied.
- Studies are needed to determine

whether the disorders of body weight and glucose and lipid metabolism are due to central nervous system or peripheral tissue actions of the SGAs. Valuable information on the direct effects of SGAs on different body tissue compartments might be obtained from studies in appropriate animal models.

- Studies of the genetic markers that are associated with, and may be causally related to, the metabolic disturbances occurring in treated patients with psychiatric disorders (e.g., 5-HT_{2C}, histamine-H1 receptor alleles) are needed.

SUMMARY—The SGAs are of great benefit to a wide variety of people with psychiatric disorders. As with all drugs, SGAs are associated with undesirable side effects. One constellation of adverse effects is an increased risk for obesity, diabetes, and dyslipidemia. The etiology of the increased risk for metabolic abnormalities is uncertain, but their prevalence seems correlated to an increase in body weight often seen in patients taking an SGA. Direct drug effects on β -cell function and insulin action could also be involved, since there is insufficient information to rule out this possibility. In the general population, being overweight or obese also carries a much higher risk of diabetes and dyslipidemia.

These three adverse conditions are closely linked, and their prevalence appears to differ depending on the SGA used. Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia. Risperidone and quetiapine appear to have intermediate effects. Aripiprazole and ziprasidone are associated with little or no significant weight gain, diabetes, or dyslipidemia, although they have not been used as extensively as the other agents.

The choice of SGA for a specific patient depends on many factors. The likelihood of developing severe metabolic disease should also be an important consideration. When prescribing an SGA, a commitment to baseline screening and follow-up monitoring is essential in order to mitigate the likelihood of developing CVD, diabetes, or other diabetes complications.

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APPENDIX

Consensus panel

Eugene Barrett, MD, PhD, Chair, Lawrence Blonde, MD, Stephen Clement, MD, John Davis, MD, John Devlin, MD, John Kane, MD, Samuel Klein, MD, William Torrey, MD.

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Presenters at the conference

David Allison, PhD, Richard Bergman, PhD, John Buse, MD, PhD, Patrizia Cavazzoni, MD, Fred Fiedorek, MD, Rohan Ganguli, MD, Andrew Greenspan, MD, David Kendall, MD, Ron Leong, MD, Antony Loebel, MD, Patrick Lustman, PhD, Herbert Meltzer, MD, John Newcomer, MD, Judy Racosin, MD, Bryan Roth, MD, Michael Sernyak, MD, Jogin Thakore, MB, Donna Wirshing, MD, William Wirshing, MD.

Bibliography

Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ: Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 156:1686-1696, 1999
Caro JJ, Ward A, Levinton C, Robinson K: The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry* 63:1135-1139, 2002
Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ: National Heart, Lung, and Blood Institute Joint National Committee on Pre-

vention, Detection, Evaluation, and Treatment of High Blood Pressure. National High Blood Pressure Education Program Coordinating Committee: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 289:2560-2572, 2003

Clark C, Burge MR: Diabetes mellitus associated with atypical anti-psychotic medications. *Diabetes Technol Ther* 5:669-683, 2003

Czobor P, Volavka J, Sheitman B, Lindenmayer JP, Cirome L, McEvoy J, Cooper TB, Chakos M, Lieberman JA: Antipsychotic-induced weight gain and therapeutic response: a differential association. *J Clin Psychopharmacol* 22:244-251, 2002

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486-2497, 2001

Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183-1197, 1997

Gianfrancesco FD, Grogg AL, Mahmoud RA, Wang RH, Nasrallah HA: Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan database. *J Clin Psychiatry* 63:920-930, 2002

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

Genuth S, Alberti KG, Bennett P, Buse J, De Fronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lennmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P: Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 26:3160-3167, 2003

Koller E, Schneider B, Bennett K, Dubitsky G: Clozapine-associated diabetes. *Am J Med* 111:716-723, 2001

Koller EA, Doraiswamy PM: Olanzapine-associated diabetes mellitus. *Pharmacotherapy* 22:841-852, 2002

Koller EA, Cross JT, Doraiswamy PM, Schneider BS: Risperidone-associated diabetes mellitus: a pharmacovigilance study. *Phar-*

macotherapy 23:735-744, 2003

Koro CE, Fedder DO, L'italien GJ, Weiss SS, Magder LS, Kreyenbuhl J, Revicki DA, Buchanan RW: Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 325:283-288, 2002

Lean ME, Pajonk FG: Patients on atypical antipsychotic drugs: another high-risk group for type 2 diabetes. *Diabetes Care* 26:1597-1605

Lindenmayer JP, Czobor P, Volavka J, Cirome L, Sheitman B, McEvoy JP, Cooper TB, Chakos M, Lieberman JA: Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *Am J Psychiatry* 160:290-296, 2003

Lund BC, Perry PJ, Brooks JM, Arndt S: Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension: a claims-based approach. *Arch Gen Psychiatry* 58:1172-1176, 2001

Meyer JM: A retrospective comparison of weight, lipid, and glucose changes between risperidone- and olanzapine-treated inpatients: metabolic outcomes after 1 year. *J Clin Psychiatry* 63:425-433, 2002

Nasrallah H: A review of the effect of atypical antipsychotics on weight. *PNEC* 28:83-96, 2003

Newcomer JW, Haupt DW, Fucetola R, Melson AK, Schweiger JA, Cooper BP, Selke G: Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry* 59:337-345, 2002

Ryan MC, Thakore JH: Physical consequences of schizophrenia and its treatment: the metabolic syndrome. *Life Sciences* 71:239-257, 2002

Ryan MC, Collins P, Thakore JH: Impaired fasting glucose tolerance in first-episode, drug-naïve patients with schizophrenia. *Am J Psychiatry* 160:284-289, 2003

Sernyak MJ, Leslie DL, Alarcon RD, Losonczy MF, Rosenheck R: Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry* 159:561-566, 2002

Wilson R, Souza L, Sarkar N, Newton M, Hammond C: New-onset diabetes and ketoacidosis with atypical antipsychotics. *Schiz Research* 59:1-6, 2002

Wirshing DA, Boyd JA, Meng LR, Ballon JS, Marder SR, Wirshing WC: The effects of novel antipsychotics on glucose and lipid levels. *J Clin Psychiatry* 63:856-865, 2002