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.

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VII. CERTIFICATE OF COUNSEL

SCDMH Laboratory Monitoring Guidelines for Antipsychotic Medications

The laboratory monitoring protocol outlined in this document serves as guidelines that need to be considered taking into account the clinical condition of the patient, other associated risk factors, feasibility issues and the clinical assessment made by the treating physician.

Introduction:

Consumers with schizophrenia have a 2-4 times greater risk of diabetes then the general population. Comorbid mental illness is associated with reduced access to and compliance with care for diabetes. Poor outcomes maybe due to direct biological mechanisms (elevated glucococorticolds), poor diet and obesity, psychoactive medications and inadequate medical care.

An elevated rate of cardiovascular disease is reported in consumers with schizophrenic and depression. There is also an increased risk of cardiovascular mortality in this group. Poor outcome maybe due to direct effects (platelet abnormalities, arrhythmias), lifestyle (smoking, lack of exercise), psychotropics and inadequate cardiac care. Sedentary lifestyle and poor dietary habits also puts patients with Schizophrenia and Depression at risk for elevated serum lipids. Atypical antipsychotics have been associated with elevated lipid levels.

Antipsychotics medications are an important component in the management of psychiatric symptoms (Table 1). Although second generation antipsychotics offer a notable advantage over conventionals their use has been associated with reports of weight gain, diabetes, increases in serum lipids.

Several studies have shown a close association between obesity, diabetes, dyslipidemias and cardiovascular disease. This issue of metabolic effects of the Second Generation Antipsychotics was addressed at the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. This expert panel had members 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, the Food and Drug Administration and representatives from various pharmaceutical companies.

Table 1
Mode of Action of Atypical Antipsychotics

Antipsychotics	D2	Cholinergic	A-1 adrenergic	Histamine	Serotonin
Aripiprazole	++	0	++	++	++
Clozapine	++	++++	++++	++++	++++
Olanzapine	+++	++	++	++	+++
Risperidone	++	+	+++	++	+++
Quetiapine	+	0	++	++	++
Ziprasidone	+++	+	+	+	+++

Ability
Clozaril
Zyprexa
Risperdal
Seroquel
Geodon

DEPOSITION EXHIBIT 13

SC DMH : 05124

Second Generation Antipsychotics and Obesity

Second Generation Antipsychotic (SGA) can cause a rapid increase in body weight in the first few days of therapy that may not reach a plateau even after 1 year of treatment. There is considerable variability in weight gain among the SGA's.

- **Role of Serotonin (5-HT) Receptors in Obesity (Wirshing et al)**

The activation of serotonin receptors and increased availability of serotonin in the synaptic cleft reduces appetite and food consumption. Since atypical antipsychotics act as antagonists to serotonin receptors, patients may feel increased appetite and increase in their food consumption.

- **Role of Histamine (H1) Receptors in Obesity (Wirshing et al)**

It has been observed that H1 antagonists increase appetite and weight and are sedating. Blockade of H1 receptor by atypical antipsychotics results in sedation and weight gain.

- **Role of Leptin in Obesity (Krause et al)**

Leptin is secreted by white adipose cells to regulate insulin secretion and energy metabolism via receptors in the hypothalamus, adipocytes and skeletal muscle. The phenomenon of leptin resistance was observed in individuals with chronic obesity who have increased leptin levels. Certain atypical are noted to have increased serum leptin levels compared to haloperidol.

Weight gain and changes in body composition may account for many of the metabolic complications with SGA therapy. These include: insulin resistance, pre-diabetes, diabetes and dyslipidemias.

Second Generation Antipsychotics and Diabetes

- Prevalence of diabetes is 2-4 times higher in Schizophrenic patients than the general population (Mukherjee et al).
- Atypicals have a greater increase in random blood glucose as compared to typicals (Allison et al).
- Each year, 5-8% of patients on antipsychotics require treatment with an antidiabetic agent (Lund et al, Melkersson et al, Sernyak et al).

Possible mechanisms for hyperglycemia include:

1. Insulin resistance.
2. Change in body fat distribution.
3. Increased insulin sensitivity.

Second Generation Antipsychotic and Dyslipidemia

Elevation of serum lipids is one of the consequences of Second Generation Antipsychotics. Although data is limited changes in serum lipids are concordant with changes in body weight. SGA's that produce the greatest weight gain are associated with increases in total cholesterol, LDL cholesterol and triglycerides and with decreased HDL cholesterol levels (Table 2).

Table 2
SGA's and Metabolic Abnormalities

Antipsychotic	Weight Gain	Risk of Diabetes	Worsening of Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	±	–	–
Ziprasidone*	±	–	–

+ = increase affect
-- = no effect
D = discrepant results
* = newer drug with limited long term data

Risk Benefit Assessment

Factors that should be considered when selecting an antipsychotic medication include:

1. Patient's psychiatric condition.
2. Target symptoms.
3. Prior response to treatment and adverse effects
4. Patient preference
5. History of Treatment Adherence
6. Other comorbidites
7. Medication Effectiveness
8. Availability of appropriate formulations
9. Need for special monitoring
10. Cost and access to the medication

SC DMH : 05126

Table 3
High Risk Factors That Require Baseline And Ongoing Monitoring

- Obesity (BMI ≥ 27 or>120% of ideal body weight)
- Having a family history of diabetes.
- Being a member of a high-risk population (African-American, Hispanic, Native American, Asian-American, and Pacific Islander.
- Having delivered a baby weighing more than 9 pounds or history of gestational diabetes.
- Hypertension (BP>140/90mm of Hg)
- HDL cholesterol<35mg/dl
- Fasting triglyceride level>250mg/dl
- Impaired glucose tolerance or impaired fasting glucose on previous testing.
- Cardiovascular Disease.

Source: American Diabetic Association

Monitoring Guidelines

The Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes recommends (Table 4):

Table 4
Monitoring Guidelines for Antipsychotics

	Vital Signs	Height/Weight (BMI)	Blood Glucose	Cholesterol/ Triglycerides	Prolactin	Tardive Dyskinesia	EPS	EKG
First Generation Antipsychotics (Conventional)	Yearly, or sooner if symptoms occur	Baseline, 3 months, 1 year	Baseline, then if pt gains >5lb. baseline wt., 1 year	Baseline, then if pt gains >5lb. baseline wt., 1 year	Baseline, 3 months, 1 year	Baseline, 6 months, 1 year (AIMS)	Baseline, monthly (AIMS)	Baseline, 1 year (thioridazine & mesoridazine only)
Second Generation Antipsychotics (Atypical)**	Baseline, monthly	Baseline, 4, 8 and 6 weeks and 3 months*	Baseline, 3 months, then if pt gains >5lb. baseline wt.*	Baseline, 3 months, then if pt gains >5lb. baseline wt*	Baseline, 3 months, 1 year*	Baseline, 6 months, 1 year (AIMS)*	Baseline, monthly (AIMS)*	Baseline, 1 year (ziprasidone)*

** Clozapine also requires white blood cell count monitoring weekly for six months, followed by every other month

* Risk Factors are present

SC DMH :05127

Baseline monitoring:

1. Personal and family history of obesity, diabetes, dyslipidemias, hypertension or cardiovascular disease.
2. Weight and height (Body Mass Index)
3. Waist circumference
4. Blood pressure
5. Fasting plasma glucose
6. Fasting lipids

{Parameters: Overweight= BMI25-29, Obesity ≥ 30, (pre-diabetes) FBS= 100-125mg/dl or (diabetes) FBS=≥126mg/dl, hypertension=>140/90mm of hg, dyslipidemias}

The panel recommends nutrition and physical activity counseling be provided for all patients who are overweight or obese. Referral to a health care professional or program with expertise in weight management is recommended.

Follow-up monitoring:

1. Weight to be reassessed at 4, 8 and 12 weeks after initiating treatment, them quarterly and annually. BMI should be used to determine if excessive weight gain has occurred.
2. Weight gain ≥ 5lbs should consider switching to another SGA (cross-titration, gradual dose reduction).
3. Fasting blood glucose, lipids and BP should be assessed 3 months after initiation and then annually or more frequently if risk factors are present.
4. If there is worsening of glycemia or dyslipidemia on the antipsychotic consider switching to an SGA with minimal weight effects.
5. Immediate care or consultations are warranted with severe hyperglycemia (glucose ≥300mg/dl or ≤30mg/dl) or presence of symptoms of Diabetic Ketoacidosis.
6. Blood pressure, lipid and glycemic goals of therapy for people with diabetes apply equally to those who have psychiatric disorders.
7. Benefits and Risk of different agents used in the treatment of diabetes and its comorbidites should be considered in the context of patient's psychiatric condition and treatment.

SC DMH : 05128

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SC DMH : 05129

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DEMOGRAPHIC BREAKDOWN

Study	Age Group	Gender	Race
RIS-CAN-19	100% Children	80% Male 20% Female	70.1% Caucasian 29.9% Black
RIS-INT-35	96.0 % Adult 4.0 % Pediatric (Adolescents)	69.9 % Male 30.1 % Female	75.7 % Caucasian 12.5 % Black 2.7 % Hispanic 1.6 % Oriental 7.6 % Other
RIS-INT-41	100% Children	80.8% Male 19.2% Female	60.2% Caucasian 33.7% Black 3.9% Hispanic 2.3% Other
RIS-INT-50	100 % Elderly	64.3 % Female 35.7 % Male	74.1 % Caucasian 19.6 % Black 3.5 % Hispanic 2.8 % Oriental
RIS-USA-79	99.2 % Adult 0.8% Elderly	68.8 % Male 31.2 % Female	47.6 % Caucasian 36.5 % Black 13.4 % Hispanic 1.3 % Oriental 1.2 % Other
RIS-USA-93 DONE	100 % Children	81 % Male 19 % Female	59.9 % Caucasian 31.7 % Black 4.9 % Hispanic 0.7 % Oriental 2.8 % Other
RIS-USA-97	100 % Children	19.6% Female 80.4% Male	52.3 % Caucasian 40.0 % Black 3.7 % Hispanic 0.8 % Oriental 3.7 % Other
RIS-USA-102	100.0 % Adult 0 % Elderly	45.7 % Female 54.3 % Male	69.1 % Caucasian 14.8 % Black 11.1 % Hispanic 1.2 % Oriental 3.7 % Other

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DEMOGRAPHIC BREAKDOWN CONT'D

Study	Age Group	Gender	Race
RIS-USA-113	100 % Adult	67.5 % Male 32.5 % Female	59.7 % Caucasian 33.8 % Black 5.2 % Hispanic 1.3 % Other

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Individual Study Information

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INDIVIDUAL STUDY INFORMATION

Studies Ongoing

Protocol: RIS-CAN-19

Title: The Safety and Efficacy of Risperidone Versus Placebo in Conduct Disorder in Mild, Moderate, and Borderline Mentally Retarded Children Aged 5 to 12 Years.

Objective: To assess the safety and efficacy of risperidone versus placebo in conduct disorder in mild, moderate and borderline mental retarded children 5 to 12 years of age.

Status: The trial is ongoing.

# Planned	# Randomized	# Complete (Randomized)	# Drop outs	# Ongoing
108	15	13	2	0

Subject Demographics:

Age Group – 100 % Children
Gender – 80 % Male and 20 % Female
Race – 70.1 % Caucasian, 29.9 % Black

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INDIVIDUAL STUDY INFORMATION

Studies Ongoing

Protocol: RIS-INT-35

Title: Double-blind evaluation of risperidone *vs* haloperidol on the long-term morbidity of early psychotic patients.

Objective: This is an international multicentre double-blind trial to explore the effect of early treatment with risperidone *vs* haloperidol on the long-term outcome of early psychotic patients.

Status: The trial is ongoing.

# Planned	# Randomized	# Complete (Randomized)	# Drop outs	# Ongoing
600	145	0	91	54

Subject Demographics:

Age Group – 96.0% Adult,4.0% Pediatric
Gender – 30.1 % Female and 69.9 % Male
Race – 75.7 % Caucasian, 2.7% Hispanic, 12.5% Black, 1.6% Oriental, 7.6% Other

Investigators:

A complete list of investigators is provided on the following pages.

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INDIVIDUAL STUDY INFORMATION

Studies Ongoing

Protocol: RIS-INT-41

Title: The Safety and Efficacy of Open Label Risperidone in Conduct Disorder in Mild, Moderate, and Borderline Mentally Retarded Children Aged 5 to 14 Years.

Objective: To assess the safety of 0.02 to 0.06 mg/kg/day of oral risperidone in conduct disorder in mild, moderate and borderline mentally retarded children. In addition, to assess the long-term impact of the test treatment in conduct disorder.

Status: The trial is ongoing.

# Planned	# Randomized	# Complete (Randomized)	# Drop outs	# Ongoing
500	31	0	4	27

Subject Demographics:

Age Group – 100% Children
Gender – 80.8% Male and 19.2% Female
Race – 60.2% Caucasian, 33.7% Black, 3.9% Hispanic, 2.3% Other

Investigators:

A complete list of investigators is provided on the following pages.

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INDIVIDUAL STUDY INFORMATION

Studies Ongoing

Protocol: RIS-INT-50

Title: Risperidone Versus Olanzapine in the Treatment of Schizophrenia in Elderly Subjects.

Objective: To compare the safety and efficacy of risperidone versus olanzapine in elderly patients with the symptoms of schizophrenia and schizoaffective disorder over an 8-week period.

Status: The trial is ongoing.

# Planned	# Randomized	# Complete (Randomized)	# Drop outs	# Ongoing
200	143	101	42	8

Subject Demographics:

Age Group – 100 % Elderly
Gender – 64.3 % Female and 35.7 % Male
Race – 74.1 % Caucasian, 19.6 % Black, 3.5 % Hispanic and 2.8 % Oriental

Investigators:

A complete list of investigators is provided on the following pages.

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INDIVIDUAL STUDY INFORMATION

Studies Completed

Protocol: RIS-USA-79

Title: A Double-Blind Comparison of Risperidone 2-8 mg/day Versus Haloperidol 5-20 mg/day in Relapse Prevention in Chronic Schizophrenic Patients.

Objective: To compare the time to relapse in stable outpatient schizophrenics and subjects with schizoaffective disorder receiving risperidone or haloperidol for at least 1 year. Secondary objectives include; comparing the effect of these two drugs on the incidence of relapse, symptom measures (PANSS, CGI) EPS effects, compliance, cognitive function (6 item test battery), subject satisfactory, quality of life and resource use.

Status: The trial is completed and the report is in preparation. The last patient completed the study on September 28, 1998.

# Planned	# Randomized	# Complete (Randomized)	# Drop outs	# Ongoing
414	397	124	273	0

Subject Demographics:

Age Group – 99.2 % Adult 0.8 % Elderly
Gender – 68.8 % Male and 31.2 % Female
Race – 47.6 % Caucasian, 36.5 % Black, 13.4 % Hispanic, 1.3 % Oriental and 1.2 % other

Investigators:

A complete list of investigators is provided on the following pages.

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INDIVIDUAL STUDY INFORMATION

Studies Completed

Protocol: RIS-USA-93

Title: The Safety and Efficacy of Open Label Risperidone versus Placebo in Conduct Disorder in Mild, Moderate, and Borderline Mentally Retarded Children Aged 5 to 12 Years.

Objective: To assess the safety and efficacy of risperidone versus placebo in conduct disorder in mild, moderate and borderline mentally retarded children 5 to 12 years of age.

Status: The trial is complete.

# Planned	# Randomized	# Complete (Randomized)	# Drop outs	# Ongoing
108	119	87	32	0

Subject Demographics:

Age Group – 100 % Children
Gender – 81 % Male and 19 % Female
Race – 59.9 % Caucasian, 31.7 % Black, 4.9 % Hispanic, 0.7 % Oriental and 2.8 % Other

Investigators:

A complete list of investigators is provided on the following pages.

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INDIVIDUAL STUDY INFORMATION

Studies Ongoing

Protocol: RIS-USA-97

Title: The Safety and Efficacy of Open Label Risperidone in Conduct Disorder in Mild, Moderate, and Borderline Mentally Retarded Children Aged 5 to 12 Years.

Objective: To assess the safety of 0.02 to 0.06 mg/kg/day of oral risperidone in conduct disorder in mild, moderate and borderline mentally retarded children. In addition, to assess the long-term impact of the test treatment in conduct disorder.

Status: The trial is ongoing.

# Planned	# Randomized	# Complete (Randomized)	# Drop outs	# Ongoing
108	107	46	57	4

Subject Demographics:

Age Group – 100 % Children
Gender – 19.6% Female and 80.4% Male
Race – 52.3 % Caucasian, 40.0 % Black, 3.7 % Hispanic, 0.8 % Oriental, 3.7 % Other

Investigators:

A complete list of investigators is provided on the following pages.

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INDIVIDUAL STUDY INFORMATION

Studies Completed

Protocol: RIS-USA-102

Title: The Safety and Efficacy of Risperdal® (risperidone) Versus Placebo Versus Haloperidol as Add-On Therapy to Mood Stabilizers in the Treatment of the Manic Phase of Bipolar Disorder.

Objective: To assess the safety and efficacy of risperidone as add-on therapy to mood stabilizers (lithium or valproate) in the treatment of the manic phase of bipolar disorder. Additional objectives during the open-label follow-up are to gather additional safety and efficacy data for 10 weeks following the double-blind treatment.

Status: The trial is complete and the report is in preparation.

# Planned	# Randomized	# Drop Out Double Blind	# Drop Out Open Label	# Complete Double Blind	# Complete Open Label
160	81	28	19	60	40

Subject Demographics:

Age Group – 100.0 % Adult and 0 % Elderly
Gender – 45.7 % Female and 54.3 % Male
Race – 69.1% Caucasian, 14.8% Black, 11.1% Hispanic, 1.2% Oriental, 3.7% Other

Investigators:

A complete list of investigators is provided on the following pages.

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INDIVIDUAL STUDY INFORMATION

Studies Completed

Protocol: RIS-USA-113

Title: Risperidone Versus Olanzapine in the Treatment of Schizophrenia (44 weeks).

Objective: To evaluate the safety and efficacy of risperidone versus olanzapine in subjects with schizophrenia and schizoaffective disorder treated up to 44 weeks. To also evaluate the efficacy of risperidone versus olanzapine on the symptoms, quality of life, and satisfaction of patients with schizophrenia and schizoaffective disorder over a 44 week period.

Status: The trial is completed.

# Planned	# Entered	# Screen Failure	# Randomized	# Complete (Randomized)	# Drop outs	# Ongoing
323	267	0	267	148	119	0

Subject Demographics:

Age Group – 100 % Adult
Gender – 67.5 % Male and 32.5 % Female
Race – 59.7 % Caucasian, 33.8 % Black, 5.2 % Hispanic and 1.3 % Other

Investigators:

A complete list of investigators is provided on the following pages.

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INDIVIDUAL CLINICAL SUMMARY

PROGRESS REPORT: RISPERIDONE LIQUID		
PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-CAN-19	The Safety and Efficacy of Risperidone vs. Placebo in Conduct Disorder in Mild, Moderate, and Borderline Mentally Retarded Children Aged 5 to 12 Years	
RIS-CAN-19	Mike Aman, Ph.D. Nisonger Center 1581 Dodd Drive, Room 175 Columbus, Ohio 43210-1296	12 randomized 11 completed 1 dropped
RIS-CAN-19	Deborah Pearson, Ph.D. Dept. of Psychiatry Univ. of Texas Medical School 1300 Moursund – Room 225 Houston, TX 77030	2 randomized 1 completed 1 dropped
RIS-CAN-19	Nirbahay Singh, M.D. Medical College of VA. Dept. of Psychiatry P.O. Box 23298-0489 Richmond, VA 23284-3039	1 randomized 0 completed 0 dropped
RIS-CAN-19	Jessica Hellings, M.D. Dept. Of Child Psychiatry 3901 Rainbow Boulevard Kansas City, KS 66160	0 randomized 0 completed 0 dropped

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PROGRESS REPORT: RISPERIDONE TABLETS		
PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-INT-35	Double-Blind Evaluation of Risperidone vs. Haloperidol on the Long-Term Morbidity of Early Psychotic Patients.	
RIS-INT-35	John Csernansky, M.D. Metropolitan Psychiatric Center 5351 Delmar Blvd. St. Louis, MO 63112	23 randomized 0 completed 15 dropped
RIS-INT-35	Lynn E. DeLisi, M.D. Department of Psychiatry Health Sciences Center, T-10 SUNY at Stony Brook, Stony Brook,NY 11794-8101	19 randomized 0 completed 9 dropped
RIS-INT-35	John Lauriello, M.D. Department of Psychiatry University of New Mexico School of Medicine 2400 Tucker Northeast Albuquerque, NM 87131	20 randomized 0 completed 11 dropped
RIS-INT-35	Theo Manschreck, M.D. Corrigan Mental Health Center 49 Hillside Street Fall River, MA 02720	13 randomized 0 completed 10 dropped
RIS-INT-35	Jorg J. Pahl, M.D. 13301 North Meridian 100 Oklahoma City, OK 73120	16 randomized 0 completed 14 dropped
RIS-INT-35	Nina Schooler, Ph.D. Western Psychiatric Institute & Clinic 3811 O'Hara Street Pittsburgh, PA 15213	16 randomized 0 completed 8 dropped
RIS-INT-35	S. Charles Schulz, M.D. Department of Psychiatry University Hospitals of Cleveland Case Western Reserve University 2074 Abington Road Cleveland, OH 44106	20 randomized 0 completed 10 dropped

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PROGRESS REPORT: RISPERIDONE TABLETS		
PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-INT-35	Steven Targum, M.D. Clinical Studies, Philadelphia 1015 Chestnut Street, Suite 1303 Philadelphia, PA 19107	10 randomized 0 completed 9 dropped
RIS-INT-35	S. Craig Risch, MD Department of Psychiatry and Behavioral Sciences Institute of Psychiatry, 502N Medical University of South Carolina 171 Ashley Avenue Charleston, SC 29425-0742	8 randomized 0 completed 5 dropped

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PROGRESS REPORT: RISPERIDONE LIQUID		
PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-INT-41	The Safety and Efficacy of Open Label Risperidone in Conduct Disorder in Mild, Moderate, and Borderline Mentally Retarded Children Aged 5 to 14 Years	
RIS- INT-41	Mike Aman, Ph.D. Nisonger Center 1581 Dodd Drive, Room 175 Columbus, Ohio 43210-1296	9 randomized 0 completed 1 dropped
RIS- INT-41	Ben Handen, Ph.D. John Merck Outpatient Clinic Wightman Community Center 5604 Solway Pittsburgh, PA 15217	3 randomized 0 completed 0 dropped
RIS- INT-41	Deborah Pearson, Ph.D. Dept. of Psychiatry Univ. of Texas Medical School 1300 Moursund – Room 225 Houston, TX 77030	3 randomized 0 completed 0 dropped
RIS- INT-41	Jim Swanson, Ph.D. UCI Child Development Center 19722 Mac Arthur Blvd Irvine, CA 92612	0 randomized 0 completed 0 dropped
RIS- INT-41	Randi Hagerman, M.D. Child Development Unit – B – 140 Children's Hospital 1056 East 19th Avenue Denver, CO 80218	2 randomized 0 completed 0 dropped
RIS- INT-41	Nirbahay Singh, M.D. Medical College of VA. Dept. of Psychiatry P.O. Box 23298-0489 Richmond, VA 23284-3039	2 randomized 0 completed 0 dropped

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PROGRESS REPORT: RISPERIDONE LIQUID		
PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS- INT-41	Jessica Hellings, M.D. Dept. Of Child Psychiatry 3901 Rainbow Boulevard Kansas City, KS 66160	2 randomized 0 completed 0 dropped
RIS- INT-41	Jeffrey Blumer, M.D. University Hospitals of Cleveland 11100 Euclid Avenue Cleveland, OH 44106-6010	5 randomized 0 completed 2 dropped
RIS- INT-41	Jorg Pahl, M.D. Pahl Brain Associates 3909 North Classen Oklahoma City, OK 73120	1 randomized 0 completed 0 dropped
RIS- INT-41	Reiser, M.D. 3046 Rio Dosa Drive Suite 100 Lexington, KY 40509	4 randomized 0 completed 1 dropped
RIS- INT-41	Timothy Bohan, M.D. Claghorn-Lesem Res. Clinic, Inc. 6750 West Loop South Suite 1050 Bellaire, TX 77401	0 randomized 0 completed 0 dropped

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PROGRESS REPORT: RISPERIDONE TABLETS		
PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-INT-50	Risperidone vs Olanzapine in the Treatment of Schizophrenia in Elderly Subjects	
RIS-INT-50	Subramonian Madhusoodanan, M.D. Ronald Brenner, M.D. Department of Psychiatry St. John's Episcopal Hospital 327 Beach 19th Street Far Rockaway, NY 11691	20 randomized 19 completed 1 dropped
RIS-INT-50	Evelyn Howanitz, M.D. Lyons VA Medical Center, 116A 151 Knollcroft Road Lyons, NJ 07939	12 randomized 8 completed 4 dropped
RIS-INT-50	Steven C. Samuels, MD Mount Sinai Medical Center Department of Psychiatry – Box 1230 One Gustave L. Levy Place New York, NY 10029	6 randomized 3 completed 3 dropped
RIS-INT-50	John Lauriello, MD Sub Lauren Bonner, MD Department of Psychiatry University of New Mexico School of Medicine 2400 Tucker Northeast Albuquerque, NM 87131	1 randomized 1 completed 0 dropped
RIS-INT-50	H. Edward Logue, M.D. Birmingham Psychiatry Pharmaceutical Studies 3490 Independence Drive Birmingham, AL 35209-5604	6 randomized 3 completed 3 dropped
RIS-INT-50	Raj Nakra, M.D. Washington University School of Medicine Department of Psychiatry 16216 Baxter Road, Suite 320 Chesterfield, MO 63017	10 randomized 5 completed 5 dropped

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PROGRESS REPORT: RISPERIDONE TABLETS		
PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-INT-50	S. Charles Schulz, M.D. Department of Psychiatry University Hospitals of Cleveland 11100 Euclid Avenue Cleveland, OH 44106	8 randomized 8 completed 0 dropped
RIS-INT-50	Alan Siegal, M.D. Geriatric and Adult Psychiatry Group 60 Washington Avenue, Suite 203 Hamden, CT 06518	3 randomized 2 completed 1 dropped
RIS-INT-50	Sanford Finkel, M.D. Northwestern University Medical School 303 East Ohio Street, Suite 550 Chicago, IL 60611	0 randomized 0 completed 0 dropped
RIS-INT-50	Mark Hamner, MD (x7799) Ralph H. Johnson VA Medical Center 109 Bee Street Charleston, SC 92161	1 randomized 0 completed 1 dropped
RIS-INT-50	Dilip Jeste, M.D. Psychiatry Service 116-A Veterans Affairs Medical Center 3350 La Jolla Village Drive San Diego, CA 92161	5 randomized 4 completed 1 dropped
RIS-INT-50	Theo Manschreck, M.D. (x360) Sub: Roger Boshes, MD, PhD Corrigan Mental Health Center 49 Hillside Street Fall River, MA 02720	6 randomized 5 completed 1 dropped
RIS-INT-50	Steven Targum, M.D. Clinical Studies New Jersey 100 Brick Road, Suite 315 Marlton, NJ 08053	0 randomized 0 completed 0 dropped

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PROGRESS REPORT: RISPERIDONE TABLETS		
PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-INT-50	Jacobo Mintzer, M.D. Alzheimer Research and Clinical Programs 5900 Core Road, Suite 203 North Charleston, SC 29406-6076	2 randomized 2 completed 0 dropped
RIS-INT-50	Carl Cohen, MD Downstate Mental Hygiene Associates 370 Lenox Road Brooklyn, NY 11226	1 randomized 0 completed 1 dropped
RIS-INT-50	Michael Plopper, M.D. Mesa Vista Hospital 7850 Vista Hill Avenue San Diego, CA 92123	3 randomized 1 completed 2 dropped
RIS-INT-50	Alexander Kopelowicz M.D. San Fernando Mental Health 15535 San Fernando Mission Blvd Mission Hills, CA 91345	3 randomized 2 completed 1 dropped
RIS-INT-50	Richard Josiassen, Ph.D. Arthur P. Noyes Clinical Research Ctr. 1001 Sterigere Street, Bldg. 52 Norristown, PA 19401	9 randomized 5 completed 1 dropped 3 ongoing
RIS-INT-50	Sumer Verma, M.D. McLean Hospital 115 Mill Street Belmont, MA 02178	0 randomized 0 completed
RIS-INT-50	David Brown, M.D. 4411 Medical Parkway Austin, TX 78756	0 randomized 0 completed

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PROGRESS REPORT: RISPERIDONE TABLETS		
PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-79	A Double-Blind comparison of Risperidone 2-8 mg/day versus Haloperidol 5-20 mg/day in relapse prevention in chronic schizophrenic patients.	
RIS-USA-79	Ronald Brenner, M.D. St. John's Episcopal Hosp. 327 Beach 19th Street Far Rockaway, NY 11691	30 randomized 16 dropped
RIS-USA-79	David Brown, M.D. 4411 Medical Parkway Drive Austin, TX 78756	15 randomized 12 dropped
RIS-USA-79	Wayne Goodman, M.D. Department of Psychiatry University of Florida PSB 11-430 1600 SW Archer Road Gainesville, FL 32610-0256	8 randomized 7 dropped
RIS-USA-79	James Chou, M.D. Department of Psychiatry Bellevue Hospital Center 550 First Avenue-Room 20N11 New York, NY 10016	19 randomized 15 dropped
RIS-USA-79	Michael DePriest, M.D. Pharmacology Research Corporation 4220 S. Maryland Pkwy Suite B 312 Las Vegas, NV 89119	14 randomized 9 dropped
RIS-USA-79	Cal K. Cohn, M.D. The Cohn Center, Psychiatry 7777 Southwest Freeway Suite 1036 Houston, TX 77074	30 randomized 27 dropped

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PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-79	John Csernansky, M.D. Washington University 4940 Children's Place Box St. Louis, MO 63110	13 randomized 9 dropped
RIS-USA-79	Lawrence Dunn, M.D. Durham VA Medical Hospital 508 Fulton Durham, NC 27705	4 randomized 4 dropped
RIS-USA-79	David Klegon, M.D. Alan Green, M.D. Brockton Multi Service Center 165 Quincy Street Brockton, MA 02402	9 randomized 3 dropped
RIS-USA-79	Alex Kopelowicz, M.D. (PI) Mission Hills Mental Health Center 15535 San Fernando Mission Blvd. Mission Hills, CA 91345	27 randomized 12 dropped
RIS-USA-79	Mark Hamner, M.D VAMC - 116A Department of Psychiatry 109 Bee Street Charleston, SC 29401	7 randomized 4 dropped
RIS-USA-79	Harold Harsch, M.D. General Hospital, Psychiatry - 175 8700 West Wisconsin Avenue Milwaukee, WI 53226	7 randomized 5 dropped
RIS-USA-79	Alan Jacobson, Ph.D. (PI) Federico Adan, M.D. (Co-PI) Miami VAMC 1201 N.W. 16th Street - 116A Miami, FL 33125	7 randomized 6 dropped

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PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-79	George G. Jaskiw, M.D. Chief, Schizophrenia Section Psychiatry Services 116-A (B) Cleveland VAMC 10,000 Brecksville Road Brecksville, OH 44141	7 randomized 4 dropped
RIS-USA-79	Bankole Johnson, M.D. The Mental Sciences Institute 1300 Moursund Houston, TX 77030	30 randomized 22 dropped
RIS-USA-79	Ari Kiev, M.D. Social Psychiatry Research Institute 75 Booth Avenue Englewood, NJ 07631	9 randomized 8 dropped
RIS-USA-79	Mary Ann Knesevich, M.D. St. Paul Medical Center 5959 Harry Hines Suite 924 Dallas, TX 75235	10 randomized 7 dropped
RIS-USA-79	Douglas Levinson, M.D. Medical College of Pennsylvania & Hahneman Univ. Hosp. 3200 Henry Avenue - Room 206A Philadelphia, PA 19129	6 randomized 5 dropped
RIS-USA-79	H.E. Logue, M.D. Birmingham Psychiatry Pharmaceutical Studies, Inc. 3490 Independence Drive Birmingham, AL 35209	27 randomized 10 dropped
RIS-USA-79	Robert M. Hamer Ph.D. (PI) Matthew Menza, M.D. (Co-PI) RWJ Medical School 675 Hoes Lane Piscataway, NJ 08854	5 randomized 4 dropped

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PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-79	Raj Nakra, M.D. 16216 Baxter Road Chesterfield, MO 63017 Midwest Psychiatry Independent Center 100 North Euclid St. Louis, MO 63103	21 randomized 15 dropped
RIS-USA-79	Charles Nemeroff, M.D. Emory University School of Med. 1639 Pierce Drive- Suite 4000 Atlanta, GA 30322	0 randomized 0 dropped
RIS-USA-79	Vernon Neppe, M.D. North West Outpatient Med. Center 10330 Meridian Ave Seattle, WA 98133	0 randomized 0 dropped
RIS-USA-79	Sheldon Preskorn, M.D. 1100 N. St. Francis - Suite 200 Wichita, KS 67214-2878	13 randomized 7 dropped
RIS-USA-79	Michael Plopper, M.D. Mesa Vista Hospital San Diego, CA 92123	27 randomized 20 dropped
RIS-USA-79	George Simpson, M.D. Professor of Psychiatry USC School of Medicine 1937 Hospital Place-Grad Hall Los Angeles, CA 90033	1 randomized 1 dropped
RIS-USA-79	Stephen Strakowski, M.D. Department of Psychiatry University of Cincinnati-ML559 231 Bethesda Avenue Cincinnati, OH 45267-0559	5 randomized 3 dropped

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PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-79	Marshall Thomas, M.D. University of Colorado 4455 East 12th Avenue Denver, CO 80220	2 randomized 2 dropped
RIS-USA-79	Jose Yaryura-Tobias, M.D. Institute for Bio-Behavioral Therapy and Research 935 Northern Blvd. Great Neck, NY 11021	14 randomized 12 dropped
RIS-USA-79	Scott A, West, M.D Psychiatric Institute of Florida, PA 77 W. Underwood Street 3rd Floor Orlando, FL 32806	9 randomized 8 dropped
RIS-USA-79	Irving S. Kolin, M.D 1065 Morse Blvd. Suite 202 Winter Park, FL 32789	4 randomized 2 dropped
RIS-USA-79	Marvin J. Miller, M.D Larue Carter Hospital 2601 Cold Springs Road Indianapolis, IN 46222	1 randomized 1 dropped
RIS-USA-79	George Pahl, M.D. 13301 North Meridian Suite 101 Oklahoma City, OK 73120	11 randomized 9 dropped
RIS-USA-79	Tai P. Yoo, M.D., F.A.P.A. Chairman of Dept. of Psychiatry Mercy Hospital 5555 Conner Avenue Detroit, MI 48213	5 randomized 4 dropped

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PROGRESS REPORT: RISPERIDONE LIQUID		
PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-93	The Safety and Efficacy of Risperidone vs. Placebo in Conduct Disorder in Mild, Moderate, and Borderline Mentally Retarded Children Aged 5 to 12 Years	
RIS-USA-93	Mike Aman, Ph.D. Nisonger Center 1581 Dodd Drive, Room 175 Columbus, Ohio 43210-1296	17 randomized 14 completed 3 dropped
RIS-USA-93	Ben Handen, Ph.D. John Merck Outpatient Clinic Wightman Community Center 5604 Solway Pittsburgh, PA 15217	5 randomized 5 completed 0 dropped
RIS-USA-93	Deborah Pearson, Ph.D. Dept. of Psychiatry Univ. of Texas Medical School 1300 Moursund – Room 225 Houston, TX 77030	10 randomized 7 completed 3 dropped
RIS-USA-93	Jim Swanson, Ph.D. UCI Child Development Center 19722 Mac Arthur Blvd Irvine, CA 92612	9 randomized 9 completed 0 dropped
RIS-USA-93	Randi Hagerman, M.D. Child Development Unit – B – 140 Children's Hospital 1056 East 19th Avenue Denver, CO 80218	8 randomized 6 completed 2 dropped
RIS-USA-93	Nirbahay Singh, M.D. Medical College of VA. Dept. of Psychiatry P.O. Box 23298-0489 Richmond, VA 23284-3039	15 randomized 6 completed 9 dropped

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PROGRESS REPORT: RISPERIDONE LIQUID		
PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-93	Ted Kastner, M.D. 45 Park Place, South Suite 275 Morristown, NJ 07960	0 randomized 0 completed 0 dropped
RIS-USA-93	Jessica Hellings, M.D. Dept. Of Child Psychiatry 3901 Rainbow Boulevard Kansas City, KS 66160	10 randomized 8 completed 2 dropped
RIS-USA-93	Robert Findling, M.D. University Hospitals of Cleveland 11100 Euclid Avenue Cleveland, OH 44106-6010	17 randomized 12 completed 5 dropped
RIS-USA-93	Jorg Pahl, M.D. Pahl Brain Associates 3909 North Classen Oklahoma City, OK 73120	7 randomized 5 completed 2 dropped
RIS-USA-93	Reiser, M.D. 3046 Rio Dosa Drive Suite 100 Lexington, KY 40509	10 randomized 9 completed 1 dropped
RIS-USA-93	Michael Lesem, M.D. Claghorn-Lesem Res. Clinic, Inc. 6750 West Loop South Suite 1050 Bellaire, TX 77401	11 randomized 6 completed 5 dropped

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PROGRESS REPORT: RISPERIDONE LIQUID		
PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-97	The Safety and Efficacy of Open Label Risperidone in Conduct Disorder in Mild, Moderate, and Borderline Mentally Retarded Children Aged 5 to 12 Years	
RIS-USA-97	Mike Aman, Ph.D. Nisonger Center 1581 Dodd Drive, Room 175 Columbus, Ohio 43210-1296	15 randomized 7 completed 8 dropped
RIS-USA-97	Ben Handen, Ph.D. John Merck Outpatient Clinic Wightman Community Center 5604 Solway Pittsburgh, PA 15217	5 randomized 4 completed 1 dropped
RIS-USA-97	Deborah Pearson, Ph.D. Dept. of Psychiatry Univ. of Texas Medical School 1300 Moursund – Room 225 Houston, TX 77030	8 randomized 2 completed 6 dropped
RIS-USA-97	Jim Swanson, Ph.D. UCI Child Development Center 19722 Mac Arthur Blvd Irvine, CA 92612	9 randomized 3 completed 6 dropped
RIS-USA-97	Randi Hagerman, M.D. Child Development Unit – B – 140 Children's Hospital 1056 East 19th Avenue Denver, CO 80218	8 randomized 6 completed 2 dropped
RIS-USA-97	Nirbahay Singh, M.D. Medical College of VA. Dept. of Psychiatry P.O. Box 23298-0489 Richmond, VA 23284-3039	15 randomized 7 completed 7 dropped
RIS-USA-97	Ted Kastner, M.D. 45 Park Place, South Suite 275 Morristown, NJ 07960	0 randomized 0 completed 0 dropped

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PROGRESS REPORT: RISPERIDONE LIQUID		
PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-97	Jessica Hellings, M.D. Dept. Of Child Psychiatry 3901 Rainbow Boulevard Kansas City, KS 66160	10 randomized 5 completed 5 dropped
RIS-USA-97	Robert Findling, M.D. University Hospitals of Cleveland 11100 Euclid Avenue Cleveland, OH 44106-6010	13 randomized 4 completed 8 dropped
RIS-USA-97	Jorg Pahl, M.D. Pahl Brain Associates 3909 North Classen Oklahoma City, OK 73120	5 randomized 2 completed 3 dropped
RIS-USA-97	Reiser, M.D. 3046 Rio Dosa Drive Suite 100 Lexington, KY 40509	10 randomized 4 completed 5 dropped
RIS-USA-97	Michael Lesem, M.D. Claghorn-Lesem Res. Clinic, Inc. 6750 West Loop South Suite 1050 Bellaire, TX 77401	9 randomized 2 completed 6 dropped

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PROGRESS REPORT: RISPERIDONE TABLETS		
PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-102	The Safety and Efficacy of Risperdal® (risperidone) vs Placebo vs Haloperidol as Add-On Therapy to Mood Stabilizers in the Treatment of the Manic Phase of Bipolar Disorder.	
RIS-USA-102	Charles Bowden, M.D. Department of Psychiatry 7703 Floyd Curl Drive San Antonio, TX 78284-7792	6 randomized 3 dropped DB 1 dropped OL 3 completed DB 0 completed OL
RIS-USA-102	Ronald Brenner, M.D. St. John's Episcopal Hospital, South Shore 327 Beach 19th Street Far Rockaway, NY 11691	8 randomized 0 dropped DB 2 dropped OL 8 completed DB 3 completed OL
RIS-USA-102	David Brown, M.D. Community Clinical Research 4411 Medical Pkwy. Austin, TX 78756	13 randomized 8 dropped DB 1 dropped OL 5 completed DB 3 completed OL
RIS-USA-102	James Chou, M.D. Department of Psychiatry Bellevue Hospital Center 462 First Avenue New York, NY 10016	1 randomized 0 dropped DB 1 dropped OL 1 completed DB 3 completed OL

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RIS-USA-102	David Daniel, M.D. Washington Clinical Research Center 6066 Leesburg Pike, Sixth Floor Falls Church, VA 22041	4 randomized 0 dropped DB 1 dropped OL 4 completed DB 3 completed OL
RIS-USA-102	Michael DePriest, M.D. Pharmacology Research Corporation 6039 Eldora Avenue, Suite H Las Vegas, NV 89102	0 randomized 0 dropped DB 0 dropped OL 0 completed DB 0 completed OL
RIS-USA-102	Nassir Ghaemi, M.D. George Washington University Dept. of Psychiatry, 8th Floor Ambulatory Care Center 2150 Pennsylvania, NW Washington, DC 20037	0 randomized 0 dropped DB 0 dropped OL 0 completed DB 0 completed OL
RIS-USA-102	Michael Lesem, M.D. Claghorn-Lesem Research Clinic Inc. 6750 West Loop South, Suite 1050 Bellaire, TX 77401	8 randomized 1 dropped DB 3 dropped OL 6 completed DB 4 completed OL
RIS-USA-102	Robert Littman, M.D. Center for Behavioral Health Research 20 Courthouse Square, Suite 217 Rockville, MD 20850	2 randomized 0 dropped DB 0 dropped OL 2 completed DB 3 completed OL
RIS-USA-102	H.E. Logue, M.D. Birmingham Psychiatry Pharmaceutical Studies, Inc. 3490 Independence Drive Birmingham, AL 35209-5604	2 randomized 1 dropped DB 0 dropped OL 2 completed DB 1 completed OL

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RIS-USA-102	Joseph McEvoy, M.D. John Umstead Hospital Clinical Research Program. Building 32, First Floor 1008 12th Street Butner, NC 27509-1626	7 randomized 1 dropped DB 0 dropped OL 6 completed DB 0 completed OL
RIS-USA-102	Charles Meredith, M.D. Medical Director Affiliated Research Institute 8080 Rio San Diego Drive San Diego, CA 92108	4 randomized 0 dropped DB 2 dropped OL 5 completed DB 5 completed OL
RIS-USA-102	Charles Nemeroff, M.D. Fox Crisis Center 3100 Clifton Springs Road Drive Decatur, GA 30034	2 randomized 2 dropped DB 0 dropped OL 0 completed DB 0 completed OL
RIS-USA-102	Fred Petty, M.D. Dallas VA Medical Center 4500 South Lancaster Road Mental Health Services, 116A Dallas, TX 75216	8 randomized 1 dropped DB 4 dropped OL 7 completed DB 7 completed OL
RIS-USA-102	Craig Risch, M.D. Clinical Neuropharmacology Program Department of Psychiatry Medical University of South Carolina 171 Ashley Avenue, PH502N Charleston, SC 29425-0742	1 randomized 0 dropped DB 0 dropped OL 2 completed DB 1 completed OL
RIS-USA-102	Gary Sachs, M.D. Massachusetts General Hospital Research 50 Staniford Street, 4th Floor Boston, MA 02114	2 randomized 2 dropped DB 0 dropped OL 0 completed DB 0 completed OL

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RIS-USA-102	Martha Sajatovic, M.D. Brecksville VA, Department of Psychiatry 10,000 Brecksville Road Brecksville, OH 44141	1 randomized 1 dropped DB 0 dropped OL 0 completed DB 0 completed OL
RIS-USA-102	David Schnur, M.D. Elmhurst Hospital Center Department of Psychiatry 7901 Broadway Elmhurst, NY 11373	4 randomized 1 dropped DB 2 dropped OL 3 completed DB 1 completed OL
RIS-USA-102	Daniel Zimbroff, M.D. Pacific Clinical Research 1317 West Foothill Boulevard Suite 410 Upland, CA 91786	8 randomized 7 dropped DB 2 dropped OL 6 completed DB 6 completed OL
RIS-USA-102	Charles Casat, M.D. 501 Billingsley Road Charlotte, NC 28211	0 randomized 0 dropped DB 0 dropped OL 0 completed DB 0 completed OL
RIS-USA-102	William McNelly, M.D./Charles Zaylor, D.O. University of Kansas Medical Center Department of Psychiatry 3901 Rainbow Boulevard Kansas City, KS 66160	0 randomized 0 dropped DB 0 dropped OL 0 completed DB 0 completed OL
RIS-USA-102	Jorg Pahl, M.D. Pahl Brain Associates, P.C. Director of Research and Education The Neuroscience Institute of Mercy 13301 North Meridan, Suite 101 Oklahoma City, OK 73120	0 randomized 0 dropped DB 0 dropped OL 0 completed DB 0 completed OL

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RIS-USA-102	Rita Shaughnessy, M.D. AUHS/NSH Clinical Research Center Norristown State Hospital Building 52, Second Floor 1001 Sterigere Street Norristown, PA 19401	0 randomized 0 dropped DB 0 dropped OL 0 completed DB 0 completed OL
RIS-USA-102	Alan Swann, M.D. UTMSH Psychiatry 1300 Moursund Street, Room 270 Houston, TX 77030	0 randomized 0 dropped DB 0 dropped OL 0 completed DB 0 completed OL

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PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-113	Risperidone vs. Olanzapine in the Treatment of Schizophrenia (44 weeks).	
RIS-USA-113	Robert W. Baker, MD University of Mississippi Medical Center Dept. of Psychiatry & Human Behavior 2500 North State Street Jackson, MS 39216-4505	4 randomized 1 completed 3 dropped
RIS-USA-113	Ileana Berman, MD Taunton State Hospital 60 Hodges Avenue Taunton, MA 02780	4 randomized 3 completed 1 dropped
RIS-USA-113	Ronald Brenner, MD/Subramoniam Madhusoodanan, MD St. Johns Episcopal Hospital Department of Psychiatry 327 Beach 19 Street Far Rockaway, NY 11691	8 randomized 7 completed 1 dropped
RIS-USA-113	David Brown, MD Community Clinic Research, Inc. 4411Medical Parkway Austin, TX 78756-3313	6 randomized 3 completed 3 dropped
RIS-USA-113	John S. Carman, MD Carman Research at Ridgeview Institute 4015 South Cobb Drive, Suite 245 Smyrna, GA 30080	2 randomized 1 completed 1 dropped
RIS-USA-113	K.N. Roy Chengappa, MD/ Nina Schooler, MD Western Psychiatric Institute and Clinic 3811 O'Hara Street Pittsburgh, PA 15213	3 randomized 2 completed 1 dropped
RIS-USA-113	Cal K. Cohn, MD The Cohn Center for Psychiatry 777 Southwest Freeway, Suite 1036 Houston, TX 77074	5 randomized 1 completed 4 dropped

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PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-113	Robert Conley, MD/ Raymond C. Love, PharmD Maryland Psychiatric Research Center Maple & Locust Streets P.O. Box 21247 Baltimore, MD 21228	1 randomized 1 completed 0 dropped
RIS-USA-113	John G. Csernansky, MD Washington University School of Medicine Department of Psychiatry 4940 Children's Place St. Louis, MO 63110	9 randomized 4 completed 5 dropped
RIS-USA-113	Hussam Mihtar, MD/Namir Damluji, MD Damluji Research Center 591 Camina De La Reina, Suite 410 San Diego, CA 92108	7 randomized 4 completed 3 dropped
RIS-USA-113	David G. Daniel, MD Neuropsychiatric Pharmacology of Northern Virginia 6404-P Seven Corners Place Falls Church, VA 22044	4 randomized 1 completed 3 dropped
RIS-USA-113	David Feifel, MD University of California, San Diego (UCSD) Medical Center Department of Psychiatry 200 West Arbor Drive San Diego, CA 92103-8620	6 randomized 2 completed 4 dropped
RIS-USA-113	Michael DePriest, MD/James Ferguson, MD Pharmacology Research Corporation 448 East 6400 South, Suite 350 Salt Lake City, UT 84107	3 randomized 2 completed 1 dropped
RIS-USA-113	Michael Flaum, MD University of Iowa Hospitals and Clinics Department of Psychiatry #2887 JPP 200 Hawkins Drive Iowa City, IA 52242	8 randomized 6 completed 2 dropped
RIS-USA-113	Evelyn Howanitz, MD East Orange VA Medical Center, 12th Fl 385 Treemont Avenue East Orange, NJ 07018	3 randomized 2 completed 1 dropped

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PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-113	Philip Kanof, MD Psychiatry Services (116A) Tucson Medical Center 3601 South Sixth Avenue Tucson, AZ 85723	10 randomized 7 completed 3 dropped
RIS-USA-113	Mary Ann Knesevich, MD/Dr. John Prosser Professional Office Building 5959 Harry Hines Boulevard, Suite 924 Dallas, TX 75235	7 randomized 5 completed 2 dropped
RIS-USA-113	Alex Kopelowicz, MD San Fernando Mental Health Center 15535 San Fernando Mission Boulevard Mission Hills, CA 91345	7 randomized 3 completed 4 dropped
RIS-USA-113	John Lauriello, MD University of New Mexico School of Medicine Department of Psychiatry 2400 Tucker Northeast Albuquerque, NM 87131	11 randomized 8 completed 3 dropped
RIS-USA-113	Michael Lesem, MD Claghorn-Lesem Clinic 6750 West Loop South, Suite 1050 Bellaire, TX 77401	3 randomized 1 completed 2 dropped
RIS-USA-113	Dr. Doug Levinson/Dr. Richard Josiassen Allegheny University EPPI (Room 206) 3200 Henry Avenue Philadelphia, PA 19129	6 randomized 2 completed 4 dropped
RIS-USA-113	Dr. H.E. Logue Birmingham Psychiatric Pharmaceutical Studies 3490 Independence Drive Birmingham, AL 35209-5604	14 randomized 9 completed 5 dropped
RIS-USA-113	Dr. Theo Manschreck Corrigan Mental Health Center 49 Hillside Street Fall River, MA 02720	8 randomized 3 completed 5 dropped

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PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-113	Dr. Donna Ames Wirshing/Dr. Steve Marder Psychiatric Department (116A) West L.A. V.A. 11301 Wilshire Boulevard Building 210, Room 15 (B151H) Los Angeles, CA 90073	6 randomized 5 completed 1 dropped
RIS-USA-113	Dr. Joseph McEvoy John Umstead Hospital Clinical Research Program Building 32, First Floor 1008 12th Street Butner, NC 27509-1626	4 randomized 1 completed 3 dropped
RIS-USA-113	Dr. Herbert Meltzer Vanderbilt University Medical Center 1500 21st Avenue, South, Suite 2200 Nashville, TN 37212	9 randomized 4 completed 5 dropped
RIS-USA-113	Dr. Alan Mendelowitz Hillside Hospital Div. of Long Island Jewish Medical Center Department of Psychiatry Research 75-59 263rd Street Glen Oaks, NY 11004	6 randomized 2 completed 4 dropped
RIS-USA-113	Dr. Alexander Miller Department of Psychiatry University of Texas Health Science Center (UTHSC) 7703 Floyd Curl Drive San Antonio, TX 78284-7792	13 randomized 10 completed 3 dropped
RIS-USA-113	Raj Nakra, MD (Washington Univ.) 16216 Baxter Road, Suite 320 Chesterfield, MO 63017	17 randomized 10 completed 7 dropped
RIS-USA-113	Jörj J. Pahl, MD, FCP (SA) Pahl Brain Associates 13301 North Meridian, Suite 101 Oklahoma City, OK 73120	17 randomized 9 completed 8 dropped

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PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-113	Anand K. Pandurangi, MD Medical College of Virginia 1300 East Marshall Street P.O. Box 710 Richmond, VA 23298-0710	4 randomized 0 completed 4 dropped
RIS-USA-113	Dr. Michael Plopper Mesa Vista Hospital 7850 Vista Hill Avenue San Diego, CA 92123-2790	7 randomized 2 completed 5 dropped
RIS-USA-113	Dr. Narayana Reddy (Alan Rosenthal, Business Devel) Health Advance Institute 222 N.E. Monroe Street Peoria, IL 61602	19 randomized 7 completed 12 dropped
RIS-USA-113	Dr. P. Roy-Byrne University of Washington, Department of Psychiatry Harborview Medical Center Box 359896 5 South Psychiatry 325 9th Avenue Seattle, WA 98104	5 randomized 3 completed 2 dropped
RIS-USA-113	Dr. Steven Strakowski University of Cincinnati Department of Psychiatry 231 Bethesda Avenue P.O. Box 670559 Cincinnati, OH 45267-0559	3 randomized 1 completed 2 dropped
RIS-USA-113	Robert Stern, MD Bronx VAMC Department of Psychiatry (116A) 130 Kingsbridge Road Bronx, NY 10468	2 randomized 1 completed 1 dropped

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PROTOCOL NUMBER	**TITLE/INVESTIGATOR**	**PATIENT TOTALS**
RIS-USA-113	Alan Swan, MD University of Texas Medical School at Houston 1300 Moursand, Room 270 Houston, TX 77030	7 randomized 3 completed 4 dropped
RIS-USA-113	Dr. Steven Targum Crozer-Chester Medical Center 1 Medical Center Boulevard Upland, PA 19013-3995	5 randomized 1 completed 4 dropped
RIS-USA-113	John Gurklis, M.D. *(formerly Dr. Daniel van Kammen)* Highland Drive VAMC (151R) 7180 Highland Drive Pittsburgh, PA 15206	6 randomized 1 completed 5 dropped

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Summary Information

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MOST FREQUENT ADVERSE REACTIONS

A summary of adverse events for RIS-CAN-19. Information unavailable at this time.

A summary of adverse events for RIS-INT-35: n =202, #AEs = 536

Body System	Adverse Experience	% Occurrence
Psychiatric	Agitation	25.2
	Insomnia	22.8
	Anxiety	18.3
	Somnolence	19.3
	Depression	17.3
CNS	Tremor	8.9
	Headache	18.3
	Extrapyramidal Disorders	18.3
	Hyperkinesia	14.9
	Hypertonia	11.4
Body as a whole	Weight Increase	10.9

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MOST FREQUENT ADVERSE REACTIONS

A summary of adverse events for RIS-INT-41: n = 32, #AEs = 144

Body System	Adverse Experience	% Occurrence
General – Body as a Whole	Fever	2.0
	Lab values abnormal	2.0
	Infection	2.4
Respiratory System	Rhinitis	4.5
	Upper Respiratory Tract Infection	8.5
Gastrointestinal System	Diarrhea	2.8
	Vomiting	3.6
Psychiatric	Somnolence	5.7
Metabolic Disorders	Weight Increase	6.1
Endocrine System	Hyperprolactinaemia	3.2

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D7294.44

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

MOST FREQUENT ADVERSE REACTIONS

A summary of adverse events for RIS-INT-50: n = 63, #AEs = 283

Body System	Adverse Experience	% Occurrence
General – Body as a Whole	Insomnia	2.8
Musculoskeletal	Joint pain	3.2
	Back pain	3.2
Psychiatric	Agitation	6.7
Neurologic	Headache	4.9
	Drowsiness	3.2
	Dizziness	2.8
Cardiac	Chest pain	2.5
Gastrointestinal	Diarrhea	2.5
Respiratory	Rhinitis	2.1

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

MOST FREQUENT ADVERSE REACTIONS

A summary of adverse events for RIS-USA-79: n = 397, total # of subjects with AEs = 355 (89.9%). Total # of AEs during the double blind period = 1894.

Body System	Adverse Experience	% Occurrence
General – Body as a Whole	Injury	10.1
	Fatigue	8.6
	Chest Pain	6.1
Respiratory System	Rhinitis	12.9
	Upper Resp Tract Infection	5.3
Gastrointestinal System	Vomiting	9.4
	Saliva Increased	7.1
	Diarrhoea	6.6
	Nausea	6.3
	Abdominal pain	6.3
	Mouth Dry	6.1
	Constipation	5.8
	Dyspepsia	5.6
Psychiatric	Insomnia	26.1
	Psychosis	22.8
	Somnolence	18.2
	Agitation	16.2
	Anxiety	6.8
CNS	Headache	17.5
	Hyperkinesia	12.2
	EPS	11.6
	Dizziness	9.4
	Hypertonia	8.9
	Tremor	7.8
Vision	Vision abnormal	5.8

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D7294.46

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

MOST FREQUENT ADVERSE REACTIONS

A summary of adverse events for RIS-USA-93: n = 142, #AEs = 351

Body System	Adverse Experience	% Occurrence
General – Body as a Whole	Infection	2.6
	Fever	2.6
	Pain	2.3
	Injury	2.0
	Abrasion NOS	2.0
Respiratory System	Rhinitis	3.1
	Upper Resp Tract Infection	3.1
CNS	Headache	12.0
Gastrointestinal System	Vomiting	4.6
	Dyspepsia	4.3
	Nausea	2.6
	Diarrhea	2.3
Psychiatric	Somnolence	12.8
	Insomnia	2.3
Metabolic Disorders	Increased Appetite	2.8
	Weight Increase	2.6
Endocrine System	Hyperprolactinaemia	2.3
Urinary System	Urinary Incontinence	2.0

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

MOST FREQUENT ADVERSE REACTIONS

A summary of adverse events for RIS-USA-97: n = 54, #AEs = 247

Body System	Adverse Experience	% Occurrence
General – Body as a Whole	Fever	2.0
	Lab values abnormal	2.0
	Infection	2.4
	Otitis media	2.0
Respiratory System	Rhinitis	4.5
	Upper Resp. Tract Infection	8.5
CNS	Headache	12.6
Gastrointestinal System	Dyspepsia	2.8
	Diarrhea	2.8
	Vomiting	3.6
Psychiatric	Somnolence	5.7
Metabolic Disorders	Increased Appetite	2.0
	Weight Increase	6.1
Endocrine System	Hyperprolactinaemia	3.2
Urinary System	Urinary Incontinence	2.0
White cell and RES disorders	Eosinophilia	2.0

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

MOST FREQUENT ADVERSE REACTIONS

A summary of adverse events for RIS-USA-102: n = 139, #AEs = 115

Body System	Adverse Experience	% Occurrence
Psychiatric disorders	Somnolence	6.7
	Insomnia	1.5
CNS	Extrapyramidal disorder	6.2
	Headache	5.2
	Tremor	3.0
	Hypertonia	3.0
	Dizziness	2.5
Gastro-intestinal system	Dyspepsia	3.9
	Constipation	2.0
	Nausea	1.5
	Saliva increased	1.5

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

MOST FREQUENT ADVERSE REACTIONS

A summary of adverse events for RIS-USA-113: n = 153, #AEs = 358

Body System	Adverse Experience	% Occurrence
General – Body as a Whole	Pain	5.2
	Back Pain	5.9
Respiratory System	Rhinitis	14.4
	Coughing	5.2
	Pharyngitis	5.2
Skin and Appendages	Rash	2.0
	Acne	2.6
Gastrointestinal System	Dyspepsia	4.6
	Dry Mouth	5.9
Psychiatric	Anxiety	10.5
	Depression	9.2
	Psychosis	10.2
CNS	Headache	13.7
	Hyperkinesia	3.3
Cardiovascular Disorders	Hypertension	1.3
	Tachycardia	4.6
Urinary Tract Disorders	Urinary Incontinence	2.0
	UTI	2.6
Metabolic Disorders	Weight Increased	3.3
	Creatine/Phosphokinase Increased	3.9
Endocrine Disorders	Hyperprolactinemia	3.9

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

SERIOUS ADVERSE REACTIONS

Attached is a tabular summary for the serious adverse events received during the reporting period.

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IND Annual Frequency Report

Body System / Adverse Experience	Serious but not immediately reportable Domestic	Serious and immediately reportable Domestic	Serious and immediately reportable Foreign
Application Site Disorders(1820)			
Cellulitis	1	0	0
	1	0	0
Body As A Whole - General Disorders(1810)			
Chest Pain	3	0	0
Condition Aggravated	48	0	0
Fever	2	0	0
Injury	3	0	0
Lab Values Abnormal	1	0	0
Pain	1	0	0
Syncope	1	0	0
Weakness Generalized	1	0	0
	60	0	0
Cardiovascular Disorders, General(1010)			
Ecg Abnormal	1	0	0
Hypertension Aggravated	1	0	0
Hypotension	1	0	0
	3	0	0
Centr & Periph Nervous System Disorders(0410)			
Dizziness	2	0	0
Extrapyramidal Disorder	2	0	0
Headache	2	0	0
Hoarseness	1	0	0
Motor Activity Retarded	2	0	0
Speech Disorder	1	0	0
Stupor	1	0	0
	11	0	0
Endocrine Disorders(0900)			
Prolactin Increased	1	0	0
	1	0	0
Foetal Disorders(1500)			
Abortion	1	0	0
	1	0	0
Gastro-Intestinal System Disorders(0600)			
Diarrhoea	1	0	0
Flatulence	1	0	0
Haematemesis	1	0	0
Nausea	2	0	0
Oesophageal Ulceration	1	0	0
Peptic Ulcer Aggravated	1	0	0
Tooth Disorder	1	0	0
Vomiting	4	0	0
	12	0	0
[illegible]ng And Vestibular Disorders(0432)			
Hearing Decreased	1	0	0
	1	0	0

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JANSSEN PHARMACEUTICA RESEARCH FOUNDATION

Generic : RISPERIDONE Approval : 31,931 Reporting Status Report Type : Expedited, Periodic
Exclude: Periodic Follow Up Cases
Received Dates: 07-01-1998 - 06-30-1999

IND Annual Frequency Report

Body System / Adverse Experience	Serious but not immediately reportable Domestic	Serious and immediately reportable Domestic	Serious and immediately reportable Foreign
Heart Rate And Rhythm Disorders(1030)			
Arrhythmia	1	0	0
Av Block	1	0	0
Bigeminy	1	0	0
Bundle Branch Block	1	0	0
Palpitation	1	0	0
Sinus Tachycardia	1	0	0
Tachycardia	2	0	0
	8	0	0
Liver And Biliary System Disorders(0700)			
Hepatic Enzymes Increased	1	0	0
	1	0	0
Metabolic And Nutritional Disorders(0800)			
Cpk Increased	2	0	0
Diabetes Mellitus Aggravated	2	0	0
Fluid Loss	1	0	0
Hyponatraemia	3	0	0
Polydipsia	1	0	0
Thirst Excessive	2	0	0
Weight Increase	1	0	0
	12	0	0
lo-Skeletal System Disorders(0200)			
Muscle Weakness	1	0	0
Rhabdomyolysis	1	0	0
	2	0	0
Myo Endo Pericardial & Valve Disorders(1020)			
Angina Pectoris	1	0	0
	1	0	0
Neoplasm(1700)			
Carcinoma	1	0	0
Pulmonary Carcinoma	1	0	0
	2	0	0
Platelet,Bleeding & Clotting Disorders(1230)			
Haematoma	1	0	0
	1	0	0
Psychiatric Disorders(0500)			
Aggressive Reaction	4	0	0
Agitation	4	0	0
Anorexia	1	0	0
Anxiety	2	0	0
Confusion	1	0	0
Depression	3	0	0
Depression Aggravated	3	0	0
Drug Abuse	8	0	0
Drug Addiction	2	0	0
Drug Dependence	1	0	0
Drug Maladministration	1	0	0

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D7294.53

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Generic : RISPERIDONE Approval : 31.931 Reporting Status Report Type : Expedited. Periodic
Exclude: Periodic Follow Up Cases
Received Dates: 07-01-1998 - 06-30-1999

IND Annual Frequency Report

Body System / Adverse Experience	Serious but not immediately reportable Domestic	Serious and immediately reportable Domestic	Serious and immediately reportable Foreign
Hallucination Auditory	1	0	0
Insomnia	1	0	0
Lethargy	1	0	0
Memory Disturbance	1	0	0
Panic Reaction	1	0	0
Paranoid Psychosis	1	0	0
Restlessness Marked	2	0	0
Suicidal Tendency	17	0	0
Suicide Attempt	1	0	0
	56	0	0
Red Blood Cell Disorders(1210)			
Anaemia	1	0	0
Spleen Disorder	1	0	0
	2	0	0
Reproductive Disorders, Female(1420)			
Amenorrhoea	1	0	0
	1	0	0
Resistance Mechanism Disorders(1830)			
Infection	1	0	0
Infection Viral	1	0	0
	2	0	0
Respiratory System Disorders(1100)			
Asthma	1	0	0
Bronchitis	1	0	0
Coughing	1	0	0
Pneumonia	2	0	0
Respiratory Disorder	1	0	0
Respiratory Distress	1	0	0
Respiratory Failure	1	0	0
Rhinitis	1	0	0
Upper Resp Tract Infection	1	0	0
	10	0	0
Secondary Terms(2000)			
Fall	3	0	0
Surgical Intervention	2	0	0
	5	0	0
Skin And Appendages Disorders(0100)			
Psoriasis Aggravated	1	0	0
	1	0	0
Urinary System Disorders(1300)			
Haematuria	1	0	0
Renal Infarction	1	0	0
Urinary Incontinence	1	0	0
	3	0	0

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D7294.54

AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type

Application Site Disorders

JAUSA35755(3) MICHAEL FLOUM MD	07-JAN-1999 RIS-USA-113	50yr	(06-MAR-1998 / Unknown)	Cellulitis (06-JAN-1999) Unspecified Psychosis	recovered Hospitalisation Required intervention Required RX therapy	not related periodic report

Event Description: PATIENT (CRF:A30192) ENROLLED IN A CASE BLIND CLINICAL TRIAL RISPERIDONE VS OLANZAPINE. PATIENT IS A KNOWN DIABETIC WHO DEVELOPED CELLULITIS OF HIS LEFT FOOT SECONDARY TO HIS UNDERLYING MEDICAL CONDITION. HE WAS HOSPITALIZED FOR INTRAVENOUS THERAPY. THE INVESTIGATOR RELATES THE EVEN TO THE DIABETES. STUDY MEDICATION CONTINUES AND THE STUDY MEDICATION CODE HAS NOT BEEN BROKEN.
F O L L O W U P (19-JAN-99):
WOUND WAS DEBRIDED AND THE ACUTE INFECTION RESOLVED.
STILL D O U B L E B L I N D.

Body As A Whole - General Disorders

JAUSA33410(3) H MINTAR MD	02-JUL-1998 RIS-USA-113	46yr M	(14-FEB-1998 / 30-JUN-1998) 20 week(s)	Condition Aggravated (01-JUL-1998) Urinary Incontinence (Unknown) Thirst Excessive (Unknown) Hyponatraemia (Unknown) Haematuria (Unknown) Unspecified Psychosis	recovered Hospitalisation	not related periodic report

Event Description: THE PATIENT (CRF:A30196) WAS ENROLLED INTO THE DOUBLE-BLIND STUDY (RISPERIDONE VS OLANZAPINE). ON 01-JUL-98, THE PATIENT HAD A CLINIC VISIT AND APPEARED TO HAVE DETERIORATED. STUDY DRUG WAS DISCONTINUED AND THE PATIENT WAS HOSPITALIZED DUE TO INCREASED PSYCHOSIS. THE INVESTIGATOR DID NO CONSIDER THE EVENT RELATED TO STUDY DRUG. ADDITIONAL INFORMATION WAS REQUESTED.
F O L L O W-U P (28-JUL-98):
THE PATIENT'S AGE WAS CORRECTED TO 46 AND TREATMENT DATES WERE ADDED TO THIS REPORT. HE ALSO EXPERIENCED URINARY INCONTINENCE. A URINALYSIS DEMONSTRATED MICROSCOPIC HAEMATURIA. THE PATIENT WAS OBSERVED DRINKING LARGE AMOUNTS OF CAFFEINATED BEVERAGES AND BEVERAGES THAT CONTAINED STIMULANT HERBS. IT WAS FEL THAT HIS ENUERESIS WAS SECONDARY TO THE FLUID OVERLOAD, WITH NOCTURNAL RECUMBENT DIURESIS. OVER A PERIOD OF ONE TO TWO WEEKS THE PATIENT DECIDED TO FAST LIMITING HIS CALORIC INTAKE AND AT TIMES HE RESTRICTED HIS WATER INTAKE. HIS SODIUM PRIOR TO ADMISSION WAS 133. HE STABLIZED AND WAS RETURNED TO THE STRUCTURED ENVIRONMENT. THE HAEMATURIA CONTINUES. THE OUTCOME OF THE SODIUM AND POLYDIPSIA IS UNKNOWN AT THIS POINT. ADDITIONAL INFORMATION HAS BEEN REQUESTED.
STILL D O U B L E B L I N D.

R. 7442

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JJRP 00012462

AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JAUSA33557(12) STEPHEN STRAKOWSKI MD MD	13-JUL-1998 RIS-USA-113	40yr M	3table (06-MAR-1998 / 30-JUN-1998) 4 month(s) 2table (01-JUL-1998 / 03-JUL-1998) 3 day(s) 3table (04-JUL-1998 / 07-JAN-1999) 6 month(s)	Condition Aggravated (01-JUL-1998) Suicidal Tendency (01-JUL-1998) Arrhythmia (02-JUL-1998) Unspecified Psychosis	unknown Hospitalisation	doubtful periodic report

Event Description: A patient #0165 (CRF #A30050) was enrolled in a double blind clinical trial (RIS-USA-113) risperdione vs olanzapine. The patient reported an increase in auditory hallucinations, paranoia, delusions and ideas of referral with mild suicidal ideation. He was hospitalized and the dose was changed (nos). The investigator doubts a relationship between the study medication and the events. The case blind medication code has not been broken Additional information has been requested.
ADDITIONAL INFORMATION 21-AUG-98:
On hospital day (1) one of his hospitalization, he was started on two tablets of study medication. by 04-JUL-98 he received three tablets daily. AN ECG done on 2-JUL-98 revealed sinus arrhythmia with a rate of 69. There were no ST-T wave changes or Q-waves observed. Compared to the ECG done on 9-JAN-98 there was no change in the wave forms. He did not complain of any chest pain or discomfort. He recovered and was discharged.
ADDITIONAL INFORMATION 22-MAR-99:
During reconciliation of the database treatment dates for the suspect medications were revised.
ADDITIONAL INFORMATION 11-MAY-99:
The treatment day, 6-Mar-98 was added to the suspect drug treatment dates. He recieved two tablets of trial medication on hospital day one of his admissio and by 4 -Jul - 98 he was taking three tablets per day. The number of tablets taken prior to the hospitalization is unknown.

JAUSA33673(8) STEVE TARGUM MD	17-JUL-1998 RIS-INT-35	83yr M	4mg (dly) (18-JUN-1998 / Unknown) 29 day(s)	Condition Aggravated (10-JUL-1998) Unspecified Psychosis	recovered	not related periodic report

Event Description: THE PATIENT WAS ENROLLED INTO THE STUDY (RISPERIDONE VS HALOPERIDOL) AND BEGAN DOUBLE-BLIND MEDICATION ON 18-JUN-98: THE PATIENT BEGAN TO DECOMPENSATE ON 10-JUL-98. HE RECOVERED ON 15-JUL-98. THE INVESTIGATOR DID NOT CONSIDER THE EVENT RELATED TO STUDY DRUG.
ADDITIONAL INFORMATION: 20-OCT-98
CRF:A3784. THE PATIENT NUMBER WAS CORRECTED TO 0720.

054

R. 7443

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JJRP 0012463

D7294.56

AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JAUSA33891(11) ROBERT BAKER MD	28-JUL-1998 RIS-USA-113	49yr F	(07-JAN-1998 / 23-JUL-1998) 6 month(s)	Condition Aggravated (23-JUL-1998) Fever (Unknown) Ecg Abnormal (24-JUL-1998) Tachycardia (23-JUL-1998) Prolactin Increased (24-JUL-1998) Cpk Increased (24-JUL-1998) Unspecified Psychosis	recovered Hospitalisation Required RX therapy	possible periodic report

Event Description: PATIENT WAS ENROLLED (CRF:A30226) IN A DOUBLE BLIND CLINICAL TRIAL RIS-USA-113 COMPARING SAFETY AND EFFICACY OF RISPERIDONE/OLANZAPINE. THE PATIENT WAS HOSPITALIZED DUE TO AN EXACERBATION OF HER PSYCHOSIS. THE SYMPTOMS SHE EXHIBITED WERE; CONCEPTUAL DISORGANIZATION, LABILE MOOD, SOCIALLY INAPPROPRIATE BEHAVIOR WITH SUCH BEHAVIOR AS LOUD SINGING IN PUBLIC, SEXUAL PREOCCUPATION, GUILTY RUMINATION REGARDING HER SON AND A MILD DEATH WISH. STUD MEDICATION WAS DISCONTINUED. THE INVESTIGATOR RELATES A POSSIBLE RELATIONSHIP BETWEEN THE EVENTS AND THE STUDY MEDICATION. THE DOUBLE BLIND TREATMENT C O D E WAS N O T B R O K E N. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

F O L L O W U P (06-OCT-98)

THE PATIENT WAS NOTED TO BE RECENTLY NON-COMPLIANT AND SEEMED TO BE UNIMPROVED PRIOR TO THIS CURRENT ADMISSION. AN ECG SHOWS NON-SPECIFIC ST-T WAVE CHANGES. LABORATORY VALUES WERE OTHERWISE NORMAL EXCEPT FOR THE PROLACTIN; 40, AND CPK; 972. THE CARDIOVASCULAR EXAM INDICATES SLIGHT TACHYCARDIA (NOS) WITH A REGULAR RHYTHM, NO MURMURS, RUBS OR GALLOPS. THE PATIENT WAS DISCONTINUED FROM THE DOUBLE BLIND STUDY AND WAS STARTED ON OLANZAPINE, BUT THE SEXUAL ACTIVITY CONTINUED. THE OLANZAPINE DOSE WAS INCREASED AND CARBAMAZEPINE WAS ADDED. THE PATIENT DEVELOPED A FEVER UP TO 104 DEGREES FOR SEVEN DAYS. SHE ALS EXPERIENCED A PERSISTANT ELEVATED SED RATE TO 62, WHICH REMAINED UNCHANGED FOR SEVERAL DAYS FOLLOWING REMISSION OF THE FEVER. THE EVENTS WERE THOUGHT TO BE VIRAL IN NATURE. SHE WAS TREATED WITH ANTIBIOTICS. OLANZAPINE WAS DISCONTINUED. SHE WAS STARTED ON RISPERIDONE AND LITHIUM AND THE SYMPTOMS IMPROVED. SHE WAS DISCHARGED IN STABLE CONDITION TO HER HOME.

F O L L O W U P (19-NOV-98):

THE PATIENT RECOVERED WITH A RESOLUTION DATE OF 31-AUG-98.

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R. 7444
JJRP 00012464
D7294.57

AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JAUSA33936(8) THEO MANSCHRECK MD	05-AUG-1998 RIS-INT-35	23yr M	(17-APR-1998 / 25-JUN-1998) 10 week(s) 5mg (dly) (26-JUN-1998 / 01-JUL-1998) 6 day(s)	Condition Aggravated (09-JUL-1998) Drug Dependence (09-JUL-1998) Unspecified Psychosis	recovered Hospitalisation Required RX therapy	possible periodic report

Event Description: THE PATIENT WAS ENROLLED INTO THE STUDY (RISPERIDONE VERSUS HALOPERIDOL) AND BEGAN DOUBLE-BLIND MEDICATION ON 17-APR-98. THE PATIENT DECOMPENSATED AND WAS HOSPITALIZED (DATE UNSPECIFIED) AFTER TAKING A HANDFUL OF PSYCHIATRIC MEDICINE "TO FEEL A BUZZ". BEFORE HE WAS TAKEN TO THE HOSPITAL HE WAS STARTED ON HALOPERIDOL AND CLONAZEPAM AS WELL AS VENLAFEXINE. STUDY MEDICATION WAS TEMPORARILY STOPPED (DATE UNSPECIFIED). IN THE OPINION OF THE INVESTIGATOR THE EVENT CAUSALITY WAS ASSESSED AS NOT RELATED TO STUDY MEDICATION. ADDITIONAL INFORMATION REQUESTED.
ADDITIONAL INFORMATION: 01-SEP-98
THE PATIENT WAS HOSPITALIZED ON 09-JUL-98 AND THE STUDY MEDICATION WAS INTERRUPTED FOR APPROXIMATELY 1-2 WEEKS. HALOPERIDOL WAS STARTED AT 5 MG BID AND HE WAS TREATED WITH VENLAFEXINE 25 MG, LORAZEPAM 2 MG, CLONAZEPAM 1 MG, AND BENZTROPINE 1 MG BID. THE PATIENT RECOVERED AND WAS DISCHARGED (DATE UNSPECIFIED) THE STUDY MEDICATION WAS PERMANENTLY STOPPED SOMETIME IN THE BEGINNING OF JULY DUE TO THE INCREASE IN HALOPERIDOL. ADDITIONAL INFORMATION REQUESTED.
F O L L O W U P (29-OCT-98):
THE PATIENT WAS DISCHARGED ON 17-JUL-98. THE PATIENT WAS TO RETURN TO THE MENTAL HEALTH CENTER. A RECOMMENDATION WAS MADE FOR TITRATION OF VENLAFEXINE AN A DAY PROGRAM FOR SOBRIETY AND SOCIALIZATION.
F O L L O W U P (13-NOV-98):
STUDY MEDICATION WAS PERMANENTLY STOPPED (DATE UNSPECIFIED, BUT SOMETIME PRIOR TO ADMISSION). CAUSALITY WAS CHANGED FROM NOT RELATED TO POSSIBLY RELATED T STUDY MEDICATION.

JAUSA34073(6) MARY ANN KNESEVICH MD	11-AUG-1998 RIS-USA-113	30yr M	(23-JAN-1998 / 04-AUG-1998) 6 month(s)	Condition Aggravated (05-AUG-1998) Unspecified Psychosis	recovered Hospitalisation	not related periodic report

Event Description: 30-YEAR-OLD PATIENT (CRF:A30275) WAS ENROLLED IN A DOUBLE BLIND CLINICAL TRIAL COMPARING THE SAFETY AND EFFICACY OF RISPERIDONE/OLANZAPINE. HE EXPERIENCED AN EXACERBATION OF HIS PSYCHOSIS INCLUDING AN INCREASE IN THE INTENSITY OF HIS PARANOID/BIZARRE DELUSIONS AND DECREASED FUNCTIONAL ABILITY. HE WAS HOSPITALIZED AND THE STUDY MEDICATION WAS DISCONTINUED. THE DOUBLE-BLIND TREATMENT CODE WAS NOT BROKEN. THE INVESTIGATOR DOES NOT ATTRIBUTE THE EVENT TO THE STUDY MEDICATION, BUT TO THE DISEASE. ADDITIONAL INFORMATION HAS BEEN REQUESTED.
F O L L O W U P (15-SEP-98):
THE PATIENT'S MEDICAL/SURGICAL HISTORY WAS RECEIVED AND UPDATED. THE PATIENT RECOVERED FROM THE EVENT.
ADDITIONAL INFORMATION (22-MAR-99):
DURING THE DATA BASE RECONCILIATION THE SUSPECT DRUGS START DATES WERE REVISED.
STILL D O U B L E B L I N D

950

R. 7445

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JJRP 00012465

D7294.58

AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JAUSA34105(2) RAJ NAKRA MD	13-AUG-1998 RIS-INT-50	77yr F	6mg (dly) (31-JUL-1998 / 02-AUG-1998) 2 day(s)	Chest Pain (07-AUG-1998) Unspecified Schizophrenia	recovered Hospitalisation	not related periodic report

Event Description: 77-YEAR-OLD FEMALE PATIENT (CRF:A31109) WAS ENROLLED INTO THE STUDY (RISPERIDONE VS OLANZAPINE) AND RECEIVED DOUBLE-BLIND MEDICATION FRC 31-JUL-98 TO 02-AUG-98. THE PATIENT WAS HOSPITALIZED ON 07-AUG-98 WITH CHEST PAIN. ECG REVEALED NORMAL SINUS RHYTHM WITH NO EVOLUTIONARY CHANGES. TELEMETRY REVEALS INTERMITTENT VENTRICULAR ECTOPY WITH OCCASIONAL EPISODES OF TRIGEMINY. CPK-MBS ARE NEGATIVE. A CARDIOLOGY CONSULTATION DONE ASSESSED TH CHEST PAIN AS APPEARING ATYPICAL OF ANGINA, MORE CONSISTENT WITH A COSTOCHONDRITIS AND VENTRICULAR ECTOPY. THE PATIENT HAS A HISTORY OF CONTROLLED HYPERTENSION. THE PATIENT WAS DISCHARGED 08-AUG-98, RECOVERED. THE PATIENT IS TO FOLLOW-UP WITH THE DOCTOR IN 2 WEEKS. IN THE OPINION OF THE INVESTIGATC THE EVENT CAUSALITY WAS ASSESSED AS NOT RELATED TO STUDY MEDICATION. ADDITIONAL INFORMATION REQUESTED.
ADDITIONAL INFORMATION: 19-AUG-98
THE PATIENT COMPLETED THE STUDY 02-AUG-98, 5 DAYS PRIOR TO SAE. HEIGHT, WEIGHT, AND DATE OF BIRTH RECEIVED.
STILL D O U B L E B L I N D.

JAUSA34146(3) JOSEPH MCEVOY MD	18-AUG-1998 RIS-USA-113	18yr M	(02-JUN-1998 / 17-AUG-1998) 11 week(s)	Condition Aggravated (13-AUG-1998) Dizziness (13-AUG-1998) Restlessness Marked (13-AUG-1998) Coughing (17-AUG-1998) Weight Increase (30-JUN-1998) Panic Reaction (07-JUL-1998) Rhinitis (17-AUG-1998) Unspecified Psychosis	unknown Hospitalisation	doubtful periodic report

Event Description: AN 18-YEAR-OLD MALE PATIENT (CRF:A30036) WAS ENROLLED IN A DOUBLE-BLIND CLINICAL TRIAL RISPERIDONE VERSUS OLANZAPINE. THE PATIENT EXPERIENCED AUDITORY AND VISUAL HALLUCINATIONS, IDEAS OF REFERENCE, DIZZINESS AND RESTLESSNESS. THE INVESTIGATOR FEELS THAT THERE IS A DOUBTFUL RELATIONSHIP BETWEEN THE EVENT AND STUDY MEDICATION. THE STUDY MEDICATION WAS DISCONTINUED. THE DOUBLE-BLIND TREATMENT CODE HAS NOT BEEN BROKEN. ADDITIONAL INFORMATION HAS BEEN REQUESTED.
F O L L O W U P (15-SEP-98):
THE STUDY MEDICATION END DATE IS CORRECTED TO 17-AUG-98. THE EVENT RESOLVED BY 28-AUG-98. THE PATIENT ALSO EXPERIENCED A PANIC ATTACK WHICH RESOLVED, A COUGH, CONGESTION AND WEIGHT GAIN.

JAUSA34294(3) RAJ NAKRA MD	25-AUG-1998 RIS-USA-113	57yr M	(25-FEB-1998 / 25-AUG-1998) 6 month(s)	Condition Aggravated (23-AUG-1998) Unspecified Psychosis	recovered Hospitalisation Required RX therapy	not related periodic report

Event Description: A PATIENT (CRF:A30395) WAS ENROLLED IN A DOUBLE BLIND RIS-USA-113 CLINICAL TRIAL RISPERIDONE VS OLANZAPINE EFFICACY AND SAFETY STUDY. H EXPERIENCED AN EXACERBATION OF HIS PSYCHOSIS BY VERBALIZING DELUSIONAL THOUGHTS, HE WOULD NOT EAT OR RESPOND TO CAREGIVER. HE WAS HOSPITALIZED AND THE STUDY MEDICATION WAS DISCONTINUED. THE INVESTIGATOR DOES NOT RELATE THE EVENT TO THE USE OF STUDY MEDICATION. THE DOUBLE BLIND MEDICATION CODE WAS NOT BROKEN. ADDITIONAL INFORMATION HAS BEEN REQUESTED. HE WAS STARTED ON RISPERIDONE 1 MG BID AND TRIHEXYPHENIDYL 2 MG OD.
F O L L O W U P (15-SEP-98)
THE PATIENT RECOVERED AND THE STUDY MEDICATION END DATE, AND THE PATIENT NUMBER WAS PROVIDED.

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AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JAUSA34558(5) HUSSAM MIHTAR MD	25-SEP-1998 RIS-USA-113	48yr M	(01-MAY-1998 / 25-JUN-1998) 7 week(s) (26-JUN-1998 / 24-SEP-1998) 13 week(s)	Condition Aggravated (24-SEP-1998) Unspecified Psychosis	no change/not yet subsided Hospitalisation	possible periodic report

Event Description: THE PATIENT WAS ENROLLED INTO THE STUDY (RISPERIDONE VERSUS OLANZAPINE) AND BEGAN DOUBLE-BLIND MEDICATION ON 01-MAY-98. THE PATIENT WAS HOSPITALIZED ON 25-SEP-98 FOR AN ACUTE EXACERBATION OF PSYCHOTIC SYMPTOMS. INCREASED SYMPTOMS BEGAN ON 24-SEP-98, INCLUDING THOUGHT BROADCASTING, PARANOID DELUSIONS, DELUSIONS OF REFERENCE, TACTILE HALLUCINATIONS, VISUAL AND TRUE AUDITORY HALLUCINATIONS (SOME COMMAND HALLUCINATIONS WHICH PATIENT FELT COMPELLE TO RESPOND TO). STUDY MEDICATION WAS PERMANENTLY STOPPED ON 25-SEP-98. THE PATIENT HAS NOT YET RECOVERED. IN THE OPINION OF THE INVESTIGATOR THE EVENT CAUSALITY WAS ASSESSED AS POSSIBLY RELATED TO STUDY MEDICATION. ADDITIONAL INFORMATION REQUESTED.
ADDITIONAL INFORMATION: 10-NOV-98
CLARIFICATION OF THERAPY DATES RECEIVED.
ADDITIONAL INFORMATION 12-JAN-99:
THE CRF NUMBER WAS ADDED TO CASE (CRF:A30195).

JAUSA34590(3) AMANDA PANDERANG MD	25-SEP-1998 RIS-USA-113	38yr M	(09-MAR-1998 / Unknown)	Condition Aggravated (13-SEP-1998) Unspecified Psychosis	recovered Hospitalisation Required RX therapy	not related periodic report

Event Description: THE PATIENT (CRF:A325585) WAS ENROLLED INTO THE STUDY (RISPERIDONE VERSUS OLANZAPINE) AND BEGAN DOUBLE-BLIND MEDICATION ON 09-MAR-98. THE PATIENT WAS HOSPITALIZED 13-SEP-98 FOR RELAPSE OF PSYCHOSIS WITH CONFUSED THINKING AND DELUSIONS. HE VOLUNTARILY SOUGHT TREATMENT AND WAS ADMITTED TO THE HOSPITAL. THE PATIENT'S CONDITION STABILIZED AND HE IMPROVED MODERATELY. THE PATIENT WAS DISCHARGED 15-SEP-98, RECOVERED. STUDY MEDICATION REMAINED UNCHANGED. THE PATIENT RECEIVED SUPPORTIVE THERAPY. IN THE OPINION OF THE INVESTIGATOR THE EVENT CAUSALITY WAS ASSESSED AS NOT RELATED TO STUDY MEDICATIO (SPONTANEOUS RELAPSE).
ADDITIONAL INFORMATION (15-APR-99):
CRF NUMBER CORRECTED TO (CRF:A30281).
STILL D O U B L E B L I N D.

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AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JAUSA34614(5) LAWRENCE DUNN MD	24-SEP-1998 RIS-USA-79	42yr M	(30-OCT-1996 / 05-NOV-1996) 6 day(s) (06-NOV-1996 / 11-NOV-1996) 5 day(s) (12-NOV-1996 / 12-NOV-1996) (13-NOV-1996 / 13-NOV-1996)	Condition Aggravated (06-NOV-1996) Drug Maladministration (06-NOV-1998) Unspecified Schizophrenia	recovered Hospitalisation Required RX therapy	not related periodic report

Event Description: PT (CRF:A30183) ENROLLED IN A DOUBLE BLIND CLINICAL STUDY OF RISPERIDONE (RISPERIDONE VS HALOPERIDOL) EXPERIENCED INCREASED PSYCHOSIS AN HIS DOSE OF STUDY DRUG WAS INCREASED TO 3 TABLETS AT BEDTIME ON 06-NOV-96. THE DOSE OF STUDY DRUG WAS INCREASED TO 4 TABLETS AT BEDTIME ON 12-NOV-96. THE PATIENT, WITHOUT PHYSICIANS KNOWLEDGE TOOK 8 TABLETS OF STUDY DRUG OVER THE ENTIRE DAY ON 13-NOV-96 IN AN ATTEMPT TO CONTROL HIS PSYCHOTIC SYMPTOMS. ON 14-NOV-96 THE PATIENT WAS HOSPITALIZED FOR EXACERBATION OF HIS PSYCHOSIS. RISPERIDONE 1 MG TWICE DAILY WAS STARTED ALONG WITH LORAZEPAM 1.5 MG EVERY 4 HOURS AS NEEDED, AND BENZTROPINE 1 MG AS NEEDED FOR EXTRAPYRAMIDAL SYMPTOMS. THE PATIENT WAS OFF STUDY MEDICATION FOR 7 DAYS WHEN THE INVESTIGATOR WAS INFORMED OF HIS HOSPITALIZATION. THE PATIENT WAS DISCONTINUED FROM THE STUDY ON 20-NOV-96. THE PATIENT STABILIZED ON THE ABOVE MEDICATIONS AND WAS DISCHARGED ON 20-NOV-96.
ADDITIONAL INFORMATION RECEIVED 03-NOV-98:INFORMATION ADDED ON STUDY DRUG, CONCOMITANT DISEASES AND DRUGS.
F O L L O W U P (20-JAN-99):
DURING DATABASE RECONCILIATION CORRECTED CAUSALITY TO NO PER REPORTER.
STILL D O U B L E B L I N D.

JAUSA34627(1) B. RAJ NAKRA MD	20-JUL-1998 RIS-USA-79	45yr F	(24-JUN-1998 / 13-JUL-1998) 20 day(s)	Condition Aggravated (13-JUL-1998) Drug Abuse (13-JUL-1998) Unspecified Schizophrenia	recovered Hospitalisation Required RX therapy	not related periodic report

Event Description: PATIENT (CRF:A30334) ENROLLED IN A DOUBLE BLIND CLINICAL STUDY OF RISPERIDONE (RISPERIDONE VS HALOPERIDOL) ON 24-JUN-98. THE PATIENT WA HOSPITALIZED ON 13-JUL-98 DUE TO EXACERBATION OF PSYCHOSIS (AGITATION. PARANOIA, AND HALLUCINATIONS) . THE PATIENT WAS ALSO INTOXICATED WHEN SHE PRESENTED AT THE HOSPITAL. STUDY DRUG WAS DISCONTINUED AND THE PATIENT WAS TREATED WITH ORAL FLUPHENAZINE 15 MG DAILY AND BENZTROPINE 6 MG DAILY. THE PATIENT RECEIVED FLUPHENAZINE 50 MG I.M. ON 14-JUL-98 AND 21-JUL-98. THE PATIENT WAS DISCONTINUED FROM THE STUDY ON 14-JUL-98. REPORTER BELIEVES THE PATIENT MAY HAVE BEEN NON COMPLIANT WITH HER STUDY MEDICATION. THE PATIENT STABILIZED AND WAS DISCHARGED ON 21-JUL-98.. THE REPORTER DOES NOT RELATE THESE EVENTS TO STUDY MEDICATION.
STILL D O U B L E B L I N D.

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AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JAUSA34633(2) RAJ NAKRA MD	24-SEP-1998 RIS-USA-79	56yr F	(06-AUG-1996 / 14-AUG-1997) 12 month(s)	Condition Aggravated (14-AUG-1997) Aggressive Reaction (14-AUG-1997) Agitation (14-AUG-1997) Unspecified Schizophrenia	recovered Hospitalisation Required RX therapy	not related periodic report

Event Description: PATIENT (CRF:A30328) ENROLLED IN A DOUBLE BLIND CLINICAL STUDY (RISPERIDONE VERSUS HALOPERIDOL) ON 06-AUG-96. THE PATIENT WAS HOSPITALIZED ON 14-AUG-97 FOR ACUTE EXACERBATION OF MANIC SYMPTOMS. ON ADMISSION THE PATIENT WAS EXTREMELY AGITATED, EXTREMELY IRRITABLE AND HOSTILE AND VERBALLY LOUD AND ABUSIVE WITH DELUSIONS OF GRANDIOSITY WITH MARKED LABILITY OF MOOD AND AFFECT AND EXPANSILE MOOD. THE PATIENT CONTINUED, TO DO POORLY AN THE STUDY DRUG WAS DISCONTINUED ON 14-AUG-97. SHE WAS STARTED ONSHE WAS STARTED ON VALPROATE SODIUM 125 MG TID, HALOPERIDOL 5 MG PO TID AND 10 MG AT BED TIME AND IN ADDITION SHE WAS GIVEN AN INJECTION OF HALOPERIDOL DECANOATE 100 MG IM. THE PATIENT CONTINUED TO HAVE MARKED LABILITY OF MOOD AND AFFECT AND SIGNIFICANT STATE OF AGITATION, IRRITABILITY AND HOSTILITY. HER VALPROATE SODIUM WAS READJUSTED TO 125 MG BID AND 250 MG AT BEDTIME. THE PATIENT'S CASEWORKER IS TAKING HER TO A TEMPORARY SHELTER. THE PATIENT WAS DISCHARGED 25-AUG-97, RECOVERED. IN THE OPINION OF THE INVESTIGATOR THE EVENT CAUSALITY WAS ASSESSED AS NOT RELATED TO STUDY MEDICATION.
STILL D O U B L E B L I N D.

JAUSA34819(6) MICHAEL FLAUM MD	07-OCT-1998 RIS-USA-113	34yr F	(04-FEB-1998 / 03-MAR-1998) 30 day(s) (04-MAR-1998 / 02-APR-1998) 29 day(s) (03-APR-1998 / 17-SEP-1998) 24 week(s) (18-SEP-1998 / 03-OCT-1998) 16 day(s)	Condition Aggravated (30-SEP-1998) Infection Viral (07-FEB-1998) Headache (01-AUG-1998) Amenorrhoea (04-FEB-1998) Unspecified Psychosis	recovered Hospitalisation Required RX therapy	not related periodic report

Event Description: A PATIENT (CRF:A30187) WAS ENROLLED IN A DOUBLE BLIND RISPERIDONE VS OLANZAPINE CLINICAL TRIAL. THE PATIENT EXPERIENCED A HEAD COLD AND IN FEB-98, AND DEVELOPED HEADACHES ON TWO OTHER OCCASIONS. SHE WAS TREATED WITH DICLOFENAC AND EXCEDRIN(R) AND RECOVERED. ON 30-SEP-98 SHE PRESENTED HERSELF TO THE HOSPITAL WITH AN INCREASE IN DELUSIONS. SHE WAS HOSPITALIZED AND A NUMBER OF ATTEMPTS WERE MADE TO HAVE HER TAKE AN ADDITIONAL TABLET DAILY BUT THE PATIENT REFUSED. HER CONDITION WORSENED AND SHE REFUSED ALL MEDICATION. SHE WAS TERMINATED FROM THE STUDY. THE INVESTIGATOR DOES NOT RELATE THES EVENTS TO THE STUDY MEDICATION. THE DOUBLE BLIND TREATMENT CODE WAS NOT BROKEN. AS OF 07-OCT-98 SHE REMAINS HOSPITALIZED AND HAS NOT RECOVERED. SHE ALSO EXPERIENCED AMENORRHEA. ADDITIONAL INFORMATION HAS BEEN REQUESTED.
STILL D O U B L E B L I N D.
ADDITIONAL INFORMATION (16-DEC-98): OUTCOME WAS PROVIDED. THE PATIENT RECOVERED ON 12-NOV-98.
ADDITIONAL INFORMATION (22-MAR-99): DURING THE DATABASE RECONCILIATION THE SUSPECT DRUG TREATMENT DATES WERE REVISED.

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AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JAUSA34951(2) S C SCHULZ MD	23-OCT-1998 RIS-INT-35	24yr F	1mg (dly) (24-SEP-1998 / 10-OCT-1998) 17 day(s)	Condition Aggravated (18-OCT-1998) Unspecified Psychosis	recovered Hospitalisation Required RX therapy	not related periodic report

Event Description: THE PATIENT WAS ENROLLED INTO THE STUDY (RISPERIDONE VERSUS HALOPERIDOL) AND BEGAN DOUBLE-BLIND MEDICATION ON 24-SEP-98. THE PATIENT WA HOSPITALIZED ON 18-OCT-98 WITH AN INCREASE IN PSYCHOTIC SYMPTOMS (I.E. PARANOID, ANXIETY, AGITATION, AND DELUSIONS), MOST LIKELY DUE TO THE PATIENT'S NON-COMPLIANCE WITH STUDY DOSING PROCEDURES. THE PATIENT REFUSES TO TAKE STUDY MEDICATION. THE LAST TIME THE PATIENT RECEIVED STUDY MEDICATION WAS 10-OCT-98. SHE HAS BEEN STARTED ON OPEN LABEL ANTIPSYCHOTIC MEDICATION. THE PATIENT HAS NOT YET RECOVERED. IN THE OPINION OF THE INVESTIGATOR THE EVENT CAUSALITY WA ASSESSED AS NOT RELATED TO STUDY MEDICATION (PATIENT'S NON-COMPLIANCE). ADDITIONAL INFORMATION REQUESTED.
STILL D O U B L E B L I N D.
A D D I T I O N A L I N F O R M A T I O N (02-NOV-98):
THE PATIENT WAS TREATED WITH OLANZAPINE AND HER PSYCHOSIS DECREASED. THE PATIENT WAS DISCHARGED ON 02-NOV-98, RECOVERED AND INSTRUCTED TO CONTINUE TAKING OLANZAPINE 10 MG DAILY.

JAUSA35019(4) DAVID BROWN MD	29-OCT-1998 RIS-USA-102	28yr M	(20-OCT-1998 / 23-OCT-1998) 3 day(s)	Condition Aggravated (28-OCT-1998) Mania	recovered Hospitalisation Required RX therapy	not related periodic report

Event Description: PATIENT (CRF:A30201) ENROLLED IN A DOUBLE BLIND CLINICAL STUDY EVALUATING THE SAFETY AND EFFICACY OF RISPERIDONE VS PLACEBO VS HALOPERIDOL AS ADD ON THERAPY TO MOOD STABILIZERS IN THE TREATMENT OF THE MANIC PHASE OF BIPOLAR DISORDER WAS STARTED ON STUDY DRUG ON 20-OCT-98 WHILE HOSPITALIZED. THE PATIENT WAS DISCHARGED ON 23-OCT-98 WITH INSTRUCTIONS TO FOLLOW-UP WITH THE INVESTIGATOR ON 27-OCT-98. PATIENT CANCELLED THE APPOINTMEN AND THE STAFF WAS UNABLE TO CONTACT HIM. THE STUDY TEAM WAS INFORMED ON 29-OCT-98 THAT THE PATIENT WAS RE-ADMITTED TO THE HOSPITAL ON 28-OCT-98 FOR EXACERBATION OF THE MANIC SYMPTOMS OF HIS BIPOLAR DISORDER. THE PATIENT ADMITTED HE DID NOT TAKE ANY STUDY MEDICATION AFTER LEAVING THE HOSPITAL ON 23-OCT 98. STUDY DRUG WAS PERMANENTLY DISCONTINUED. THE REPORTER DOES NOT RELATE THIS EVENT TO STUDY MEDICATION BUT TO THE PATIENT'S NON-COMPLIANCE.
F O L L O W U P (11-MAR-99):
THE PATIENT DID MAKE SOME PROGRESS WHILE IN THE HOSPITAL. HE WAS DISCHARGED AGAINST MEDICAL ADVICE (AMA) ON 03-NOV-98. HE FOLLOWED UP AS AN OUTPATIENT AN STABLIZED ON VALPROATE SODIUM. PATIENT HISTORY PROVIDED.

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AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JAUSA35031(5) H E LOGUE MD	27-OCT-1998 RIS-USA-102	24yr M	(13-OCT-1998 / 19-OCT-1998) 6 day(s) (20-OCT-1998 / 25-OCT-1998) 5 day(s) (26-OCT-1998 / 27-OCT-1998)	Condition Aggravated (26-OCT-1998) Mania	recovered Hospitalisation	doubtful periodic report

Event Description: PATIENT (CRF:A30010) ENROLLED IN A DOUBLE BLIND CLINICAL STUDY (EVALUATING THE SAFETY AND EFFICACY OF RISPERIDONE VS PLACEBO VS HALOPERIDOL AS ADD ON THERAPY TO MOOD STABLIZERS IN THE TREATMENT OF THE MANIC PHASE OF BIPOLAR DISORDER). HE WAS HOSPITALIZED ON 26-OCT-98. THE PATIENT WAS DISCHARGED FROM THE HOSPITAL ON 19-OCT-98 AND WAS REPORTEDLY IMPROVING. HE WAS SEEN FOR VISIT 5 ON 26-OCT-98 AND IT WAS FOUND THAT THERE WAS AN INCREASE IN HIS MANIC SYMPTOMS, PARANOIA, PRESSURED SPEECH AND RELIGIOSITY AND THE STUDY MEDICATION WAS CHANGED (NOS). THE DOUBLE BLIND STUDY CONTINUES. TH INVESTIGATOR DOUBTS THAT THERE IS A RELATIONSHIP BETWEEN STUDY MEDICATION AND THE EVENT. ADDITIONAL INFORMATION HAS BEEN REQUESTED.
STILL D O U B L E B L I N D.
F O L L O W U P (04-FEB-99):
ON 28-OCT-98 THE PATIENT WAS DROPPED FROM THE STUDY DUE TO NOT BEING COMPLIANT WITH TAKING MEDICATIONS. HE BEGAN TAKING VALPROATE AGAIN, RECOVERED AND WAS DISCHARGED.

JAUSA35181(7) EVELYN HOWANITZ MD	10-NOV-1998 RIS-INT-50	80yr M	(03-NOV-1998 / 06-NOV-1998) 3 day(s)	Syncope (06-NOV-1998) Nausea (06-NOV-1998) Vomiting (06-NOV-1998) Dizziness (06-NOV-1998) Av Block (06-NOV-1998) Bundle Branch Block (06-NOV-1998) Unspecified Schizophrenia	recovered Hospitalisation	not related periodic report

Event Description: THE PATIENT (CRF:A31031) WAS ENROLLED INTO THE STUDY (RISPERIDONE VERSUS OLANZAPINE) AND BEGAN DOUBLE-BLIND MEDICATION ON 03-NOV-98. TH PATIENT WAS HOSPITALIZED ON 06-NOV-98, AFTER HE HAD AN EPISODE OF NEAR SYNCOPE. HE STATED HE WAS VERY NAUSEOUS AND WAS RELIEVED AFTER VOMITING. HE ALSO STATED THAT HE FELT DIZZY. HE WAS ADMITTED TO ICU. STUDY MEDICATION WAS PERMANENTLY STOPPED ON 06-NOV-98. THE PATIENT RECOVERED WITH A RESOLUTION DATE O 09-NOV-98. IN THE OPINION OF THE INVESTIGATOR THE EVENT CAUSALITY WAS ASSESSED AS NOT RELATED TO STUDY MEDICATION. ADDITIONAL INFORMATION REQUESTED.
F O L L O W-U P (04-DEC-98):
THE PATIENT'S SUPINE BLOOD PRESSURE AND PULSE OBTAINED 5 MINUTES AFTER REST WAS 148/64 AND 57. STANDING BLOOD PRESSURE AND PULSE TAKEN AFTER 1 MINUTE OF STANDING WAS 120/70 AND 67. ECG DONE 06-NOV-98 AT 12:19:48 HOURS SHOWED SINUS BRADYCARDIA WITH FIRST DEGREE ATRIOVENTRICULAR BLOCK AND RIGHT BUNDLE BRANCH BLOCK.

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AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JAUSA35289(5) HUSSAM MIHTAR MD	20-NOV-1998 RIS-USA-113	37yr M	(08-MAY-1998 / 10-NOV-1998) 6 month(s)	Condition Aggravated (14-NOV-1998) Drug Abuse (01-NOV-1998) Unspecified Psychosis	no change/not yet subsided Hospitalisation	not related periodic report

Event Description: THIS PATIENT (CRF:A30194) WAS ENROLLED INTO THE DOUBLE BLIND CLINICAL STUDY (RISPERIDONE VERSUS OLANZAPINE) FOR SCHIZOPHRENIA AND BEGAN STUDY MEDICATION ON 12-MAR-98. THE PATIENT RELAPSED ON CRYSTAL METHAMPHETAMINE ABUSE ON 01-NOV-98. STUDY MEDICATION WAS STOPPED ON 10-NOV-98 (ESTIMATED STOP DATE) AND HE BEGAN USING CRYSTAL AGAIN ON 11-NOV-98. THE PATIENT EXPERIENCED EXACERBATION OF HIS AUDITORY HALLUCINATIONS AND WAS HOSPITALIZED ON 14-NOV-98. THE PATIENT HAS NOT YET RECOVERED. IN THE OPINION OF THE INVESTIGATOR THE EVENT CAUSALITY WAS ASSESSED AS NOT RELATED TO STUDY MEDICATION (DUE TC CRYSTAL USE). ADDITIONAL INFORMATION REQUESTED.
ADDITIONAL INFORMATION 22-MAR-99: DURING THE DATA RECONCILIATION THE PATIENT'S BIRTH DATE WAS CORRECTED. PATIENT EXPERIENCED INCREASED PSYCHOSIS AND EXACERBATION OF HIS AUDITORY HALLUCINATIONS SECONDARY TO COCAINE ABUSE.

JAUSA35328(3) DAVID BROWN MD	25-NOV-1998 RIS-USA-102	32yr M	(06-NOV-1998 / 21-NOV-1998) 15 day(s)	Condition Aggravated (25-NOV-1998) Suicidal Tendency (25-NOV-1998) Psoriasis Aggravated (24-NOV-1998) Agitation (25-NOV-1998) Mania	recovered Hospitalisation	not related periodic report

Event Description: PATIENT (CRF:A30202) ENROLLED IN A DOUBLE BLIND CLINICAL STUDY (EVALUATING THE SAFETY AND EFFICACY OF RISPERIDONE VS PLACEBO VS HALOPERIDOL AS ADD ON THERAPY TO MOOD STABILIZERS IN THE TREATMENT OF THE MANIC PHASE OF BIPOLAR DISORDER) CAME IN FOR VISIT 6 OF THE STUDY ON 25-NOV-98. HE REPORTED THAT HE HAD GONE TO THE HOSPITAL EMERGENCY ROOM THE PREVIOUS EVENING FOR UNBEARABLE DISCOMFORT WITH PSORIASIS. HIS MEDICATION PACKAGE INDICATE THAT THE PATIENT HAD ONLY TAKEN 2 TABLETS FOR THE PAST FOUR DAYS. THE PATIENT WAS DECOMPENSATING. HE STATED THAT HE NEEDS HELP AND HAS CONTEMPLATED SUICIDE (LAST NIGHT AND THIS MORNING). STUDY MEDICATION WAS PERMANENTLY STOPPED ON 21-NOV-98. THE PATIENT HAS NOT YET RECOVERED. IN THE OPINION OF THE INVESTIGATOR THE EVENT CAUSALITY WAS ASSESSED AS NOT RELATED TO STUDY MEDICATION (THE PATIENT HAD PSORIASIS PRIOR TO ENTERING STUDY). ADDITIONAL INFORMATION REQUESTED.
F O L L O W U P (11-MAR-99)
THE PATIENT WAS REHOSPITALIZED ON 25-NOV-98. PATIENT PRESENTED WITH SUICIDAL IDEATION AND AGITATION DUE TO INCREASED DISCOMFORT FROM PSORIASIS. ALL EVENT RESOLVED BY 04-DEC-98.

JAUSA35376(3) JOHN LAURIELLO MD	01-DEC-1998 RIS-USA-113	44yr M	(03-JUN-1998 / Unknown)	Condition Aggravated (30-NOV-1998) Unspecified Psychosis	no change/not yet subsided Hospitalisation	not related periodic report

Event Description: THIS PATIENT (CRF: A30242) WAS ENROLLED INTO THE DOUBLE BLIND CLINICAL STUDY (RISPERIDONE VERSUS OLANZAPINE) AND BEGAN STUDY MEDICATION ON 03-JUN-98. ON 30-NOV-98, THE PATIENT'S MOTHER REPORTED THAT THE PATIENT APPEARED MORE WITHDRAWN, PARANOID, AND ISOLATIVE OVER THE WEEKEND. THE PATIENT WAS SEEN IN THE CLINIC AND APPEARED MORE IRRITABLE AND DISORGANIZED THAN BASELINE. THE PATIENT WAS ADMITTED VOLUNTARILY TO THE MENTAL HEALTH CENTER. THE PATIENT HAS NOT YET RECOVERED. IN THE OPINION OF THE INVESTIGATOR THE EVENT CAUSALITY WAS ASSESSED AS NOT RELATED TO STUDY MEDICATION (DUE TO ILLNESS, SCHIZOPHRENIA). ADDITIONAL INFORMATION REQUESTED.

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AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JAUSA35379(2) SC SCHULZ MD	01-DEC-1998 RIS-INT-35	18yr M	(26-NOV-1998 / 29-NOV-1998) 3 day(s)	Condition Aggravated (30-NOV-1998) Unspecified Psychosis	no change/not yet subsided Hospitalisation	not related periodic report

Event Description: THE PATIENT WAS ENROLLED INTO THE STUDY (RISPERIDONE VERSUS HALOPERIDOL) AND BEGAN DOUBLE-BLIND MEDICATION ON 26-NOV-98. THE PATIENT WA HOSPITALIZED 30-NOV-98 WITH INCREASE IN PSYCHOSIS. THE PATIENT WAS EXPERIENCING PARANOIA, HEARING VOICES AND DISORGANIZATION, RESULTING IN THE NEED FOR HOSPITAL SUPERVISION. STUDY MEDICATION WAS RAISED BY 1 MG. THE PATIENT HAS NOT YET RECOVERED. IN THE OPINION OF THE INVESTIGATOR THE EVENT CAUSALITY WAS ASSESSED AS NOT RELATED TO STUDY MEDICATION (DUE TO CAUSE OF ILLNESS). ADDITIONAL INFORMATION REQUESTED.

JAUSA35380(3) SC SCHULZ MD	01-DEC-1998 RIS-INT-35	21yr	6mg (dly) (25-NOV-1998 / 29-NOV-1998) 4 day(s)	Condition Aggravated (30-NOV-1998) Unspecified Psychosis	no change/not yet subsided Hospitalisation	not related periodic report

Event Description: THE PATIENT WAS ENROLLED INTO THE STUDY (RISPERIDONE VERSUS HALOPERIDOL) AND BEGAN DOUBLE-BLIND MEDICATION ON 25-NOV-98. THE PATIENT WA HOSPITALIZED 30-NOV-98 WITH INCREASE IN PSYCHOSIS. HE WAS EXPERIENCING PARANOIA, AUDIBLE HALLUCINATIONS AND ANXIETY, RESULTING IN THE NEED FOR HOSPITAL SUPERVISION. STUDY MEDICATION DOSE WAS INCREASED. THE PATIENT HAS NOT YET RECOVERED. IN THE OPINION OF THE INVESTIGATOR THE EVENT CAUSALITY WAS ASSESSEI AS NOT RELATED TO STUDY MEDICATION. ADDITIONAL INFORMATION REQUESTED.

JAUSA35386(3) CHARLES B NEMEROFF MD PHD	02-DEC-1998 RIS-USA-102	29yr F	(18-NOV-1998 / 28-NOV-1998) 10 day(s)	Condition Aggravated (30-NOV-1998) Mania	recovered Hospitalisation Required RX therapy	doubtful periodic report

Event Description: PATIENT (CRF:A30206) ENROLLED IN A DOUBLE BLIND CLINICAL STUDY (EVALUATING THE SAFETY AND EFFICACY OF RISPERIDONE VS PLACEBO VS HALOPERIDOL AS ADD ON THERAPY TO MOOD STABILIZERS IN THE TREATMENT OF THE MANIC PHASE OF BIPOLAR DISORDER) WAS HOSPITALIZED ON 30-NOV-98 FOR SYMPTOM EXACERBATION OF MANIC PHASE BIPOLAR DISORDER. STUDY MEDICATION WAS PERMANENTLY STOPPED ON 28-NOV-98. THE PATIENT HAS NOT YET RECOVERED. IN THE OPINION C THE INVESTIGATOR THE EVENT CAUSALITY WAS ASSESSED AS DOUBTFULLY RELATED TO STUDY MEDICATION. ADDITIONAL INFORMATION REQUESTED.
ADDITIONAL INFORMATION RECEIVED ON 29-MAR-99: THE PATIENT RECOVERED AND WAS DISCONTINUED FROM THE STUDY. SHE WAS TREATED WITH THIORIDAZINE. THE INVESTIGATOR BELIEVES THE DECOMPENSATION WAS RELATED TO VALPROATE SODIUM NON-COMPLIANCE, WHICH ELICITED A DECREASED VALPROATE SODIUM LEVEL.
STILL D O U B L E B L I N D.

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D7294.66
R. 7453
JJRP 00012473

AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JAUSA35389(8) ANANDA PANDURANGI MD	02-DEC-1998 RIS-USA-113	38yr M	(09-MAR-1998 / Unknown)	Condition Aggravated (28-NOV-1998) Unspecified Psychosis	recovered Hospitalisation Required RX therapy	not related periodic report

Event Description: THE PATIENT WAS ENROLLED INTO THE STUDY (RISPERIDONE VERSUS OLANZAPINE) AND BEGAN DOUBLE-BLIND MEDICATION ON 09-MAR-98. THE PATIENT DEVELOPED PSYCHOTIC DECOMPENSATION, ACUTELY WITHOUT KNOWN PRECIPITANT. HE HAS BEEN COMPLIANT WITH MEDICATION. HE WAS ADMITTED FOR STABILIZATION. THE PATIENT HAS A HISTORY OF SHORT PSYCHOTIC EPISODES SEVERAL TIMES A YEAR. HE WAS TREATED WITH BENZTROPINE, DIPHENHYDRAMINE, LORAZEPAM AND TEMAZEPAM. THE PATIENT HAS NOT YET RECOVERED. IN THE OPINION OF THE INVESTIGATOR THE EVENT CAUSALITY WAS ASSESSED AS NOT RELATED TO STUDY MEDICATION. ADDITIONAL INFORMATION REQUESTED.
F O L L O W - U P (18-DEC-98):
THE PATIENT WAS TERMINATED FROM THE STUDY, SECONDARY TO LACK OF IMPROVEMENT. HE WAS TREATED WITH LOXAPINE UP TO 75 MG. THE PATIENT RECOVERED AND WAS DISCHARGED HOEM, 16-DEC-98 TO FOLLOW-UP AS OUTPATIENT.
ADDITIONAL INFORMATION 04-JAN-99:
THE CRF NUMBER IS (CRF:A30115).
ADDITIONAL INFORMATION (12-APR-99): DURING THE DATABASE RECONCILIATION THE FOLLOWING WAS REVISED; THE CRF NUMBER WAS CORRECTED TO (CRF A:30281) AND THE PATIENT'S OUTCOME (CONDITION AGGRAVATED) WAS CORRECTED TO RECOVERED.
STILL D O U B L E B L I N D

JAUSA35473(5) RONALD BRENNER MD	08-DEC-1998 RIS-USA-113	61yr F	(26-MAR-1998 / 29-MAY-1998) 9 week(s) (30-MAY-1998 / 03-DEC-1998) 6 month(s) (18-DEC-1998 / 25-JAN-1999) 5 week(s)	Condition Aggravated (03-DEC-1998) Unspecified Psychosis	recovered Hospitalisation	not related periodic report

Event Description: THIS PATIENT (CRF:A30154) WAS ENROLLED INTO THE DOUBLE BLIND CLINICAL STUDY (RISPERIDONE VERSUS OLANZAPINE) FOR SCHIZOPHRENIA AND BEGAN STUDY MEDICATION ON 26-MAR-98. THE PATIENT WAS HOSPITALIZED 03-DEC-98 FOR SOMATIC DELUSIONS. STUDY MEDICATION WAS TEMPORARILY STOPPED ON 03-DEC-98. THE PATIENT HAS NOT YET RECOVERED. IN THE OPINION OF THE INVESTIGATOR THE EVENT CAUSALITY WAS ASSESSED AS NOT RELATED TO STUDY MEDICATION (CAUSE UNKNOWN). ADDITIONAL INFORMATION REQUESTED.
F O L L O W U P (10-FEB-99):
THE SOMATIC DELUSIONS WERE SECONDARY TO DEPRESSIVE NEUROSIS. THE PATIENT RECOVERED WITH A RESOLUTION DATE OF 17-DEC-98. STUDY MEDICATION WAS RESTARTED 18-DEC-98. THE PATIENT COMPLETED THE STUDY ON 25-JAN-99.
ADDITIONAL INFORMATION (22-MAR-99):
DUE TO DATA BASE RECONCILIATION THE DOSING WAS ADDED TO THE STUDY MEDICATION.
STILL D O U B L E B L I N D.

590

R. 7454

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JJRP 00012474

AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JAUSA36530(5) JOHN CSERNANSKY MD	04-MAR-1999 RIS-INT-35	25yr M	1mg (dly) (24-SEP-1998 / 28-SEP-1998) 4 day(s) 2mg (dly) (29-SEP-1998 / 05-OCT-1998) 7 day(s) 3mg (dly) (06-OCT-1998 / 11-OCT-1998) 5 day(s) 2mg (dly) (12-OCT-1998 / 01-MAR-1999) 20 week(s) 3mg (dly) (02-MAR-1999 / Unknown)	Drug Addiction (01-MAR-1999) Paranoid Psychosis (01-MAR-1999) Unspecified Psychosis	recovered Hospitalisation	not related periodic repo

Event Description: THE PATIENT, ENROLLED INTO THE STUDY (RISPERIDONE VERSUS HALOPERIDOL) AND WHO BEGAN DOUBLE-BLIND MEDICATION ON (DATE UNSPECIFIED), WAS HOSPITALIZED ON 01-MAR-99 FOR ALCOHOL DEPENDENCY. HIS MAIN COMPLAINT WAS "PARANOID IDEATIONS OF PHYSICIANS PASSING HIS PERSONAL INFORMATION AROUND TO ALL PHYSICIANS". STUDY MEDICATION WAS CHANGED TO 3 MG DAILY AT BEDTIME. IT IS UNKNOWN IF THE PATIENT HAS RECOVERED. IN THE OPINION OF THE INVESTIGATOR THE EVENT CAUSALITY WAS ASSESSED AS NOT RELATED TO STUDY MEDICATION (DUE TO EXCESSIVE ALCOHOL). THE DOUBLE BLIND TREATMENT CODE HAS NOT BEEN BROKEN. ADDITION INFORMATION REQUESTED.
F O L L O W - U P (11-MAR-99):
STUDY MEDICATION THERAPY DATES AND DOSES PROVIDED. (CRF:A3861)
STILL DOUBLE BLIND.

R. 7455
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D7294.68
JJRP 00012475

AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JAUSA36998(5) JOHN LAURIELLO MD MD	01-APR-1999 RIS-INT-35	22yr M	1mg (dly) (14-OCT-1998 / Unknown) 2mg (dly) 3mg (dly)	Suicidal Tendency (31-MAR-1999) Anxiety (31-MAR-1999) Agitation (31-MAR-1999) Unspecified Psychosis	recovered Hospitalisation	not related periodic repo.

Event Description: PATIENT ENROLLED IN (RIS-INT-35) CLINICAL TRIAL DOUBLE BLIND (RISPERIDONE VS HALOPERIDOL) AND STARTED MEDICATION ON 14-OCT-98. PATIENT WAS BROUGHT INTO THE EMERGENCY SERVICE BY HIS WIFE AND MOTHER, AS HE WAS ANXIOUS AND AGITATED ABOUT THE PAROLE OFFICE WANTING HIM TO GO TO JAIL. HE WAS HOSPITALIZED DUE TO SUICIDAL IDEATIONS. THE DOUBLE BLIND CODE WAS NOT BROKEN AND THERAPY CONTINUES. THE INVESTIGATOR DOES NOT RELATE THE EVENTS TO STUDY MEDICATION, BUT TO HIS ILLNESS. ADDITIONAL INFORMATION WAS REQUESTED.
Additional information 13-May-99:
Outcome and dosing changes added to case. The patient's study medication dose was increased from 1mg to 2 mg then 3mg daily. The psychosis, anxiety and agitation improved. He recovered and was released from the hospital.

JAUSA37290(6) C BOWDEN MD	17-APR-1999 RIS-USA-102	49yr M	4mg (dly) (08-FEB-1999 / 12-APR-1999) 9 week(s)	Suicidal Tendency (13-APR-1999) Bronchitis (09-FEB-1999) Flatulence (22-FEB-1999) Extrapyramidal Disorder (08-MAR-1999) Chest Pain (Unknown) Pain (Unknown) Manic Disorder, Recurrent Episode	no change/not yet subsided Hospitalisation Required RX therapy	not related periodic repor

Event Description: PATIENT ENROLLED (CRF:A30227) CLINICAL TRIAL RIS-USA-102 FOR THE SAFETY AND EFFICACY OF RISPERIDONE VS. PLACEBO, VS. HALOPERIDOL AS ADD ON THERAPY TO MOOD STABLIZERS IN THE MANIC PHASE OF BIPOLAR DISORDER. PATIENT REQUIRED HOSPITALIZATION DUE TO DEVELOPING SUICIDAL IDEATION. THIS WAS RELATED TO INCREASED PSYCHOLOGICAL STRESS SINCE HIS EX-WIFE THREW HIM OUT OF THE HOME. THE INVESTIGATOR DOES NOT ATTRIBUTE THE EVENT TO STUDY MEDICATION B TO PSYCHOSOCIAL STRESSORS. THE PATIENT RECOVERED. THE PATIENT ALSO EXPERIENCED FLATULENCE, EXTRAPYRAMIDAL SYMPTOMS (NOS) AND BRONCHITIS; HE RECOVERED WI RX TREATMENT.
ADDITIONAL INFORMATION 27-APR-99:
Patient's medical history and concomitant diseases and medications added to the case. Concomitant medications valproate semi sodium, sucralfate, and ibruprofen started pre-trial.
Additional Information 10-May-99:
Patient history and concomitant medications and study medication treatment end date revised. Patient also experienced chest pain for one week, and shoulder pain. ECGs showed no acute changes and pain did not respond to motrin. Shoulder X-ray pending.

JRFUSA19990003831(1) JESSICA HELLINGS MD	20-MAY-1999 RIS-USA-97	6yr F	1.2mL (20-JUL-1998 / 04-SEP-1998) 47 day(s)	Aggressive Reaction (27-JUL-1998) Lab Values Abnormal (29-JUL-1998) Unspecified Disturbance Of Conduct	recovered Hospitalisation	not related periodic repor

Event Description: Child enrolled in an open label study RIS-USA-97 for treatment of conduct disorder in the mentally ill. Patient had been exhibiting self-injurious behavior when angry, by poking her eye with a fork, burning, and scratching herself. She was hospitalized because of the escalation of the angry outbursts and concerns about her safety. Risperidone therapy continued and the investigator does not relate the event to study medication. During her hospitalization the following labs were found to be abnormal ; bun/creatinine ratio and monocytes. See diagnostic data. The events abated.

R. 7456

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JJRP 00012476

D7294.69

AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JRFUSA19990008 40(3) JOHN LAURIELLO MD	15-JUN-1999 RIS-INT-35	22yr M	1mg (dly) (14-OCT-1998 / Unknown) 2mg (dly) (02-APR-1999 / Unknown) 3mg (dly)	Aggressive Reaction (12-JUN-1999) Unspecified Psychosis	recovered Hospitalisation	not related periodic repor

Event Description: Patient enrolled in (RIS-INT-35) clinical trial double blind (risperidone vs haloperidol) started medication on 14-Oct-98. He was hospitalized for threatening behavior towards his wife. Patient admitted to drinking alcohol. Patient discharged from the hospital without any threatening behavior. Investigator does not relate the event to study medication but to his illness under study. Additional information has been requested.
Additional information 22-Jun-99:
Additional information received indicates what the adverse event dose was for this case.

Resistance Mechanism Disorders

JAUSA34690(4) MICHAEL FLAUM MD	09-OCT-1998 RIS-USA-113	50yr M	(06-MAR-1998 / Unknown)	Infection (07-OCT-1998) Unspecified Psychosis	recovered Hospitalisation Required RX therapy	not related periodic report

Event Description: A PATIENT (CRF:A30192) WAS ENROLLED IN A DOUBLE-BLIND CLINICAL TRIAL OF RISPERIDONE VS OLANZAPINE. HE HAS TYPE II DIABETES AND DEVELOPI AN INFECTION OF HIS FOOT SECONDARY TO HIS UNDERLYING CONCOMITANT DISEASE. HE WAS HOSPITALIZED AND TREATED WITH INTRAVENOUS ANTIBIOTICS. STUDY MEDICATION CONTINUES. THE INVESTIGATOR DOES NOT RELATE THE EVENT TO STUDY MEDICATION, BUT TO THE DIABETES. THE DOUBLE-BLIND TREATMENT MEDICATION CODE WAS NOT BROKEN.
ADDITIONAL INFORMATION RECEIVED ON 16-DEC-98: OUTCOME WAS PROVIDED. THE PATIENT RECOVERED ON 13-NOV-98.
ADDITIONAL INFORMATION RECEIVED ON 30-MAR-99: EVENT DATE CORRECTED TO OCT-98 DURING DATA RECONCILIATION.
ADDITIONAL INFORMATION (30-MAR-99):
EVENT DATE CORRECTED TO 07-OCT-98 DURING DATA RECONCILIATION.
STILL D O U B L E B L I N D.

Respiratory System Disorders

JAUSA33579(5) RAJ NAKRA MD	15-JUL-1998 RIS-INT-50	72yr F	(11-JUL-1998 / 13-JUL-1998) 3 day(s)	Respiratory Distress (13-JUL-1998) Unspecified Schizophrenia	no change/not yet subsided Hospitalisation	not related periodic report

Event Description: THE PATIENT (CRF: A31110) WAS ENROLLED INTO THE STUDY (RISPERIDONE VS OLANZAPINE) AND BEGAN DOUBLE-BLIND MEDICATION ON 11-JUL-98. ON 13 JUL-98, SHE WAS HOSPITALIZED WITH RESPIRATORY DISTRESS. THE PATIENT IS STABLE BUT REMAINS HOSPITALIZED. THE INVESTIGATOR DID NOT CONSIDER THE EVENT RELATED TO STUDY DRUG. ADDITIONAL INFORMATION WAS REQUESTED.
F O L L O W-U P (22-JUL-98):
THE PATIENT WAS DIAGNOSED WITH COPD, PN (NOT SPECIFIED) AND RESPIRATORY DISTRESS.
ADDITIONAL INFORMATION (AUG-98): TRIAL MEDICATION WAS STOPPED ON 13-JUL-98.

R. 7457

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JJRP 00012477

AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
JAUSA34166(6) TAI YOO MD	12-AUG-1998 RIS-USA-79	38yr M	(10-SEP-1997 / 30-MAY-1998) 8 month(s)	Pneumonia (12-APR-1998) Unspecified Schizophrenia	recovered Hospitalisation Required intervention Required RX therapy	doubtful periodic repor

Event Description: PATIENT (CRF:A30547) ENROLLED IN A DOUBLE BLIND CLINICAL STUDY OF RISPERIDONE (RISPERIDONE VS HALOPERIDOL) PRESENTED AT THE EMERGENCY ROOM WITH SHORTNESS OF BREATH, FEVER (101?F), INCREASED RESPIRATORY RATE (32) AND TACHYCARDIA (126 BPM). PATIENT WAS NOTED TO HAVE BILATERAL RHONCHI, DECREASED BREATH SOUNDS, AND BIBASILAR DULLNESS ON PERCUSSION. THE PATIENT WAS ADMITTED WITH A DIAGNOSIS OF PNEUMONIA, ASTHMA AND CONGESTIVE HEART FAILUR PATIENT WAS TREATED IN THE EMERGENCY ROOM WITH CEFTZOXIME 30 MG IV, ERYTHROMYCIN 50 MG IV, METHYLPREDNISOLONE 125 MG IV AND BREATHING TREATMENT (NOS). AFTER ADMISSION THE PATIENT WAS GIVEN IV FLUIDS, ELECTROLYTES, RANITIDINE, HEPARIN SUBCUTANEOUS AND SALBUTAMOL HE WAS STARTED ON CLINDAMYCIN 600 MG IV EVE 6 HOURS. MULTIPLE X-RAYS WERE PERFORMED ON 12-APR-98 WHICH SHOWED AIR SPACE DISEASE AND EDEMA. CONGESTIVE HEART FAILURE MIGHT CAUSE THIS AND A TWO-DIMENSIONAL ECHO WAS DONE AND WAS GROSSLY NORMAL. PATIENT GRADUALLY IMPROVED AND WAS SWITCHED TO ORAL ANTIBIOTICS. THE PATIENT WAS DISCHARGED IN STABLE CONDITION ON 18-APR-98.
ADDITIONAL INFORMATION RECEIVED 23-NOV-98: DURING DATABASE REVIEW STUDY DRUG START DATE WAS CORRECTED TO 10-SEP-97.
STILL D O U B L E B L I N D.

JAUSA34849(6) DAN ZIMBROFF MD	15-OCT-1998 RIS-USA-102	43yr F	(01-SEP-1998 / 27-SEP-1998) 26 day(s) 6mg (dly) (28-SEP-1998 / Unknown)	Asthma (09-OCT-1998) Chest Pain (09-OCT-1998) Condition Aggravated (09-OCT-1998) Mania	recovered Hospitalisation	not related periodic repor

Event Description: PATIENT (CRF:A30145) ENROLLED IN A DOUBLE BLIND CLINICAL STUDY EVALUATING THE SAFETY AND EFFICACY OF RISPERIDONE VS PLACEBO VS HALOPERIDOL AS ADD ON THERAPY TO MOOD STABILIZERS IN THE TREATMENT OF THE MANIC PHASE OF BIPOLAR DISORDER STARTED THE OPEN LABEL PHASE OF THE STUDY ON 28-SEP-98. THE PATIENT WAS HOSPITALIZED WITH CHEST PAIN ON 09-OCT-98. THE SYMPTOM RESOLVED AND THE PATIENT WAS DISCHARGED ON 11-OCT-98. THE REPORTER DOES NOT RELATE THIS EVENT TO STUDY DRUG BUT TO THE PATIENT'S EXTREME OBESITY.
STILL D O U B L E B L I N D.
F O L L O W U P (08-JAN-99):
PHYSICIAN REPORTS THE CHEST PAIN WAS RELATED TO AN EXACERBATION OF THE PATIENT'S UNDERLYING ASTHMA. ELECTRO CARDIOGRAMS PERFORMED IN HOSPITAL WERE UNCHANGED FROM EKG DONE ON 07-MAR-95. THE PATIENT'S EXTREME OBESITY CONTRIBUTED TO THE ASTHMA FLARE-UP. REPORTER DOES NOT RELATE THESE EVENTS TO STUDY DRUG.
STILL D O U B L E B L I N D.

R. 7458

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D7294.71

JJRP 00012478

AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
Secondary Terms						
JAUSA35561(4) ALEX KOPELOWICZ MD	17-DEC-1998 RIS-INT-50	66yr F	(21-APR-1998 / 13-JUN-1998) 7 week(s)	Surgical Intervention (13-JUL-1998) Unspecified Schizophrenia	recovered Hospitalisation Required intervention Required RX therapy	doubtful periodic repor

Event Description: THE PATIENT WAS ENROLLED INTO THE STUDY (RISPERIDONE VS OLANZAPINE) AND BEGAN DOUBLE-BLIND MEDICATION ON 21-APR-98. ON 13-JUL-98, SHE WAS HOSPITALIZED FOR ELECTIVE BLADDER SUSPENSION, ANTERIOR REPAIR, AND SUPRAPUBIC CYSTOSTOMY. SHE RECOVERED. THE INVESTIGATOR WAS DOUBTFUL THAT THE EVEN WAS RELATED TO STUDY DRUG.
ADDITIONAL INFORMATION 23-MAR-99:
TREATMENT MEDICATION INCLUDED AMLODIPINE, CONJUGATED ESTROGEN, LEVOTHYROXINE, SIMVASTATIN, NITROFURANTOIN MACRO AND IV CEFAZOLINE. THE PATIENT WAS ADMITTE FOR TREATMENT OF URINARY STRESS INCONTINENCE AND A CYSTOCELE. THE PATIENT WAS DISCHARGED ON 16-JUL-98 TO FOLLOW-UP WITH DOCTOR IN ONE WEEK. DISCHARGE MEDICATION WAS CEFALEXINE AND DARVOCET(R) N-100 FOR PAIN.

JAUSA35646(3) NARAYANA REDDY MD	22-DEC-1998 RIS-USA-113	46yr F	(02-APR-1998 / Unknown)	Surgical Intervention (21-DEC-1998) Upper Resp Tract Infection (21-OCT-1998) Headache (13-JUL-1998) Unspecified Psychosis	recovered Hospitalisation Required RX therapy	not related periodic repor

Event Description: PATIENT (CRF:AJ0412) ENROLLED IN A DOUBLE BLIND RISPERIDONE/OLANZAPINE CLINICAL TRIAL. PATIENT HAS A DOCUMENTED HISTORY OF UTERINE BLEEDING AND KNOWN HIATAL HERNIA SINCE 1994. SHE HAD ELECTIVE SURGERY FOR SAME ON 21-DEC-98. SHE REOVERED WITHOUT SEQUELAE. THE INVESTIGATOR DOES NOT RELATE THIS EVENT TO STUDY MEDICATION AND STUDY MEDICATION CONTINUES. THE DOUBLE-BLIND TREATMENT CODE WAS NOT BROKEN. DURING STUDY COURSE THE PATIENT AL EXPERIENCED HEADACHE AND AN UPPER RESPIRATORY INFECTION-BOTH WERE TREATED WITH MEDICATION AND SHE RECOVERED.

JAUSA36915(6) JACOBO E MINTZER MD MD	23-MAR-1999 RIS-INT-50	75yr F	24mg (dly) (25-FEB-1999 / Unknown)	Fall (22-MAR-1999) Injury (22-MAR-1999) Unspecified Psychosis	recovered Hospitalisation Required intervention Required RX therapy	not related periodic repor

Event Description: THE PATIENT (CRF:AJ1262) WAS ENROLLED INTO THE STUDY (RISPERIDONE VERSUS OLANZAPINE) AND BEGAN DOUBLE-BLIND MEDICATION ON 25-FEB-99. T PATIENT WAS HOSPITALIZED ON 22-MAR-99 AFTER SHE SLIPPED AND FELL. SHE DENIES ANY DIZZINESS. THE PATIENT FRACTURED HER RIGHT ANKLE AND PELVIS. THE PATIE REMAINS HOSPITALIZED. IN THE OPINION OF THE INVESTIGATOR THE EVENT CAUSALITY WAS ASSESSED AS NOT RELATED TO STUDY MEDICATION. ADDITIONAL INFORMATION REQUESTED.
STILL D O U B L E B L I N D.
Additional information: 26-Apr-99
On 23-Mar-99 the patient's ankle fracture was fixed internally under general anesthesia. She received enoxaparin prophylaxis. She was discharged to a rehabilitation facility on 26-Mar-99. She recovered and on 8-Apr-99 was discharged with partial weight bearing to the right foot. The trial medication continued uninterrupted. Patient history updated.

R. 7459
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D7294.72
JJRP 00012479

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

IND SAFETY REPORTS SUBMITTED

There were no 7/15 Day IND reports for Risperidone Tablets for this reporting period. Included on the following pages are five reports that were inadvertently left out of last year's report: JAUSA29378, JAUSA34611, JAUSA34619, JAUSA34623 and JAUSA34628.

JJRP 00012480
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D7294.73

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Mfr report # JAUSA29378

UF/Dist report #

FDA Use this

A. Patient information

1. Identifier: [redacted] In confidence

2. Age at time of event: or 63 yr

Date of birth: 12/31/1933

3. Sex: [x] female [ ] male

4. Weight: ____ lbs or 69.85 kgs

B. Adverse event or product problem

1. [x] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

- [ ] death ____ (mm/dd/yyyy)
- [ ] life-threatening
- [x] hospitalization - initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other: ____

3. Date of event (mm/dd/yyyy): 08/14/97

4. Date of this report (mm/dd/yyyy): 08/05/99

5. Describe event or problem

PATIENT (CRF:A30349) ENROLLED IN A DOUBLE BLIND CLINICAL TRIAL OF RISPERIDONE (RISPERIDONE VS HALOPERIDOL) WAS HOSPITALIZED ON 14-AUG-97 FOR MYOCARDIAL INFARCTION, HYPERGLYCEMIA AND LETHARGY. STUDY MEDICATION WAS TEMPORARILY DISCONTINUED. REPORTER DOES NOT RELATE THESE EVENTS TO THE STUDY MEDICATION. ADDITIONAL INFORMATION HAS BEEN REQUESTED.
F O L L O W-U P (08-SEP-97):
THE PATIENT RECOVERED. STUDY MEDICATION WAS PERMANENTLY DISCONTINUED.
ADDITIONAL INFORMATION RECEIVED ON 27-OCT-97: STATES STUDY MEDICATION WAS PERMANENTLY DISCONTINUED ON 14-AUG-97.
F L L O W-U P (27-OCT-97):
)MITANT MEDICATIONS WERE ADDED TO THE

F O L L O W-U P (17-APR-98):
STUDY MEDICATION TREATMENT DATES WERE CORRECTED TO 23-JUL-97 AND 02-SEP-97. THE DOUBLE BLIND TREATMENT CODE WAS NOT BROKEN.

ADDITIONAL INFORMATION RECEIVED 23-NOV-98:
DURING DATABASE RECONCILIATION THE STOP DATE FOR THE STUDY DRUG WAS CONFIRMED BY THE CLINICAL SITE TO BE 13-AUG-97.

(Cont.)

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Allergy
ALLERGY // SEASONAL
PNEUMONIA

Untreated Disease:
HYPERTENSION
CONGESTIVE HEART FAILURE

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 RISPERIDONE(RISPERIDONE)
#2 HALOPERIDOL(HALOPERIDOL)

2. Dose, frequency & route used
#1 4 in 1 day(s), oral
#2 4 in 1 day(s), oral

3. Therapy dates (if unknown, give duration) (from/to or best estimate)
#1 07/23/97 - 08/13/97
#2 07/23/97 - 08/13/97

4. Diagnosis for use (indication)
#1 UNSPECIFIED SCHIZOPHRENIA
#2 UNSPECIFIED SCHIZOPHRENIA

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [ ] doesn't apply
#2 [ ] yes [ ] no [ ] doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [ ] doesn't apply
#2 [ ] yes [ ] no [ ] doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)
1) PROCARDIA(NIFEDIP-INE)
2) GLUCOPHAGE(METFOR-MIN)
3) DIABETA(GLIBENCLA-

(Cont.)

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)
JANSSEN RESEARCH FOUNDATION, USA
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville NJ 08560-0200
USA
(Printing Unit)

2. Phone number: 800-526-7736

3. Report source (check all that apply)
- [ ] foreign
- [x] study
- [ ] literature
- [ ] consumer
- [x] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other: ____

4. Date received by manufacturer (mm/dd/yyyy): 04/17/98

5. (A)NDA # ____
IND # 31,931
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #: RIS-USA-79

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [x] periodic
- [x] initial [ ] follow-up # ____

8. Adverse event term(s)
1) MYOCARDIAL INFARCTION
2) HYPERGLYCAEMIA
3) SOMNOLENCE

9. Mfr. report number: JAUSA29378

E. Initial reporter

1. Name, address & phone #
RONALD BRENNER MD
327 BEACH 19TH ST
ST JOHN'S EPISCOPAL HOSPITAL
NEW YORK NY,
USA

2. Health professional? [x] yes [ ] no

3. Occupation: UNK

4. Initial reporter also sent report to FDA: [ ] yes [ ] no [ ] unk

FDA 500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

091

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1125 Trenton-Harbourton Road
P.O. Box 200
Titusville NJ 08560-0200
USA

Mfr. report # : JAUSA29378

Date of this report : 08/05/99

:rse event or product problem

B.5 Describe event or problem (Cont...)

STILL DOUBLE BLIND.

C. Suspect medication (Cont...)

Seq No. : 2
C.1 Suspect medication : HALOPERIDOL (HALOPERIDOL)
Approval information
NDA # :

C10. Concomitant medical products

Seq No. : 2
Concomitant Medical Product : GLUCOPHAGE (METFORMIN)
Diagnosis for use(indication) : 1) DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION

Seq No. : 3
Concomitant Medical Product : DIABETA (GLIBENCLAMIDE)
Diagnosis for use(indication) : 1) DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION

Seq No. : 4
Concomitant Medical Product : HUMULIN M3 (INSULIN HUMAN)
Diagnosis for use(indication) : 1) DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION

Seq No. : 5
Concomitant Medical Product : VANCENASE (BECLOMETASONE DIPROPIONATE)
Diagnosis for use(indication) : 1) RHINITIS

: 6
Concomitant Medical Product : MYCELEX (CLOTRIMAZOLE)
Diagnosis for use(indication) : 1) CANDIDIASIS

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MED WATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Mfr report # JAUSA34611

FDA Use Only

A. Patient information

1. Patient identifier: RED (In confidence)
2. Age at time of event: 55 YR or Date of birth: 04/14/1943
3. Sex: ☐ female ☒ male
4. Weight: UNK lbs or UNK kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death (mo/day/yr)
- ☐ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☒ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event (mo/day/yr): 05/04/98

4. Date of this report (mo/day/yr): 08/05/99

5. Describe event or problem

PATIENT (CRF:A30045) ENROLLED IN A DOUBLE BLIND CLINICAL STUDY OF RISPERIDONE (RISPERIDONE VS HALOPERIDOL) ON 26-SEP-96 AND COMPLETED STUDY ON 16-APR-98. THE PATIENT BEGAN HALDOL 5MG AT BEDTIME BUT ON 20-APR-98 THE PATIENT SWITCHED TO RISPERIDONE 3 MG AT BEDTIME AND BENZTROPINE 2MG DAILY. THE PATIENT WAS HOSPITALIZED ON 04-MAY-98 DUE TO AGGRESSIVE BEHAVIOR AND EXACERBATION OF HIS PSYCHOSIS (HALLUCINATIONS). THE PATIENT ADMITTED HE DID NOT WANT TO EAT AND HAD LOST WEIGHT. THE PATIENT WAS NOTED TO BE MILDLY ANEMIC AND WAS TREATED WITH FERROUS SULFATE AND GIVEN AN ADA DIET OF 2400 CALORIES PER DAY. DOSE OF RISPERIDONE WAS INCREASED TO 4MG ON 05-MAY-98 AND CONTINUED TO BE INCREASED TO 8MG DAILY. THE PATIENT HAD SOME IMPROVEMENT IN HIS AUDITORY HALLUCINATIONS. THE PATIENT'S AGGRESSION ALSO ABATED. THE PATIENT WAS DISCHARGED IN STABLE CONDITION ON 01-JUN-98. THE REPORTER DOES NOT RELATE THESE EVENTS TO STUDY MEDICATION.

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Alcohol use
ALCOHOL // ABUSE

Past Disease:
GASTRIC ULCER

Untreated Disease:
[illegible]OR
[illegible]OMA

(Cont.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 RISPERIDONE(RISPERIDONE)
#2 HALOPERIDOL(HALOPERIDOL) (Cont.)

2. Dose, frequency & route used
#1 (1 DAILY 26-SEP-96) : 7
#2 (1 DAILY 26-SEP-96) : 7

3. Therapy dates (if unknown, give duration)
#1 09/26/96 - 04/16/98
#2 09/26/96 - 04/16/98

4. Diagnosis for use (indication)
#1 UNSPECIFIED SCHIZOPHRENIA
#2 UNSPECIFIED SCHIZOPHRENIA

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)
No Concomitant Products Reported

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)
JANSSEN RESEARCH FOUNDATION, USA
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville NJ 08560-0200
USA
(Printing Unit)

2. Phone number: 800-526-7736

3. Report source (check all that apply)
- ☐ foreign
- ☒ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer (mo/day/yr): 06/02/98

5. (A)NDA #
IND # 31,931
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #: RIS-USA-79

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up # ___

8. Adverse event term(s)
1) CONDITION AGGRAVATED
2) AGGRESSIVE REACTION
3) ANAEMIA
4) ANOREXIA
5) WEIGHT DECREASE

9. Mfr. report number: JAUSA34611

E. Initial reporter

1. Name, address & phone #
JOHN CSERNANSKY MD
MPC
5351 DELMAR
WASHINGTON UNIVERSITY
SAINT LOUIS, MO, 63112
USA

2. Health professional? ☒ yes ☐ no

3. Occupation: UNK

4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

093

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MED WATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Mfr report # JAUSA34611

UF/Dist report #

FDA Use Only

A. Patient information

1. identifier	2. Age at time of event: or Date of birth:	3. Sex	4. Weight
In confidence		☐ female ☐ male	____lbs or ____kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death ____ (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other: ____

3. Date of event (mo/day/yr)

4. Date of this report (mo/day/yr)

5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

☐ A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#3 RISPERDAL(TABLET 3 MG)(RISPERIDONE)
#4 (Cont.)

2. Dose, frequency & route used
#3 (3 MG 1 DAILY 20-APR-98) : HS
#4

3. Therapy dates (if unknown, give duration)
#3 04/20/98 - 05/04/98
#4

4. Diagnosis for use (indication)
#3 UNK
#4

5. Event abated after use stopped or dose reduced
#3 ☐ yes ☐ no ☐ doesn't apply
#4 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#3
#4

7. Exp. date (if known)
#3
#4

8. Event reappeared after reintroduction
#3 ☐ yes ☐ no ☐ doesn't apply
#4 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)

2. Phone number

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other: ____

4. Date received by manufacturer (mo/day/yr)

5. (A)NDA # ____
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☐ periodic
- ☐ initial ☐ follow-up # ____

8. Adverse event term(s)

9. Mfr. report number

E. Initial reporter

1. Name, address & phone #

2. Health professional?
☐ yes ☐ no

3. Occupation

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☐ unk

094

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R. 7464

1125 Trenton-Harbourton Road
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Titusville NJ 08560-0200
USA

B se event or product problem

B.7 Other relevant history, including preexisting medical conditions (Cont...)

DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION
COPD

C. Suspect medication (Cont...)

Seq No.	: 1
C.1 Suspect medication	: RISPERIDONE(RISPERIDONE)
C.2 Dose, frequency & route used	: (1 DAILY 26-SEP-96) : 7 TABLETS AT BEDTIME
Seq No.	: 2
C.1 Suspect medication	: HALOPERIDOL(HALOPERIDOL)
C.2 Dose, frequency & route used	: (1 DAILY 26-SEP-96) : 7 TABLETS AT BEDTIME. (5 MG 1 DAILY 17-APR-98) : HS
C.3 Therapy Dates (or duration)	: 2) 04/17/98 - 04/19/98
Approval information	
NDA #	:
Seq No.	: 3
C.1 Suspect medication	: RISPERDAL(TABLET 3 MG)(RISPERIDONE)
C.2 Dose, frequency & route used	: (3 MG 1 DAILY 20-APR-98) : HS (05-MAY-98) : TITRATED TO 8 MG DAILY
C.3 Therapy Dates (or duration)	: 2) 05/05/98 - Ongoing
Approval information	
NDA #	: 20-272

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MED WATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

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Page 1 of 2

Mfr report # JAUSA34619

UF/Dist report #

FDA Use Only

A. Patient information

1. Identifier: RED — In confidence

2. Age at time of event: 35 yr or Date of birth: 09/17/1961

3. Sex: [x] female [ ] male

4. Weight: UNK lbs or UNK kgs

B. Adverse event or product problem

1. [x] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death (mm/dd/yr)
- [ ] life-threatening
- [x] hospitalization - initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event (mm/dd/yr): 08/05/97

4. Date of this report (mm/dd/yr): 08/05/99

5. Describe event or problem

PATIENT (CRF:A30048) ENROLLED IN A DOUBLE BLIND CLINICAL STUDY OF RISPERIDONE (RISPERIDONE VS HALOPERIDOL) ON 21-NOV-96. THE PATIENT DISPLAYED CATATONIC BEHAVIOR (STARING, REFUSED TO ANSWER QUESTIONS OR JOIN IN GROUP ACTIVITIES) AND WAS HOSPITALIZED ON 05-AUG-97. THE STUDY MEDICATION WAS INITIALLY CONTINUED AT THE SAME DOSE, BUT WAS INCREASED TO 3 TABLETS AT BEDTIME ON 07-AUG-97. THE PATIENT ADMITTED SHE HAD BEEN NON-COMPLIANT WITH HER STUDY MEDICATION AT HER GROUP HOME. THE PATIENT HAD A SERUM GLUCOSE LEVEL OF 303 MG/DL. ON ADMISSION, THE PATIENT WAS TREATED WITH ORAL HYPOGLYCEMIC AGENTS (NOS) AND RECOVERED. PATIENT'S SYMPTOMS IMPROVED AND SHE WAS DISCHARGED IN STABLE CONDITION ON 03-SEP-97.

6. Relevant tests/laboratory data, including dates

(Lab data cont.)

(Cont.)

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Allergy
ALLERGY // CODEINE

0A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 RISPERIDONE(TABLET)(RISPERIDONE)
#2 HALOPERIDOL(TABLET)(HALOPERIDOL) (Cont.)

2. Dose, frequency & route used
#1 (1 DAILY 21-NOV-96) : TWO
#2 (1 DAILY 21-NOV-96) : TWO

3. Therapy dates (if unknown, give duration)
#1 11/21/96 - 08/06/97
#2 11/21/96 - 08/06/97

4. Diagnosis for use (indication)
#1 UNSPECIFIED SCHIZOPHRENIA
#2 UNSPECIFIED SCHIZOPHRENIA

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [ ] doesn't apply
#2 [ ] yes [ ] no [ ] doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [ ] doesn't apply
#2 [ ] yes [ ] no [ ] doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)
1) MICRONASE(GLIBENCLAMIDE) 03/18/97 - 08/04/97
2) ALBUTEROL(SOLUTION)(SALBUTAMOL) ??/???/?? - Ongoing

(Cont.)

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)
JANSSEN RESEARCH FOUNDATION,
USA
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville NJ 08560-0200
USA
(Printing Unit)

2. Phone number: 800-526-7736

3. Report source (check all that apply)
- [ ] foreign
- [x] study
- [ ] literature
- [ ] consumer
- [x] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer (mm/dd/yr): 11/12/97

5. (A)NDA #
IND # 31,931
PLA #
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #: RIS-USA-79

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [x] periodic
- [x] Initial [ ] follow-up # ____

8. Adverse event term(s)
1) CATATONIC REACTION
2) DIABETES MELLITUS AGGRAVATED

9. Mfr. report number: JAUSA34619

E. Initial reporter

1. Name, address & phone #
JOHN CSERNANSKY MD
METROPOLITAN ST LOUIS PSYCH
5351 DELMAR
ST LOUIS MO, 63112
USA
Phone #:314-877-0522

2. Health professional? [x] yes [ ] no

3. Occupation: UNK

4. Initial reporter also sent report to FDA [ ] yes [ ] no [ ] unk

096

1125 Trenton-Harbourton Road
P.O. Box 200
Titusville NJ 08560-0200
USA

B. Relevant tests/laboratory data, including dates (Cont...)

Lab Result :

Sl.No.	Test date	Test name	Test result	Normal value
1	08/05/97	GLUCOSE	303 MG/DL	

C. Suspect medication (Cont...)

Seq No. : 1
C.1 Suspect medication : RISPERIDONE(TABLET)(RISPERIDONE)
C.2 Dose, frequency & route used : (1 DAILY 21-NOV-96) : TWO TABLETS TAKEN AT BEDTIME.
(1 DAILY 07-AUG-97) : THREE TABLETS TAKEN AT BEDTIME.
C.3 Therapy Dates (or duration) : 2) 08/07/97 - Ongoing

Seq No. : 2
C.1 Suspect medication : HALOPERIDOL(TABLET)(HALOPERIDOL)
C.2 Dose, frequency & route used : (1 DAILY 21-NOV-96) : TWO TABLETS TAKEN AT BEDTIME.
(1 DAILY 07-AUG-97) : THREE TABLETS TAKEN AT BEDTIME.
C.3 Therapy Dates (or duration) : 2) 08/07/97 - Ongoing
Approval information
NDA # :

C10. Concomitant medical products

Seq No. : 1
Concomitant Medical Product : MICRONASE(GLIBENCLAMIDE)
Dose, frequency & route used : 1) oral
Diagnosis for use(indication) : 1) DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION

Seq No. : 2
Concomitant Medical Product : ALBUTEROL(SOLUTION)(SALBUTAMOL)
Dose, frequency & route used : 1) inhala
Diagnosis for use(indication) : 1) ASTHMA

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

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Page 1 of 2

Mfr report # JAUSA34623

USER/Distr report #

FDA Use Only

A. Patient information

1. Patient identifier: RED

In confidence

2. Age at time of event: or 37 yr

Date of birth: 09/17/1961

3. Sex: [x] female [ ] male

4. Weight: UNK lbs or UNK kgs

B. Adverse event or product problem

1. [x] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

- [ ] death ____ (mo/day/yr)
- [ ] life-threatening
- [x] hospitalization - initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other: ____

3. Date of event (mo/day/yr): 10/16/97

4. Date of this report (mo/day/yr): 08/05/99

5. Describe event or problem

PATIENT (CRF:A30048) ENROLLED IN A DOUBLE BLIND CLINICAL STUDY OF RISPERIDONE (RISPERIDONE VS HALOPERIDOL) WAS HOSPITALIZED ON 16-OCT-97 DUE TO CATATONIC BEHAVIOR. THE PATIENT DISPLAYED SELECTIVE MUTISM, STARING AND UNRESPONSIVE TO QUESTIONS. THE PATIENT HAS A HISTORY OF NON COMPLIANCE WITH HER MEDICATIONS. THE PATIENT HAD A NEGATIVE URINE SCREEN FOR ILLICIT DRUGS AND A PREGNANCYY TEST WHICH WAS ALSO NEGATIVE. THE PATIENT'S DIABETES WAS WELL CONTROLLED ON GLIBENCLAMINE AND ADA DIET OF 1800 CALORIES. THE PATIENT WAS TREATED WITH ORAL HALOPERIDOL 15MG DAILY. THE PATIENT RECEIVED ONE DOSE OF HALOPERIDOL `NOATE ON 07-NOV-97. THE DOSE OF ORAL ?ERIDOL WAS TAPERED DOWN AND ONTINUED. THE PATIENT WAS DISCHARGED IN ...BLE CONDITION TO HER GROUP HOME ON 10-NOV-98.

6. Relevant tests/laboratory data, including dates

(Lab data cont.)

(Cont.)

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Allergy
ALLERGY // CODEINE
AE-HISTORY (RIS-USA-79):
05-AUG-97: CATATONIC REACTION (REFNO-71135).

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 RISPERIDONE(TABLET)(RISPERIDONE)

#2 HALOPERIDOL(TABLET)(HALOPERIDOL)

(Cont.)

2. Dose, frequency & route used

#1 (1 DAILY 21-NOV-96) : TWO

#2 (1 DAILY 21-NOV-96) :

3. Therapy dates (if unknown, give duration)

#1 11/21/96 - 08/06/97

#2 11/21/96 - 08/06/97

4. Diagnosis for use (indication)

#1 UNSPECIFIED SCHIZOPHRENIA

#2 UNSPECIFIED SCHIZOPHRENIA

5. Event abated after use stopped or dose reduced

#1 [ ] yes [ ] no [ ] doesn't apply

#2 [ ] yes [ ] no [ ] doesn't apply

6. Lot # (if known)

#1

#2

7. Exp. date (if known)

#1

#2

8. Event reappeared after reintroduction

#1 [ ] yes [ ] no [ ] doesn't apply

#2 [ ] yes [ ] no [ ] doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

1) MICRONASE(TABLET)-(GLIBENCLAMIDE) 09/03/97 - Ongoing

2) ALBUTEROL(SOLUTIO-N)(SALBUTAMOL) ??/???/?? - Ongoing

(Cont.)

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)

JANSSEN RESEARCH FOUNDATION,
USA
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville NJ 08560-0200
USA
(Printing Unit)

2. Phone number: 800-526-7736

3. Report source (check all that apply)

- [ ] foreign
- [x] study
- [ ] literature
- [ ] consumer
- [x] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other: ____

4. Date received by manufacturer (mo/day/yr): 11/13/97

5. (A)NDA # ____ IND # 31,931 PLA # ____ pre-1938 [ ] yes OTC product [ ] yes

6. If IND, protocol #: RIS-USA-79

7. Type of report (check all that apply)

- [ ] 5-day [ ] 15-day
- [ ] 10-day [x] periodic
- [x] Initial [ ] follow-up # ____

8. Adverse event term(s)

1) CATATONIC REACTION

9. Mfr. report number: JAUSA34623

E. Initial reporter

1. Name, address & phone #

JOHN CSERNANSKY MD
METROPOLITAN ST LOUIS PSYCH
5351 DELMAR
ST LOUIS MO, 63112
USA
Phone #:314-877-0522

2. Health professional? [x] yes [ ] no

3. Occupation: UNK

4. Initial reporter also sent report to FDA [ ] yes [ ] no [ ] unk

OA Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

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R. 7468

1125 Trenton-Harbourton Road
P.O. Box 200
Titusville NJ 08560-0200
USA

Mfr. report # : JAUSA34623

Date of this report : 08/05/99

F vant tests/laboratory data, including dates (Cont...)

Lab Result :

Sl.No.	Test date	Test name	Test result	Normal value
1	10/16/97	GLUCOSE	NORMAL	
		URINALYSIS	UNK	
		NEGATIVE FOR ILLICIT DRUGS.		
2	10/20/97	LAB DATA	NEGATIVE	
		Comments : PREGNANCY		

C. Suspect medication (Cont...)

Seq No.	: 1
C.1 Suspect medication	: RISPERIDONE(TABLET)(RISPERIDONE)
C.2 Dose, frequency & route used	: (1 DAILY 21-NOV-96) : TWO TABLETS TAKEN AT BEDTIME.
	(1 DAILY 07-AUG-97) : THREE TABLETS TAKEN AT BEDTIME.
C.3 Therapy Dates (or duration)	: 2) 08/07/97 - Ongoing
Seq No.	: 2
C.1 Suspect medication	: HALOPERIDOL(TABLET)(HALOPERIDOL)
C.2 Dose, frequency & route used	: (1 DAILY 21-NOV-96) : THREE TABLETS TAKEN AT BEDTIME.
	(1 DAILY 07-AUG-97) : TWO TABLETS TAKEN AT BEDTIME.
C.3 Therapy Dates (or duration)	: 2) 08/07/97 - Ongoing
Approval information	
NDA #	:

C10. Concomitant medical products

Seq No.	: 1
Co- -itant Medical Product	: MICRONASE(TABLET)(GLIBENCLAMIDE)
F uency & route used	: 1) oral
I for use(indication)	: 1) DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION
Seq No.	: 2
Concomitant Medical Product	: ALBUTEROL(SOLUTION)(SALBUTAMOL)
Dose, frequency & route used	: 1) inhala
Diagnosis for use(indication)	: 1) ASTHMA

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JANSSEN RESEARCH FOUNDATION, USA

MED WATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Page 1 of 2

Mfr report # JAUSA34628

UF/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier: RED

In confidence

2. Age at time of event: or 31 yr

Date of birth: 07/28/1966

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or 73.18 kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

☐ death ____ (mo/day/yr)
☐ life-threatening
☒ hospitalization - initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other: ____

3. Date of event (mo/day/yr): 07/30/97

4. Date of this report (mo/day/yr): 08/05/99

5. Describe event or problem

PATIENT (CRF:A30504) ENROLLED IN A DOUBLE BLIND CLINICAL STUDY OF RISPERIDONE (RISPERIDONE VS HALOPERIDOL) PRESENTED AT THE HOSPITAL ON 30-JUL-97 COMPLAINING OF EXCESSIVE SEDATION (SLEEPING 18 HOURS A DAY), HEADACHES, AND DEPRESSION. SUICIDAL IDEATION WAS NOTED. THE PATIENT ADMITTED GOING TO A GUN SHOP TO PURCHASE A GUN TO KILL HIMSELF. THE PATIENT WAS NOTED TO HAVE FLAT AFFECT, POOR COMMUNICATION, ANXIETY, PARANOIA, POOR SELF-ESTEEM, AND THOUGHT DISORDER. THE PATIENT WAS STARTED ON OLANZAPINE 10MG DAILY WHICH WAS INCREASED TO 50MG DAILY WITH MARKED RESOLUTION OF PSYCHOTIC SYMPTOMS. THE PATIENT WAS DISCHARGED IN STABLE CONDITION ON 20-AUG-97.

F O L L O W U P (20-JAN-99):
CLEANING DATABASE RECONCILIATION CORRECTED CAUSALITY TO NO PER REPORTER.
STILL D O U B L E B L I N D.

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

No Pat Profiles Rptd
AE HISTORY RIS-USA-79:
27-MAY-98: SUICIDE ATTEMPT (REFNO: 58044)

Untreated Disease:
UNSPECIFIED PARANOID STATE

☐ FDA Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 RISPERIDONE (RISPERIDONE)
#2 HALOPERIDOL (HALOPERIDOL) (Cont.)

2. Dose, frequency & route used
#1 (1 DAILY 28-APR-97) : 2
#2 (1 DAILY 28-APR-97) : 2

3. Therapy dates (if unknown, give duration)
#1 04/28/97 - 07/21/97
#2 04/28/97 - 07/21/97

4. Diagnosis for use (indication)
#1 UNSPECIFIED SCHIZOPHRENIA
#2 UNSPECIFIED SCHIZOPHRENIA

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)
No Concomitant Products Reported

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)
JANSSEN RESEARCH FOUNDATION, USA
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville NJ 08560-0200
USA
(Printing Unit)

2. Phone number: 800-526-7736

3. Report source (check all that apply)
☐ foreign
☒ study
☐ literature
☐ consumer
☒ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other: ____

4. Date received by manufacturer (mo/day/yr): 11/12/97

5. (A)NDA # ____
IND # 31,931
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #: RIS-USA-79

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up # ____

8. Adverse event term(s)
1) SUICIDE ATTEMPT
2) CONDITION AGGRAVATED
3) SOMNOLENCE
4) HEADACHE
5) DEPRESSION

9. Mfr. report number: JAUSA34628

E. Initial reporter

1. Name, address & phone #
JOHN CSERNANSKY MD
MPC
5351 DELMAR
WASHINGTON UNIVERSITY
SAINT LOUIS, MO, 63112
USA

2. Health professional? ☒ yes ☐ no

3. Occupation: UNK

4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

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1125 Trenton-Harbourton Road
P.O. Box 200
Titusville NJ 08560-0200
USA

C. ect medication (Cont...)

Seq No.	: 1
C.1 Suspect medication	: RISPERIDONE(RISPERIDONE)
C.2 Dose, frequency & route used	: (1 DAILY 28-APR-97) : 2 TABLETS AT BEDTIME
Seq No.	: 2
C.1 Suspect medication	: HALOPERIDOL(HALOPERIDOL)
C.2 Dose, frequency & route used	: (1 DAILY 28-APR-97) : 2 TABLETS AT BEDTIME
Approval Information	
NDA #	:

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LIST OF SUBJECTS WHO DIED DURING THIS REPORTING PERIOD

There were no deaths reported during this reporting period in RIS-INT-50, RIS-INT-35, RIS-USA-79, RIS-USA-97, RIS-USA-113, RIS-CAN-19 and RIS-INT-41.

One death was reported during this reporting period for Clinical Trial RIS-USA-102, patient #A30071 of Dr. Sajatovic; vomiting, history of GI bleed. Died at home from streptococcal pneumonia.

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AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type
Gastro-Intestinal System Disorders						
JAUSA34658(18) MARTHA SAJATOVIC MD	01-OCT-1998 RIS-USA-102	56yr M	2table(dly) (16-SEP-1998 / 22-SEP-1998) 7 day(s) 3table(dly) (23-SEP-1998 / 26-SEP-1998) 4 day(s) 2table(dly) (28-SEP-1998 / 29-SEP-1998) 2 day(s) 3table(dly) (30-SEP-1998 / 30-SEP-1998) 1 day(s)	Haematemesis (01-OCT-1998) Peptic Ulcer Aggravated (01-OCT-1998) Respiratory Disorder (05-OCT-1998) Fever (01-OCT-1998) Oesophageal Ulceration (05-OCT-1998) Hoarseness (??-OCT-1998) Tooth Disorder (??-OCT-1998) Hearing Decreased (??-OCT-1998) Fall (01-OCT-1998) Injury (01-OCT-1998) Pneumonia (01-OCT-1998) Respiratory Failure (01-OCT-1998) Renal Infarction (Unknown) Haematoma (Unknown) Spleen Disorder (Unknown) Bipolar Affective Disorder, Manic	death Death Hospitalisation Required intervention Required RX therapy	not related periodic repor

Event Description: PATIENT (CRF:A30071) ENROLLED IN A DOUBLE BLIND CLINICAL STUDY EVALUATING THE SAFETY AND EFFICACY OF RISPERIDONE VS PLACEBO VS HALOPERIDOL AS ADD ON THERAPY TO MOOD STABILIZERS IN THE TREATMENT OF THE MANIC PHASE OF BIPOLAR DISORDER STARTED THE OPEN-LABEL PHASE OF THE STUDY ON 28-SEP-98 AND RECEIVED RISPERIDONE 3MG DAILY. THE PATIENT EXPERIENCED ONE EPISODE OF VOMITING ON 30-SEP-98, AND TWO EPISODES OF COFFEEGROUND LIKE EMESIS ON 01-OCT-98. THE PATIENT WAS ADMITTED TO THE MEDICAL UNIT ON 01-OCT-98. RISPERIDONE WAS PERMANENTLY DISCONTINUED. THE PATIENT HAS A HISTORY OF PEPTIC ULC DISEASE. THE REPORTER DOES NOT RELATE THESE EVENTS TO RISPERIDONE.
ADDITIONAL INFORMATION (22-OCT-98):
PATIENT WAS DISCHARGED FROM THE HOSPITAL ON 16-OCT-98. THE PATIENT DIED ON 20-OCT-98 DUE TO COMPLICATIONS ASSOCIATED WITH PEPTIC ULCER DISEASE. THE REPORTER DOES NOT RELATE THIS EVENT WITH THE STUDY MEDICATION. ADDITIONAL INFORMATION HAS BEEN REQUESTED.
ADDITIONAL INFORMATION RECEIVED 17-FEB-99:
DURING RECONCILIATION OF THE DATABASE, THE DATE OF BIRTH WAS CORRECTED TO 25-JUL-42.
ADDITIONAL INFORMATION (15-APR-99):
DISCHARGE SUMMARY RECEIVED. PATIENT SUSTAINED A FALL AGAINST A RAIL AND SUSTAINED TWO RIB FRACTURES (8TH AND 9TH RIBS). HE WAS TRANSFERRED TO ANOTHER VETERANS ADMINISTRATION HOSPITAL FOR FURTHER EVALUATION. DURING HIS HOSPITALIZATION HE WAS FOUND TO BE HYPOXIC WITH A PO2-44, PH-0.4 HAVING INCREASED BREATHING DIFFICULTIES. WHILE IN THE ACUTE TREATMENT ROOM HE HAD A COFFEE GROUND EMESIS AND HEME - POSITIVE STOOLS. MEDICATIONS LISTED ON ADMISSSION WER NAPROXENE, VALPROATE SODIUM, OLANZAPINE, CLONAZEPAM, FERROUS SULFATE AND PREDNISONE. PAST MEDICAL HISTORY; DIVERTICULAR GI BLEED, AND ULCERATIVE GASTRITI HE WAS INTUBATED AND UNDERWENT LEFT ARTERIAL LINE PLACEMENT. HE EXPERIENCED COFFEE GROUND EMESIS AND A DECREASING HEMATOCRIT. HE WAS TRANSFUSED TWO UNI OF PRBC'S AND TREATED WITH PIPERACILLIN\TAZOBACTAM, CIPRO, BUT CONTINUED TO HAVED ELEVATED TEMPERATURES. BY 3-OCT-98 HE WAS TRANSFERRED TO THE FLOOR, HAVING BEEN EXTUBATED THE PREVIOUS DAY. ZOSYN(R) AND CIPRO WAS CONTINUED TO RULE OUT ASPIRATION PNEUMONIA. AN X-RAY WAS DONE BECAUSE OF COMPLAINTS OF BA PAIN; NEGATIVE FOR FRACTURES. HE WAS PLACED ON (DVT) DEEP VEIN THROMBOSIS PROPHYLAXIS. AN EGD SHOWED ESOPHAGEAL ULCERS AND MEDICATIONS WERE STARTED AS TREATMENT. BIOPSY CONSISTENT WITH BARRET'S DISEASE AND CHEST X-RAY REVEALED A RIGHT PLEURAL EFFUSION. HE CONTINUED TO HAVE FEVERS AND SPUTUM CULTURES GREW NO ORGANISMS. ON 05-OCT-98 A THORACENTESIS WAS PERFORMED WITH AN ASPIRATION OF ABOUT 100CC OF SEROSANGUINOUS FLUID. BLOOD AND CULTURES OF THE PLEURAL FLU WERE NEGATIVE. BECAUSE IT WAS THOUGHT THAT ZOSYN(R) CAUSED DRUG FEVER IT WAS DISCONTINUED. TREATMENT WITH CIPRO AND VANCOMYCIN CONTINUED AND HIS

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R. 7473

D7294.86

AER Number (Version)/ Reporter	Received Date/ Protocol Number	Age/ Sex	Total Daily Dose/ Therapy Dates	Reaction (Onset Date)/ Indication	Outcome/ Case Characteristics	Causality/ Report Type

104

TEMPERATURES NORMALIZED. THERE WERE COMPLAINTS OF HOARSENESS, AND DECREASED HEARING AND CONCERNS ABOUT HIS TEETH. AN ORAL CONSULT AND EAR, NOSE AND THROAT CONSULT WAS DONE. VOCAL CORD PARALYSIS WAS RULED OUT. RECOMMENDATIONS FOR TEETH EXTRACTIONS WERE MADE. BY 16-OCT-98 THE PULSE OXIMETER WAS 96% IN ROOM AIR AND HE WAS DISCHARGED TO HOME. HE UNDERWENT TEETH EXTRACTIONS ON 16-OCT-98. DIAGNOSES; 1. GASTROINTESTINAL BLEED 2. RIB FRACTURES 3. STATUS POST PROBABLE PNEUMONIA 4. STATUS POST RESPIRATORY FAILURE 5. SCHIZOAFFECTIVE DISORDER THE REMAINDER OF THE RECORD DOES NOT ADDRESS HIS PSYCHIATRIC STATUS OR CONTINUATION OF PSYCHIATRIC MEDICATIONS, ESPECIALLY THE USE OF OLANZAPINE WHICH WAS FIRST MENTIONED IN THE DISCHARGE SUMMARY ADMISSION MEDICATION NOTE. HE WAS REPORTEDLY DISCHARGED ON RISPERIDONE, VALPROATE SODIUM, SERTRALINE, RANITIDINE, PREDNISONE TAPER, LANSOPRAZOLE, IPRATROPIUM BROMIDE, FUROSEMIDE, AND SALBUTAMOL.

STILL D O U B L E B L I N D.

ADDITIONAL INFORMATION 07-JUN-99:

Additional information received caused the concomitant medication information to be revised, and patient history was added to case. An autopsy was performed, but results were not provided. Additional information was requested.

Additional information 16-Jun-99:

Additional information received identifies a gap in the study medication dosing schedule on 27-Sep-98. Study medication was not given on that date, but was resumed on 28-Sep-98. Risperidone 3 mg daily was given on 3-Oct-98 through 16-Oct-98.

ADDITIONAL INFORMATION 7-JUL-99:

Autopsy report received: Cause of death streptococcal pneumonia. The rib fractures may have contributed to the infection if the pain from the fractures inhibited effective coughing. See diagnostic data for Final diagnosis. Based on the results of the final diagnosis the following events were added to the case; hematoma, splenic disorder, and renal infarction.

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R. 7474
D7294.87

LIST OF SUBJECTS WHO DISCONTINUED DUE TO AN ADVERSE EVENT

No patients discontinued due to an adverse event for trial RIS-CAN-19.

Seven patients discontinued due to an adverse event from trial RIS-INT-35 for the following reasons:

Investigator	Patient No.	Adverse event
Csernansky	A3702	Akathesia
Delisi	A3836	Akathesia, dyskinesia
Lauriello	A3737	Pregnancy, spontaneous abortion
Pahl	A3793	Exacerbation of psychosis
Targum	A3784	Suicide attempt
Targum	A3785	EPS
Targum	A3787	Somnolence

No patients discontinued due to an adverse event for trial RIS-INT-41.

The following is a list of patients who discontinued due to an adverse event for trial RIS-INT-50:

Investigator	Patient No.	Adverse event
Howanitz	A31031	Nausea, vomiting, dizziness, constipation
Nakra	A31110	Respiratory distress
Samuels	A31356	Exacerbation of psychoses

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LIST OF SUBJECTS WHO DISCONTINUED DUE TO AN ADVERSE EVENT

The following is a list of patients who discontinued due to an adverse event for trial RIS-USA-79:

Investigator	Patient No.	Adverse event
Thomas	0192	Increased auditory hallucinations
Brown	0116	Depression
Logue	0242	Akathesia
Logue	0464	Oculogyric crisis
Yoo	0547	Infection in leg

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LIST OF SUBJECTS WHO DISCONTINUED DUE TO AN ADVERSE EVENT

The following is a list of patients who discontinued due to an adverse event for trial RIS-USA-97:

Investigator	Patient No.	Adverse event
Aman	A3001	Depression with suicidal threats
Aman	A3004	Dystonic reaction
Aman	A3069	Weight gain
Aman	A3123	Weight gain
Aman	A3125	Weight gain
Hagerman	A3026	Extrapyramidal symptoms
Hagerman	A3057	Depressed feelings, worsening behavior problems
Singh	A3119	Separation anxiety
Lesem	A3110	Exacerbation of depression, suicidal ideation

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LIST OF SUBJECTS WHO DISCONTINUED DUE TO AN ADVERSE EVENT

The following is a list of patients who discontinued due to an adverse event for trial RIS-USA-102:

Investigator	Patient No.	Adverse event
Bowden	A30227	Suicidal Ideation due to stress 04/13/99
Brenner	A30029	Moderate Sinus tachycardia & Moderate CPK level increase 12/18/98-12/19/98
Daniel	A30181	Moderate fatigue 1/18/99
Logue	A30010	Increased manic symptoms 10/26/98
Petty	A30140	EPS – Insomnia, restlessness, rigidity 9/05/98
Sajatovic	A30071	Moderate emisis, possible GI bleed 10/01/98
Zimbroff	A30110	Exacerbation of bipolar symptoms with suicidal ideation 7/20/98

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LIST OF SUBJECTS WHO DISCONTINUED DUE TO AN ADVERSE EVENT

The following is a list of patients who discontinued due to an adverse event for trial RIS-USA-113:

Investigator	Patient No.	Adverse event
Baker	30226	Increased psychosis (hospitalization)
Flaum	30157	Increased psychosis (hospitalization)
Knesevich	30275	Increased psychosis (hospitalization)
Plopper	30075	Drug abuse
Wirshing	30115	Pulmonary Carcinoma
Pandurangi	30281	Increased psychosis (hospitalization)
Csernansky	30175	Abnormal Hepatic Function
Mihtar	30200	Increased psychosis
Mihtar	30194	Increased psychosis
Mihtar	30196	Increased psychosis
Manschreck	30333	Increased psychosis/suicidal ideation (hospitalization)
Strakowski	30051	Pregnancy
McEvoy	30036	Agitation/Dizziness/Psychosis

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NEW INFORMATION ON THE DRUG'S ACTIONS

No new information on the drug's action has been obtained during this reporting period.

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NONCLINICAL STUDIES

No new nonclinical safety studies have been reported, planned or are in progress during this reporting period.

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CHEMISTRY, MANUFACTURING AND CONTROLS

Summary of any Significant Manufacturing or Microbiological Changes Made During the Past Year

C, M & C Submissions During Reporting Period

There were no new amendments for Chemistry, Manufacturing and Controls filed to this IND during the reporting period.

Information Update

The following facility is being added to this IND to perform packaging and labeling of risperidone clinical supplies:

Clinical Trial Services (CTS)
2661 Audubon Road
Audubon, Pennsylvania 19407

Reference to Risperdal® Tablets NDA 20-272

As previously cited in this IND, please continue to refer to approved NDA 20-272 for Risperdal® (risperidone) Tablets for additional chemistry, manufacturing and controls information.

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Other Information

GENERAL INVESTIGATIONAL PLAN FOR THE COMING YEAR

Three new clinical trials are scheduled to begin in coming year.

- **RIS-USA-126** is a 12-week, randomized, double-blind, placebo controlled trial to determine the efficacy and safety of risperidone, olanzapine, and placebo for the treatment of psychosis and delusions in subjects with dementia. This study is scheduled to begin in the 2Q00.

- **RIS-INT-67** is a trial designed to evaluate the acute treatment of the manic phase in 400 bipolar patients during a randomized, double-blind, parallel group phase lasting 3 weeks. The primary objective is to assess the efficacy and safety of risperidone in the treatment of the manic phase of bipolar disorder. This trial is scheduled to begin in the 2Q00 and will be conducted in the U.S.

- **RIS-USA-68:** same as 67, except trial will be conducted internationally.

- **RIS-USA-161** is a trial designed to evaluate conduct disorder in children aged 5 to 12 years of normal intelligence. This is a placebo controlled, double-blind trial of 8 weeks duration. The primary objective is to assess the efficacy and safety of risperidone oral solution in the treatment of conduct disorder. This trial is scheduled to begin 2Q00.

- **RIS-USA-160:** pk trial in children/adolescents age 12-16 years. Trial to begin in 2000.

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PHASE I PROTOCOL CHANGES

There were no Phase 1 studies conducted under this IND during the reporting period.

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R. 7486

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SIGNIFICANT MARKETING DEVELOPMENTS

During the past year, risperidone tablets were approved for marketing in the following countries:

Country	Approval Date
Lithuania	February, 1998
Yugoslavia	December, 1997

During the previous reporting period, the following countries also approved risperidone tablets for marketing but were not included in last year's annual report:

Country	Approval Date
Bahrain	October, 1996
Honduras	October, 1996
India	April, 1997
Lebanon	January, 1997
Malaysia	January, 1997
Taiwan	July, 1997
United Arab Emirates	January, 1997

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REVISED INVESTIGATOR'S BROCHURE

A copy of the revised Investigator's Brochure is attached. Recent amendments, dated July 4, 1999, April 15, 1999, March 11, 1999 and November 2, 26, 1998, and July 1, 25, 1999 are attached.

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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)748-0016 HID-SC 232

D7336.1

SOUTH CAROLINA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
DRUG UTILIZATION REVIEW PROGRAM

PRESCRIBER RESPONSE

All information used to generate the enclosed letter, including Prescriber identification, was obtained from Pharmacy Claims Data. If there appears to be an error in the information provided, please note the discrepancy. Thank you for your cooperation.

1. This patient is under my care:

_____ I have reviewed the information and will continue without change.
_____ however, I did not prescribe the following medication(s)_____.
_____ and has an appointment to discuss drug therapy.
_____ however, has not seen me recently.
_____ however, I was not aware of other prescribers.
_____ I have reviewed the information and modified drug therapy.
_____ I have not modified drug therapy because benefits outweigh the risks.
_____ I have tried to modify therapy, however the patient refuses to change.
_____ I have tried to modify therapy, however symptoms reoccurred.

2. This patient is not under my care:

_____ however, I did prescribe medication while covering for other MD or in the ER.
_____ but has previously been a patient of mine.
_____ because the patient recently expired.
_____ and has never been under my care.

3. I have reviewed the enclosed information and found it:
_____ very useful_____ useful_____ neutral_____ somewhat useful_____ not useful.

4. Please check here if you wish to receive reference information on the identified problem___.(Please provide a fax number if available_____-_____-_____.)

Comments:_____
_____
_____
_____

ENGLES, TODD H Case# 259
Letter Type 500
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.
586

Administered by Health Information Designs, Inc.
1550 Pumphrey Ave.
Auburn, AL 36832-9956
(800)225-6998 x 37 Fax(800)748-0016HID-SC 233

Health Information Designs, Inc.

South Carolina Department Of Health And Human Services
Drug Utilization Review Program
Patient Drug History Profile

9/19/2002

[redacted] Case Number: 259

[redacted]

HID-SC 229

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	019346
07/10/02	6646752	LOTREL	5-20MG	30	30	736224	00000195
07/10/02	6646750	SUCRALFATE	1G	90	30	736224	00000195
07/01/02	6644694	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	6643602	SUCRALFATE	1G	100	33	736224	005408

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DEFENDANT'S EXHIBIT

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Health Information Designs, Inc.

South Carolina Department Of Health And Human Services
Drug Utilization Review Program
Patient Drug History Profile

9/19/2002

[redacted] [redacted] [redacted] [redacted] Case Number: 259

Date of Service	NT 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
05/03/02	6644895	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	6644564	DOXYCYCLINE HICLATE	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
01/08/02	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	31	761274	005408
11/02/01	6001817	PROZAC	40MG	30	30	761274	005408

HID-SC 230

Health Information Designs, Inc.

South Carolina Department Of Health And Human Services
Drug Utilization Review Program
Patient Drug History Profile

9/18/2002

[redacted] [redacted] [redacted] [redacted] Case Number: 259

Date of Service	RX 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	6001691	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

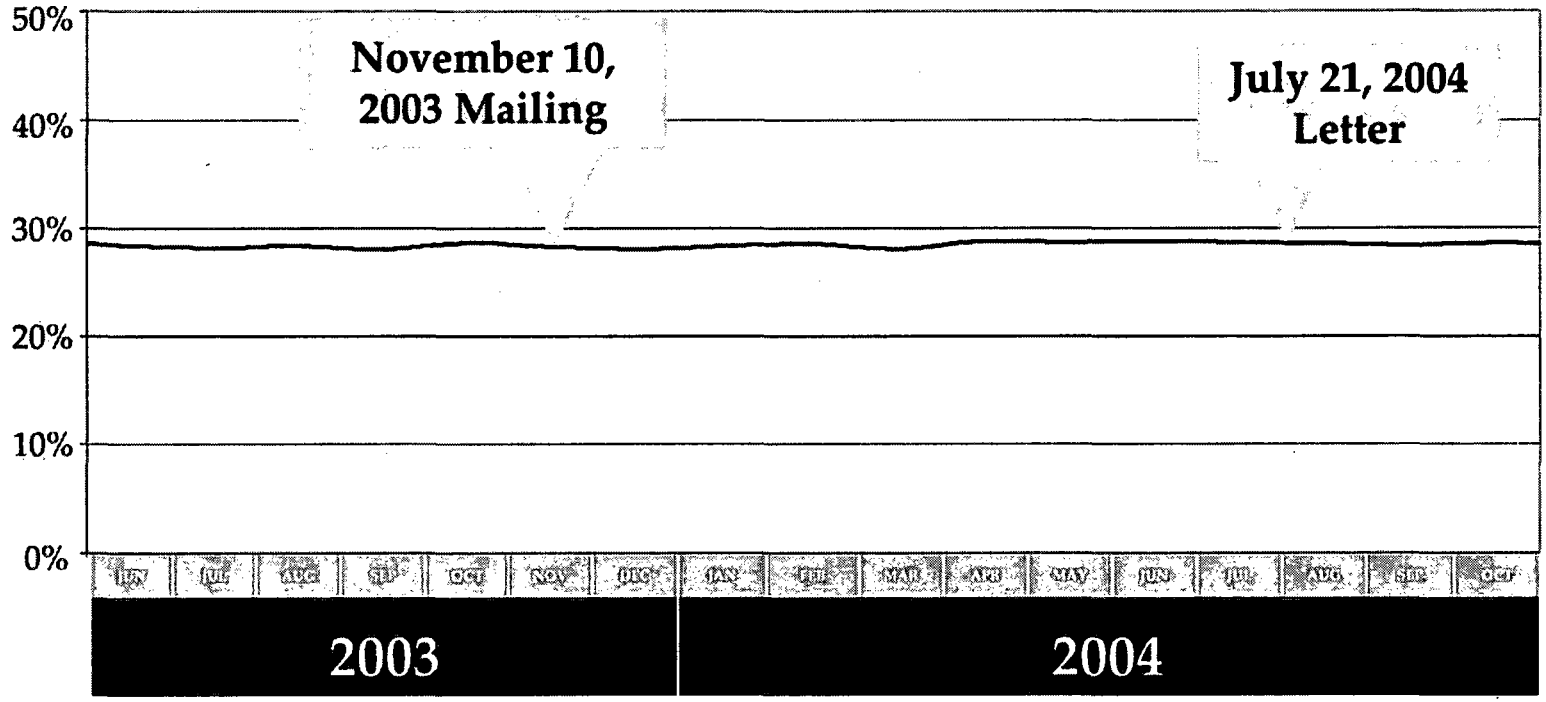
HID-SC 231

[redacted]

Current Date of Service	ICD Code	Diagnosis Description	Reference Date	Number of Occurrences Since Reference Date
09/02/02	29635	MAJOR DEPRESSIVE AFFECTIVE DISORDER RECURRENT EPISODE IN PARTIAL OR UNSPECIFIED REMISSION	07/26/01	6

Risperdal Prescriptions: No Change

South Carolina Medicaid & SHP Claims Data, Jun. 2003 – Oct. 2004



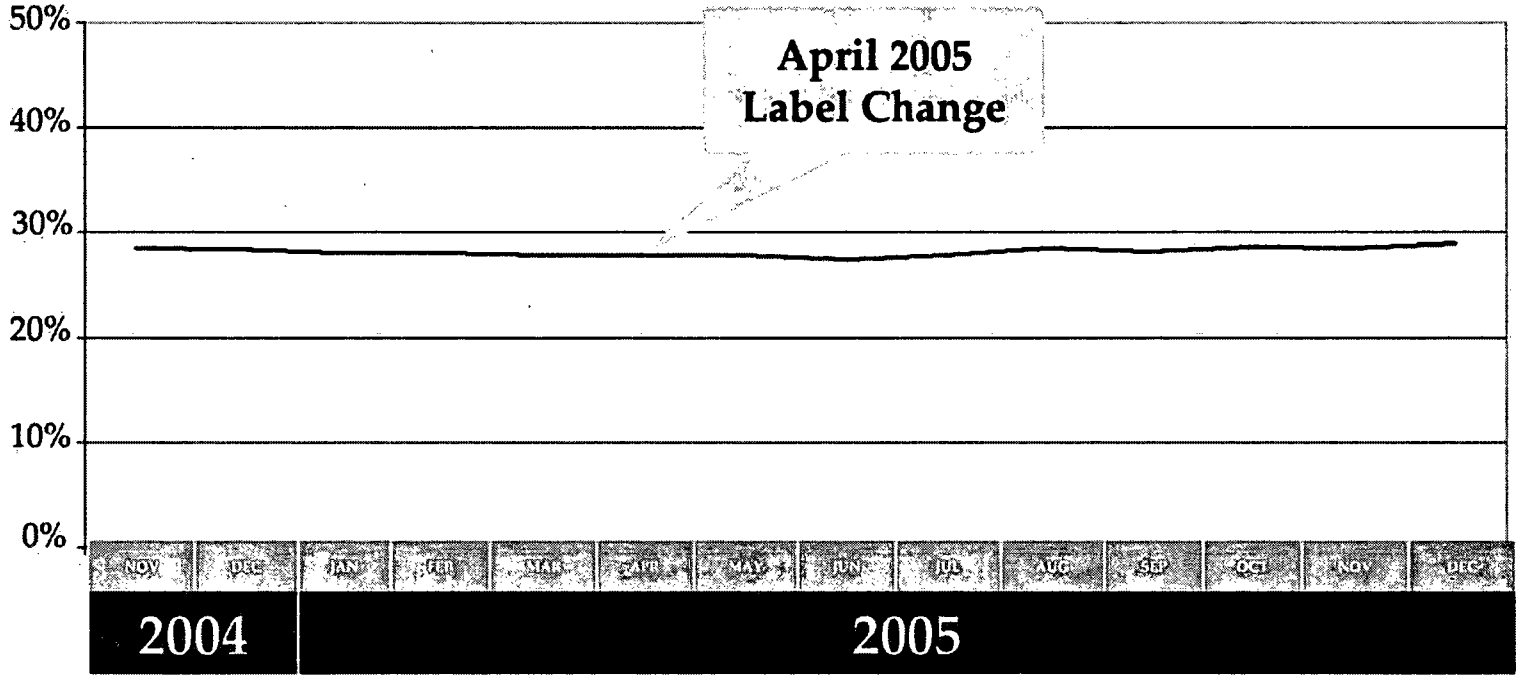
Source: South Carolina Medicaid and State Health Plan Claims Databases.

R. 7494

D7337.1

Risperdal Prescriptions: No Change

South Carolina Medicaid & SHP Claims Data, Nov. 2004 – Dec. 2005



Source: South Carolina Medicaid and State Health Plan Claims Databases.

R. 7495

D7338.1

PV 5199 AMP

ZYPREXA®
Olanzapine Tablets

ZYPREXA® ZYDIS®
Olanzapine Orally Disintegrating Tablets

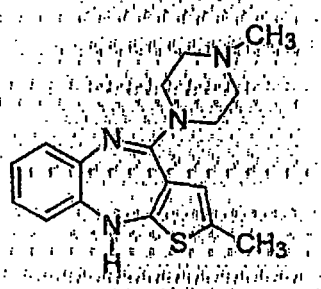
ZYPREXA® IntraMuscular
Olanzapine for Injection

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis — Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis (*see* WARNINGS).

DESCRIPTION

ZYPREXA (olanzapine) is a psychotropic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44. The chemical structure is:



Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8 µmol), 5 mg (16 µmol), 7.5 mg (24 µmol), 10 mg (32 µmol), 15 mg (48 µmol), or 20 mg (64 µmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5, 7.5, and 10 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

DEFENDANT'S EXHIBIT NO. 2 ID

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 μmol), 10 mg (32 μmol), 15 mg (48 μmol) or 20 mg (64 μmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben and sodium propyl paraben.

ZYPREXA IntraMuscular (olanzapine for injection) is intended for intramuscular use only.

Each vial provides for the administration of 10 mg (32 μmol) olanzapine with inactive ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_6$, (K_i=4, 11, and 5 nM, respectively), dopamine D_{1-4} (K_i=11-31 nM), histamine H_1 (K_i=7 nM), and adrenergic α_1 receptors (K_i=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ (K_i=57 nM) and muscarinic M_{1-5} (K_i=73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds weakly to $GABA_A$, BZD, and β adrenergic receptors (K_i>10 μM).

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 ($5HT_2$) antagonism. The mechanism of action of olanzapine in the treatment of acute manic episodes associated with Bipolar I Disorder is unknown.

Antagonism at receptors other than dopamine and $5HT_2$ may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic-like effects. Olanzapine's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Oral Administration

Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about one week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age (*see* Special Populations).

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α_1-acid glycoprotein.

Metabolism and Elimination — Following a single oral dose of ^{14}C labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4′-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Intramuscular Administration

ZYPREXA IntraMuscular results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a 5 mg dose of intramuscular olanzapine for injection produces, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5 mg dose of oral olanzapine. Area under the curve achieved after an intramuscular dose is similar to that achieved after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are qualitatively similar to metabolic profiles after oral administration.

Special Populations

Renal Impairment — Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment — Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Age — In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (>65 years) than in non-elderly subjects (≤65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity (*see* DOSAGE AND ADMINISTRATION).

Gender — Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status — Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Race — In vivo studies have shown that exposures are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine (*see* DOSAGE AND ADMINISTRATION).

For specific information about the pharmacology of lithium or valproate, refer to the CLINICAL PHARMACOLOGY section of the package inserts for these other products.

CLINICAL EFFICACY DATA

Schizophrenia

The efficacy of oral olanzapine in the treatment of schizophrenia was established in 2 short-term (6-week) controlled trials of inpatients who met DSM III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in one of the two trials, but this trial did not compare these two drugs on the full range of clinically relevant doses for both.

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 scales were employed; these included the 30-item Positive and Negative Symptoms Scale (PANSS), in which are embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative subscale or SANS; and CGI Severity. The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=149) involving two fixed olanzapine doses of 1 and 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis cluster, on the PANSS Negative subscale, and on CGI Severity.

(2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine (5 ± 2.5 mg/day, 10 ± 2.5 mg/day, and 15 ± 2.5 mg/day) on a once daily schedule, the two highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest olanzapine dose group was superior to placebo on the SANS. There was no clear advantage for the high dose group over the medium dose group.

Examination of population subsets (race and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine during open label treatment for at least 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms of increases in BPRS positive symptoms or hospitalization, was planned for 12 months, however, criteria were met for stopping the trial early due to an excess of placebo relapses compared to olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in patients stabilized for approximately 8 weeks and followed for an observation period of up to 8 months.

Bipolar Disorder

Monotherapy — The efficacy of oral olanzapine in the treatment of acute manic or mixed episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome.

(2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar disorder who had responded during an initial open-label treatment phase for about two weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response during the open-label phase was defined by having a decrease of the Y-MRS total score to ≤12 and HAM-D 21 to ≤8. Relapse during the double-blind phase was defined as an increase of the Y-MRS or HAM-D 21 total score to ≥15, or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

Combination Therapy — The efficacy of oral olanzapine with concomitant lithium or valproate in the treatment of acute manic episodes was established in two controlled trials in patients who

met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course. The results of the trials follow:

(1) In one 6-week placebo-controlled combination trial, 175 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 6-week placebo-controlled combination trial, 169 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

Agitation Associated with Schizophrenia and Bipolar I Mania

The efficacy of intramuscular olanzapine for injection for the treatment of agitation was established in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated inpatients from two diagnostic groups: schizophrenia and Bipolar I Disorder (manic or mixed episodes). Each of the trials included a single active comparator treatment arm of either haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar mania study). Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of ≥14 on the five items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness and excitement items) with at least one individual item score ≥4 using a 1-7 scoring system (1=absent, 4=moderate, 7=extreme). In the studies, the mean baseline PANSS Excited Component score was 18.4, with scores ranging from 13 to 32 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to three injections during the 24 hour IM treatment periods; however, patients could not receive the second injection until after the initial 2 hour period when the primary efficacy measure was assessed. The results of the trials follow:

(1) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=270), four fixed intramuscular olanzapine for injection doses of 2.5 mg, 5 mg, 7.5 mg and 10 mg were evaluated. All doses were statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consistent for the three highest doses. There were no significant pairwise differences for the 7.5 and 10 mg doses over the 5 mg dose.

(2) In a second placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=311), one fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

(3) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for Bipolar I Disorder (and currently displaying an acute manic or mixed episode with or without psychotic features) (n=201), one fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

INDICATIONS AND USAGE

Schizophrenia

Oral ZYPREXA is indicated for the treatment of schizophrenia.

The efficacy of ZYPREXA was established in short-term (6-week) controlled trials of schizophrenic inpatients (*see* CLINICAL EFFICACY DATA).

The effectiveness of oral ZYPREXA at maintaining a treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for a period of up to 8 months has been demonstrated in a placebo-controlled trial (*see* CLINICAL EFFICACY DATA). Nevertheless, the physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

Bipolar Disorder

Acute Monotherapy — Oral ZYPREXA is indicated for the treatment of acute mixed or manic episodes associated with Bipolar I Disorder.

The efficacy of ZYPREXA was established in two placebo-controlled trials (one 3-week and one 4-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (*see* CLINICAL EFFICACY DATA).

Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA after achieving a responder status for an average duration of two weeks was demonstrated in a controlled trial (*see* CLINICAL EFFICACY DATA). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

Combination Therapy — The combination of oral ZYPREXA with lithium or valproate is indicated for the short-term treatment of acute mixed or manic episodes associated with Bipolar I Disorder.

The efficacy of ZYPREXA in combination with lithium or valproate was established in two placebo-controlled (6-week) trials with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (*see* CLINICAL EFFICACY DATA).

Agitation Associated with Schizophrenia and Bipolar I Mania

ZYPREXA IntraMuscular is indicated for the treatment of agitation associated with schizophrenia and bipolar I mania. "Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation.

The efficacy of ZYPREXA IntraMuscular for the treatment of agitation associated with schizophrenia and bipolar I mania was established in 3 short-term (24 hours) placebo-controlled trials in agitated inpatients with schizophrenia or Bipolar I Disorder (manic or mixed episodes) (*see* CLINICAL EFFICACY DATA).

CONTRAINDICATIONS

ZYPREXA is contraindicated in patients with a known hypersensitivity to the product.

For specific information about the contraindications of lithium or valproate, refer to the CONTRAINDICATIONS section of the package inserts for these other products.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis — **Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis (*see* BOX WARNING).**

In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively).

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis — Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia — Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. 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. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the two highest serum concentrations was 15.0 mg/dL.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (patients diagnosed with diabetes mellitus or related adverse events, patients treated with anti-diabetic agents, patients with a baseline random glucose level ≥200 mg/dL, and/or a baseline fasting glucose level ≥126 mg/dL).

These patients had a statistically significantly greater mean increase in HbA_{1c} compared to placebo. In patients with baseline normal fasting glucose levels (<100 mg/dL), 2.2% (N=543) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 3.4% (N=293) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and ≤126 mg/dL), 17.4% (N=178) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 11.5% (N=96) of those treated with placebo.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a statistically significantly greater mean change in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). In patients with baseline normal fasting glucose levels (<100 mg/dL), zero out of 124 (0%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 1 out of 53 (1.9%) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 2 out of 14 (14.3%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus zero out of 13 (0%) of those treated with placebo.

Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100-126 mg/dL, non-fasting 140-200 mg/dL). Patients taking olanzapine should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Hyperlipidemia — Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using olanzapine, is advised.

Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had statistically significant increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at

baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse events, patients treated with lipid lowering agents, or patients with high baseline lipid levels. Table 1 shows categorical changes in fasting lipid values.

Table 1
Changes in Fasting Lipids Values
from Adult Placebo-Controlled Olanzapine Monotherapy Studies
with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	745	39.6%[a]
		Placebo	402	26.1%
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Olanzapine	457	9.2%[a]
		Placebo	251	4.4%
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	135	39.3%[a]
		Placebo	65	20.0%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	745	21.6%[a]
		Placebo	402	9.5%
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Olanzapine	392	2.8%
		Placebo	207	2.4%
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Olanzapine	222	23.0%[a]
		Placebo	112	12.5%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	536	23.7%[a]
		Placebo	304	14.1%
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Olanzapine	154	0%
		Placebo	82	1.2%
	Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL)	Olanzapine	302	10.6%
		Placebo	173	8.1%

[a] Statistically significant compared to placebo.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the mean increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), for fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Table 2 shows categorical changes in fasting lipid values in adolescent patients.

Table 2
Changes in Fasting Lipids Values
from Adolescent Placebo-Controlled Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
	Increase by ≥50 mg/dL	Olanzapine	138	37.0%[a]

Fasting Triglycerides		Placebo	66	15.2%
	Normal to High (<90 mg/dL to >130 mg/dL)	Olanzapine	67	26.9%
		Placebo	28	10.7%
	Borderline to High (≥90 mg/dL and ≤130 mg/dL to >130 mg/dL)	Olanzapine	37	59.5%
		Placebo	17	35.3%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	138	14.5%[a]
		Placebo	66	4.5%
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	87	6.9%
		Placebo	43	2.3%
	Borderline to High (≥170 mg/dL and <200 mg/dL to ≥240 mg/dL)	Olanzapine	36	38.9%[a]
		Placebo	13	7.7%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	137	17.5%
		Placebo	63	11.1%
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	98	5.1%
		Placebo	44	4.5%
	Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	29	48.3%[a]
		Placebo	9	0%

[a] Statistically significant compared to placebo.

Weight Gain — Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight.

Olanzapine Monotherapy in Adults — In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg, which was statistically significantly different compared to an average 0.3 kg weight loss in placebo-treated patients with a median exposure of 6 weeks; 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight, which was statistically significantly different compared to 3% of placebo-treated patients, with a median exposure of 8 weeks; 4.2% of olanzapine-treated patients gained at least 15% of their baseline weight, which was statistically significantly different compared to 0.3% of placebo-treated patients, with a median exposure of 12 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients and in zero placebo-treated patients.

During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

Table 3 includes data on weight gain with olanzapine pooled from 68 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 3
Weight Gain with Olanzapine Use

Amount Gained kg (lb)	6 Weeks (N=2976) (%)	6 Months (N=1536) (%)	12 Months (N=778) (%)	24 Months (N=422) (%)
≤0	27	21	20	22
0-5 (0-11 lb)	57	34	25	22
5-10 (11-22 lb)	15	26	25	22
10-15 (22-33 lb)	2	12	16	18

>15 (>33 lb)	0	6	14	16

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 4 placebo-controlled olanzapine monotherapy studies of adolescent patients (ages 13 to 17 years), including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine-treated patients gained an average of 4.6 kg, which was statistically significantly different compared to an average of 0.3 kg in placebo-treated patients, with a median exposure of 3 weeks; 40.6% of olanzapine-treated patients gained at least 7% of their baseline body weight, which was statistically significantly different compared to 9.8% of placebo-treated patients, with a median exposure of 4 weeks; 7.1% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 2.7% of placebo-treated patients, with a median exposure of 19 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories, but mean changes in weight were greater in adolescents with BMI categories above normal at baseline. Discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to zero placebo-treated patients.

During long-term continuation therapy with olanzapine, 65% of olanzapine-treated patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 7.4 kg.

Neuroleptic Malignant Syndrome (NMS) — A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including olanzapine. 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 exclude 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 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, olanzapine 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 (1) who suffer from a chronic illness that 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 olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

For specific information about the warnings of lithium or valproate, refer to the WARNINGS section of the package inserts for these other products.

PRECAUTIONS

General

Hemodynamic Effects — Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonistic properties. Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in non-agitated patients with schizophrenia in which the safety and tolerability of intramuscular olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (i.e., decrease ≥30 mmHg) (*see* DOSAGE AND ADMINISTRATION). Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the events occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs.

For oral olanzapine therapy, the risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD (*see* DOSAGE AND ADMINISTRATION). A more gradual titration to the target dose should be considered if hypotension occurs.

For intramuscular olanzapine for injection therapy, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation.

Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression (*see* Drug Interactions). Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine has not been studied and is therefore not recommended. If use of intramuscular olanzapine in combination with parenteral benzodiazepines is considered, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

Seizures — During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hyperprolactinemia — As with other drugs that antagonize dopamine D_2 receptors, olanzapine elevates prolactin levels, and a modest 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 of this type. 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 mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats (*see* Carcinogenesis). However, neither clinical studies nor epidemiologic studies 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.

Transaminase Elevations — In placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. In two of these patients, liver enzymes decreased toward normal despite continued treatment and in two others, enzymes decreased upon discontinuation of olanzapine. In the remaining two patients, one, seropositive for hepatitis C, had persistent enzyme elevation for four months after discontinuation, and the other had insufficient follow-up to determine if enzymes normalized.

Within the larger premarketing database of about 2400 patients with baseline SGPT ≤90 IU/L, the incidence of SGPT elevation to >200 IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued.

Among 2500 patients in oral olanzapine clinical trials, about 1% (23/2500) discontinued treatment due to transaminase increases.

Rare postmarketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the postmarketing period.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of transaminases is recommended in patients with significant hepatic disease (*see* Laboratory Tests).

Potential for Cognitive and Motor Impairment — Somnolence was a commonly reported adverse event associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse event was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

Since olanzapine 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 olanzapine therapy does not affect them adversely.

Body Temperature Regulation — Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

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 disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide — The possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine 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 olanzapine in patients with certain concomitant systemic illnesses (*see* Renal Impairment and Hepatic Impairment *under* CLINICAL PHARMACOLOGY, Special Populations) is limited.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with olanzapine, olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse events possibly related to cholinergic antagonism. Such adverse events were not often the basis for discontinuations from olanzapine, but olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus.

In five placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse events were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse events was significantly greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to

treat elderly patients with dementia-related psychosis, vigilance should be exercised (*see* BOX WARNING *and* WARNINGS).

Olanzapine 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 premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients (*see* Hemodynamic Effects).

For specific information about the precautions of lithium or valproate, refer to the PRECAUTIONS section of the package inserts for these other products.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe olanzapine:

Hyperglycemia — Patients should be advised of the potential risk of hyperglycemia-related adverse events. Patients should be monitored regularly for worsening of glucose control.

Weight Gain — Patients should be counseled that olanzapine is associated with weight gain. Patients should have their weight monitored regularly.

Orthostatic Hypotension — Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or alcohol (*see* Drug Interactions).

Interference with Cognitive and Motor Performance — Because olanzapine 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 olanzapine 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 with olanzapine.

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

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 olanzapine.

Heat Exposure and Dehydration — Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Phenylketonurics — ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5, 10, 15, or 20 mg tablet, respectively).

Laboratory Tests

Periodic assessment of transaminases is recommended in patients with significant hepatic disease (*see* Transaminase Elevations).

Drug Interactions

The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, olanzapine may enhance the effects of certain antihypertensive agents.

Olanzapine may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on Olanzapine — Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 could potentially inhibit olanzapine clearance. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, a dosage increase (for induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs.

Charcoal — The administration of activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

Cimetidine and Antacids — Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

Carbamazepine — Carbamazepine therapy (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Ethanol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics.

Fluoxetine — Fluoxetine (60 mg single dose or 60 mg daily for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended.

Fluvoxamine — Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine Cmax following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

Warfarin — Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics.

Effect of Olanzapine on Other Drugs — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium.

Valproate — Studies in vitro using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. In vivo administration of olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam and its active metabolite N-desmethyldiazepam, ethanol, or biperiden. However, the co-administration of either diazepam or ethanol with olanzapine potentiated the orthostatic

hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

Lorazepam — Administration of intramuscular lorazepam (2 mg) 1 hour after intramuscular olanzapine for injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone (*see* Hemodynamic Effects).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8-5 times the maximum recommended human daily oral dose on a mg/m^2 basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily oral dose on a mg/m^2 basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human daily oral dose on a mg/m^2 basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily oral dose on a mg/m^2 basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the maximum recommended human daily oral dose on a mg/m^2 basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the maximum recommended human daily oral dose on a mg/m^2 basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland 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 finding of prolactin mediated endocrine tumors in rodents is unknown (*see* Hyperprolactinemia *under* PRECAUTIONS, General).

Mutagenesis — No evidence of mutagenic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Impairment of Fertility — In an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the maximum recommended human daily oral dose on a mg/m^2 basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the maximum recommended human daily oral dose on a mg/m^2 basis). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a mg/m^2 basis); therefore olanzapine may produce a delay in ovulation.

Pregnancy

Pregnancy Category C — In oral reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily oral dose on a mg/m^2 basis, respectively) no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the maximum recommended human daily oral dose on a mg/m^2 basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily oral dose on a mg/m^2 basis). In an oral rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the maximum recommended human daily oral dose on a mg/m^2 basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled trials with olanzapine in pregnant females. Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery in humans is unknown.

Nursing Mothers

In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose. It is recommended that women receiving olanzapine should not breast-feed.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the 2500 patients in premarketing clinical studies with oral olanzapine, 11% (263) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient (*see* BOX WARNING, WARNINGS, PRECAUTIONS, *and* DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The information below is derived from a clinical trial database for olanzapine consisting of 8661 patients with approximately 4165 patient-years of exposure to oral olanzapine and 722 patients with exposure to intramuscular olanzapine for injection. This database includes: (1) 2500 patients who participated in multiple-dose oral olanzapine premarketing trials in

schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in oral olanzapine premarketing bipolar mania trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in an oral olanzapine trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; (4) 5788 patients from 88 additional oral olanzapine clinical trials as of December 31, 2001; and (5) 722 patients who participated in intramuscular olanzapine for injection premarketing trials in agitated patients with schizophrenia, Bipolar I Disorder (manic or mixed episodes), or dementia. In addition, information from the premarketing 6-week clinical study database for olanzapine in combination with lithium or valproate, consisting of 224 patients who participated in bipolar mania trials with approximately 22 patient-years of exposure, is included below.

The conditions and duration of treatment with olanzapine varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely, dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar mania or agitation. However, this information is also generally applicable to bipolar mania and agitation.

Adverse events during 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 events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used initially to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The reported events do not include those event terms that were so general as to be uninformative. Events listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the events occurred during treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

The prescriber should be aware that the figures in the tables and tabulations 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 that prevailed in the clinical trials. 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 adverse event incidence in the population studied.

Incidence of Adverse Events in Short-Term, Placebo-Controlled and Combination Trials

The following findings are based on premarketing trials of (1) oral olanzapine for schizophrenia, bipolar mania, a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease, and premarketing combination trials, and (2) intramuscular olanzapine for injection in agitated patients with schizophrenia or bipolar mania.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Schizophrenia — Overall, there was no difference in the incidence of discontinuation due to adverse events (5% for oral olanzapine vs 6% for placebo). However, discontinuations due to increases in SGPT were considered to be drug related (2% for oral olanzapine vs 0% for placebo) (*see* PRECAUTIONS).

Bipolar Mania Monotherapy — Overall, there was no difference in the incidence of discontinuation due to adverse events (2% for oral olanzapine vs 2% for placebo).

Agitation — Overall, there was no difference in the incidence of discontinuation due to adverse events (0.4% for intramuscular olanzapine for injection vs 0% for placebo).

Adverse Events Associated with Discontinuation of Treatment in Short-Term Combination Trials

Bipolar Mania Combination Therapy — In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse events were 11% for the combination of oral olanzapine with lithium or valproate compared to 2% for patients who remained on lithium or valproate monotherapy. Discontinuations with the combination of oral olanzapine and lithium or valproate that occurred in more than 1 patient were: somnolence (3%), weight gain (1%), and peripheral edema (1%).

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials

The most commonly observed adverse events associated with the use of oral olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of Oral Olanzapine in 6-Week Trials — SCHIZOPHRENIA

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=248)	Placebo (N=118)
Postural hypotension	5	2
Constipation	9	3
Weight gain	6	1
Dizziness	11	4
Personality disorder	8	4
Akathisia	5	1

Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

Common Treatment-Emergent Adverse Events Associated with the Use of Oral Olanzapine in 3-Week and 4-Week Trials — BIPOLAR MANIA

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=125)	Placebo (N=129)

Asthenia	15	6
Dry mouth	22	7
Constipation	11	5
Dyspepsia	11	5
Increased appetite	6	3
Somnolence	35	13
Dizziness	18	6
Tremor	6	3

There was one adverse event (somnolence) observed at an incidence of 5% or greater among intramuscular olanzapine for injection-treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) during the placebo-controlled premarketing studies. The incidence of somnolence during the 24 hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar mania was 6% for intramuscular olanzapine for injection and 3% for placebo.

Adverse Events Occurring at an Incidence of 2% or More Among Oral Olanzapine-Treated Patients in Short-Term, Placebo-Controlled Trials

Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 2% or more of patients treated with oral olanzapine (doses ≥2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of placebo-controlled trials.

Table 4
Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Clinical Trials[1]
with Oral Olanzapine

	Percentage of Patients Reporting Event	
Body System/Adverse Event	**Olanzapine (N=532)**	**Placebo (N=294)**
Body as a Whole		
Accidental injury	12	8
Asthenia	10	9
Fever	6	2
Back pain	5	2
Chest pain	3	1
Cardiovascular System		
Postural hypotension	3	1
Tachycardia	3	1
Hypertension	2	1
Digestive System		
Dry mouth	9	5
Constipation	9	4
Dyspepsia	7	5
Vomiting	4	3
Increased appetite	3	2
Hemic and Lymphatic System		
Ecchymosis	5	3
Metabolic and Nutritional Disorders		
Weight gain	5	3
Peripheral edema	3	1
Musculoskeletal System		

Extremity pain (other than joint)	5	3
Joint pain	5	3
Nervous System		
Somnolence	29	13
Insomnia	12	11
Dizziness	11	4
Abnormal gait	6	1
Tremor	4	3
Akathisia	3	2
Hypertonia	3	2
Articulation impairment	2	1
Respiratory System		
Rhinitis	7	6
Cough increased	6	3
Pharyngitis	4	3
Special Senses		
Amblyopia	3	2
Urogenital System		
Urinary incontinence	2	1
Urinary tract infection	2	1

Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, agitation, anorexia, anxiety, apathy, confusion, depression, diarrhea, dysmenorrhea (denominator used was for females only [olanzapine, N=201; placebo, N=114]), hallucinations, headache, hostility, hyperkinesia, myalgia, nausea, nervousness, paranoid reaction, personality disorder (COSTART term for designating non-aggressive objectionable behavior), rash, thinking abnormal, weight loss.

Commonly Observed Adverse Events in Short-Term Combination Trials

In the bipolar mania combination placebo-controlled trials, the most commonly observed adverse events associated with the combination of olanzapine and lithium or valproate (incidence of ≥5% and at least twice placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of Oral Olanzapine in 6-Week Combination Trials — BIPOLAR MANIA

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine with lithium or valproate (N=229)	Placebo with lithium or valproate (N=115)
Dry mouth	32	9
Weight gain	26	7
Increased appetite	24	8
Dizziness	14	7
Back pain	8	4
Constipation	8	4
Speech disorder	7	1
Increased salivation	6	2
Amnesia	5	2
Paresthesia	5	2

Adverse Events Occurring at an Incidence of 2% or More Among Oral Olanzapine-Treated Patients in Short-Term Combination Trials

Table 5 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 2% or more of patients treated with the combination of olanzapine (doses ≥5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials.

Table 5
Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Combination Clinical Trials[1]
with Oral Olanzapine

	Percentage of Patients Reporting Event	
Body System/Adverse Event	Olanzapine with lithium or valproate (N=229)	Placebo with lithium or valproate (N=115)
Body as a Whole		
Asthenia	18	13
Back pain	8	4
Accidental injury	4	2
Chest pain	3	2
Cardiovascular System		
Hypertension	2	1
Digestive System		
Dry mouth	32	9
Increased appetite	24	8
Thirst	10	6
Constipation	8	4
Increased salivation	6	2
Metabolic and Nutritional Disorders		
Weight gain	26	7
Peripheral edema	6	4
Edema	2	1
Nervous System		
Somnolence	52	27
Tremor	23	13
Depression	18	17
Dizziness	14	7
Speech disorder	7	1
Amnesia	5	2
Paresthesia	5	2
Apathy	4	3
Confusion	4	1
Euphoria	3	2
Incoordination	2	0
Respiratory System		
Pharyngitis	4	1
Dyspnea	3	1
Skin and Appendages		
Sweating	3	1
Acne	2	0
Dry skin	2	0
Special Senses		
Amblyopia	9	5

Abnormal vision	2	0
Urogenital System		
Dysmenorrhea[2]	2	0
Vaginitis[2]	2	0

[1] Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, abnormal dreams, abnormal ejaculation, agitation, akathisia, anorexia, anxiety, arthralgia, cough increased, diarrhea, dyspepsia, emotional lability, fever, flatulence, flu syndrome, headache, hostility, insomnia, libido decreased, libido increased, menstrual disorder (denominator used was for females only [olanzapine, N=128; placebo, N=51]), myalgia, nausea, nervousness, pain, paranoid reaction, personality disorder, rash, rhinitis, sleep disorder, thinking abnormal, vomiting.

[2] Denominator used was for females only (olanzapine, N=128; placebo, N=51).

For specific information about the adverse reactions observed with lithium or valproate, refer to the ADVERSE REACTIONS section of the package inserts for these other products.

Adverse Events Occurring at an Incidence of 1% or More Among Intramuscular Olanzapine for Injection-Treated Patients in Short-Term, Placebo-Controlled Trials

Table 6 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 1% or more of patients treated with intramuscular olanzapine for injection (dose range of 2.5-10 mg/injection) and with incidence greater than placebo who participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar mania.

Table 6
Treatment-Emergent Adverse Events:
Incidence in Short-Term (24 Hour), Placebo-Controlled Clinical Trials with Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia or Bipolar Mania[1]

	Percentage of Patients Reporting Event	
Body System/Adverse Event	**Olanzapine (N=415)**	**Placebo (N=150)**
Body as a Whole		
Asthenia	2	1
Cardiovascular System		
Hypotension	2	0
Postural hypotension	1	0
Nervous System		
Somnolence	6	3
Dizziness	4	2
Tremor	1	0

[1] Events reported by at least 1% of patients treated with olanzapine for injection, except the following events which had an incidence equal to or less than placebo: agitation, anxiety, dry mouth, headache, hypertension, insomnia, nervousness.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

Extrapyramidal Symptoms — The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during acute therapy in a controlled clinical trial comparing oral olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia.

Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence

in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase*

	Percentage of Patients Reporting Event			
	Placebo	Olanzapine 5 ± 2.5 mg/day	Olanzapine 10 ± 2.5 mg/day	Olanzapine 15 ± 2.5 mg/day
Parkinsonism[1]	15	14	12	14
Akathisia[2]	23	16	19	27

* No statistically significant differences.
1 Percentage of patients with a Simpson-Angus Scale total score >3.
2 Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse events during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia.

Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Events Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase

	Percentage of Patients Reporting Event			
	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Dystonic events[1]	1	3	2	3
Parkinsonism events[2]	10	8	14	20
Akathisia events[3]	1	5	11*	10*
Dyskinetic events[4]	4	0	2	1
Residual events[5]	1	2	5	1
Any extrapyramidal event	16	15	25	32*

* Statistically significantly different from placebo.
1 Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.
2 Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.
3 Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.
4 Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.
5 Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during controlled clinical trials comparing fixed doses of intramuscular olanzapine for injection with placebo in agitation. Patients in each dose group could receive up to three injections during the trials (*see* CLINICAL EFFICACY DATA). Patient assessments were conducted during the 24 hours following the initial dose of intramuscular olanzapine for injection. There were no statistically significant differences from placebo.

Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial

of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia*

	Percentage of Patients Reporting Event				
	Placebo	Olanzapine IM 2.5 mg	Olanzapine IM 5 mg	Olanzapine IM 7.5 mg	Olanzapine IM 10 mg
Parkinsonism[1]	0	0	0	0	3
Akathisia[2]	0	0	5	0	0

* No statistically significant differences.
1 Percentage of patients with a Simpson-Angus total score >3.
2 Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse events in the same controlled clinical trial comparing fixed doses of intramuscular olanzapine for injection with placebo in agitated patients with schizophrenia. There were no statistically significant differences from placebo.

Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Events Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia*

	Percentage of Patients Reporting Event				
	Placebo (N=45)	Olanzapine IM 2.5 mg (N=48)	Olanzapine IM 5 mg (N=45)	Olanzapine IM 7.5 mg (N=46)	Olanzapine IM 10 mg (N=46)
Dystonic events[1]	0	0	0	0	0
Parkinsonism events[2]	0	4	2	0	0
Akathisia events[3]	0	2	0	0	0
Dyskinetic events[4]	0	0	0	0	0
Residual events[5]	0	0	0	0	0
Any extrapyramidal event	0	4	2	0	0

* No statistically significant differences.
1 Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.
2 Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.
3 Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.
4 Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.
5 Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

Other Adverse Events — The following table addresses dose relatedness for other adverse events using data from a schizophrenia trial involving fixed dosage ranges of oral olanzapine. It enumerates the percentage of patients with treatment-emergent adverse events for the three fixed-dose range groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and the table includes only those adverse events for which there was a statistically significant trend.

Adverse Event	Percentage of Patients Reporting Event			
	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Asthenia	15	8	9	20
Dry mouth	4	3	5	13
Nausea	9	0	2	9
Somnolence	16	20	30	39
Tremor	3	0	5	7

Additional Findings

In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of olanzapine in patients with schizophrenia or schizoaffective disorder, statistically significant differences among 3 dose groups were observed for the following safety outcomes: weight gain, prolactin elevation, fatigue and dizziness. Mean baseline to endpoint increase in weight (10 mg/day: 1.9 kg; 20 mg/day: 2.3 kg; 40 mg/day: 3 kg) was observed with significant differences between 10 vs 40 mg/day. Incidence of treatment-emergent prolactin elevation >24.2 ng/mL (female) or >18.77 ng/mL (male) at any time during the trial (10 mg/day: 31.2%; 20 mg/day: 42.7%; 40 mg/day: 61.1%) with significant differences between 10 vs 40 mg/day and 20 vs 40 mg/day; fatigue (10 mg/day: 1.5%; 20 mg/day: 2.1%; 40 mg/day: 6.6%) with significant differences between 10 vs 40 and 20 vs 40 mg/day; and dizziness (10 mg/day: 2.6%; 20 mg/day: 1.6%; 40 mg/day: 6.6%) with significant differences between 20 vs 40 mg, was observed.

Additional Findings Observed in Clinical Trials

The following findings are based on clinical trials.

Vital Sign Changes — Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (*see* PRECAUTIONS).

Laboratory Changes — An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in SGPT, SGOT, and GGT (*see* PRECAUTIONS). Olanzapine administration was also associated with increases in serum prolactin (*see* PRECAUTIONS), with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

Given the concern about neutropenia associated with other psychotropic compounds and the finding of leukopenia associated with the administration of olanzapine in several animal models (*see* ANIMAL TOXICOLOGY), careful attention was given to examination of hematologic parameters in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

ECG Changes — Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine use was associated with a mean increase in heart rate of 2.4 beats per minute compared to no change among placebo patients. This slight tendency to tachycardia may be related to olanzapine's potential for inducing orthostatic changes (*see* PRECAUTIONS).

Other Adverse Events Observed During the Clinical Trial Evaluation of Olanzapine

Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with oral olanzapine (at multiple doses ≥1 mg/day) in clinical trials (8661 patients, 4165 patient-years of exposure). This listing may not include those events already listed in previous tables or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening.

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.

Body as a Whole — *Frequent:* dental pain and flu syndrome; *Infrequent:* abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, and suicide attempt; *Rare:* chills and fever, hangover effect, and sudden death.

Cardiovascular System — *Frequent:* hypotension; *Infrequent:* atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, and ventricular extrasystoles; *Rare:* arteritis, heart failure, and pulmonary embolus.

Digestive System — *Frequent:* flatulence, increased salivation, and thirst; *Infrequent:* dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, and tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, and tongue discoloration.

Endocrine System — *Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis and goiter.

Hemic and Lymphatic System — *Infrequent:* anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, and thrombocytopenia; *Rare:* normocytic anemia and thrombocythemia.

Metabolic and Nutritional Disorders — *Infrequent:* acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, and upper extremity edema; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, and water intoxication.

Musculoskeletal System — *Frequent:* joint stiffness and twitching; *Infrequent:* arthritis, arthrosis, leg cramps, and myasthenia; *Rare:* bone pain, bursitis, myopathy, osteoporosis, and rheumatoid arthritis.

Nervous System — *Frequent:* abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, and schizophrenic reaction; *Infrequent:* akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, and withdrawal syndrome; *Rare:* circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, and tobacco misuse.

Respiratory System — *Frequent:* dyspnea; *Infrequent:* apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, and voice alteration; *Rare:* atelectasis, hiccup, hypoventilation, lung edema, and stridor.

Skin and Appendages — *Frequent:* sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, and vesiculobullous rash; *Rare:* hirsutism and pustular rash.

Special Senses — *Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, and tinnitus; *Rare:* corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, and pigment deposits lens.

Urogenital System — *Frequent:* vaginitis*; *Infrequent:* abnormal ejaculation*, amenorrhea*, breast pain, cystitis, decreased menstruation*, dysuria, female lactation*, glycosuria, gynecomastia, hematuria, impotence*, increased menstruation*, menorrhagia*, metrorrhagia*, polyuria, premenstrual syndrome*, pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged*, and vaginal hemorrhage*; *Rare:* albuminuria, breast enlargement, mastitis, and oliguria.

* Adjusted for gender.

Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with intramuscular olanzapine for injection (at one or more doses ≥2.5 mg/injection) in clinical trials (722 patients). This listing may not include those events already listed in previous tables or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

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.

Body as a Whole — *Frequent:* injection site pain; *Infrequent:* abdominal pain and fever.

Cardiovascular System — *Infrequent:* AV block, heart block, and syncope.

Digestive System — *Infrequent:* diarrhea and nausea.

Hemic and Lymphatic System — *Infrequent:* anemia.

Metabolic and Nutritional Disorders — *Infrequent:* creatine phosphokinase increased, dehydration, and hyperkalemia.

Musculoskeletal System — *Infrequent:* twitching.

Nervous System — *Infrequent:* abnormal gait, akathisia, articulation impairment, confusion, and emotional lability.

Skin and Appendages — *Infrequent:* sweating.

Postintroduction Reports

Adverse events reported since market introduction that were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice, neutropenia, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Olanzapine is not a controlled substance.

Physical and Psychological Dependence

In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily oral dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily oral dose on a mg/m^2 basis.

Olanzapine has not been systematically studied in 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 misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs were usually within normal limits following overdoses.

In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and one patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In one case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of 1500 mg.

Overdosage Management

The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. 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.

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. (Do not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Schizophrenia

Usual Dose — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of 15 mg/day or greater) is recommended only after clinical assessment. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations — The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine (*see* CLINICAL PHARMACOLOGY; also *see* Use in Patients with Concomitant Illness and Drug Interactions *under* PRECAUTIONS). When indicated, dose escalation should be performed with caution in these patients.

Maintenance Treatment — While there is no body of evidence available to answer the question of how long the patient treated with olanzapine should remain on it, the effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for a period of up to 8 months has been demonstrated in a placebo-controlled trial (*see* CLINICAL EFFICACY DATA). Patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

Bipolar Disorder

Usual Monotherapy Dose — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of two weeks, was demonstrated in a controlled trial (*see* CLINICAL EFFICACY DATA). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Bipolar Mania Usual Dose in Combination with Lithium or Valproate — When administered in combination with lithium or valproate, oral olanzapine dosing should generally begin with 10 mg once-a-day without regard to meals.

Short-term (6 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations — *See* Dosing in Special Populations *under* DOSAGE AND ADMINISTRATION, Schizophrenia.

Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)

After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without liquid.

Agitation Associated with Schizophrenia and Bipolar I Mania

Usual Dose for Agitated Patients with Schizophrenia or Bipolar Mania — The efficacy of intramuscular olanzapine for injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant (*see* CLINICAL EFFICACY DATA). If agitation warranting additional intramuscular doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for injection in agitated patients has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (e.g., three doses of 10 mg administered 2-4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension (*see* PRECAUTIONS, Hemodynamic Effects). Thus, it is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended.

If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate (*see* Schizophrenia or Bipolar Disorder *under* DOSAGE AND ADMINISTRATION).

Intramuscular Dosing in Special Populations — A dose of 5 mg per injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg per injection should be considered for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine (*see* CLINICAL PHARMACOLOGY; also *see* Use in Patients with Concomitant Illness and Drug Interactions *under* PRECAUTIONS).

Administration of ZYPREXA IntraMuscular

ZYPREXA IntraMuscular is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for preparation of ZYPREXA IntraMuscular with Sterile Water for Injection

Dissolve the contents of the vial using 2.1 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow. ZYPREXA IntraMuscular reconstituted with Sterile Water for Injection should be used immediately (within 1 hour) after reconstitution. **Discard any unused portion.**

The following table provides injection volumes for delivering various doses of intramuscular olanzapine for injection reconstituted with Sterile Water for Injection.

Dose, mg Olanzapine	Volume of Injection, mL
10	Withdraw total contents of vial
7.5	1.5
5	1
2.5	0.5

Physical Incompatibility Information

ZYPREXA IntraMuscular should be reconstituted only with Sterile Water for Injection. ZYPREXA IntraMuscular should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed. Lorazepam injection should not be used to reconstitute ZYPREXA IntraMuscular as this combination results in a delayed reconstitution time. ZYPREXA IntraMuscular should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

HOW SUPPLIED

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. The tablets are available as follows:

	TABLET STRENGTH					
	2.5 mg	5 mg	7.5 mg	10 mg	15 mg	20 mg
Tablet No, Identification	4112 LILLY 4112	4115 LILLY 4115	4116 LILLY 4116	4117 LILLY 4117	4415 LILLY 4415	4420 LILLY 4420
NDC Codes:						
Bottles 30	NDC 0002-4112-30	NDC 0002-4115-30	NDC 0002-4116-30	NDC 0002-4117-30	NDC 0002-4415-30	NDC 0002-4420-30
Blisters - ID* 100	NDC 0002-4112-33	NDC 0002-4115-33	NDC 0002-4116-33	NDC 0002-4117-33	NDC 0002-4415-33	NDC 0002-4420-33
Bottles 1000	NDC 0002-4112-04	NDC 0002-4115-04	NDC 0002-4116-04	NDC 0002-4117-04	NDC 0002-4415-04	NDC 0002-4420-04

* Identi-Dose® (unit dose medication, Lilly).

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. The tablets are available as follows:

ZYPREXA ZYDIS Tablets	TABLET STRENGTH 5 mg	10 mg	15 mg	20 mg
Tablet No.	4453	4454	4455	4456
Debossed	5	10	15	20
NDC Codes:				
Dose Pack 30 (Child-Resistant)	NDC 0002-4453-85	NDC 0002-4454-85	NDC 0002-4455-85	NDC 0002-4456-85

ZYPREXA is a registered trademark of Eli Lilly and Company.
ZYDIS is a registered trademark of Catalent Pharma Solutions.
ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and Company by Catalent Pharma Solutions, United Kingdom, SN5 8RU.

ZYPREXA IntraMuscular is available in:
NDC 0002-7597-01 (No. VL7597) - 10 mg vial (1s)

Store ZYPREXA tablets, ZYPREXA ZYDIS, and ZYPREXA IntraMuscular vials (before reconstitution) at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP]. Reconstituted ZYPREXA IntraMuscular may be stored at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP] for up to 1 hour if necessary. **Discard any unused portion of reconstituted ZYPREXA IntraMuscular.** The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Protect ZYPREXA tablets and ZYPREXA ZYDIS from light and moisture. Protect ZYPREXA IntraMuscular from light, do not freeze.

ANIMAL TOXICOLOGY

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily oral dose on a mg/m^2 basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily oral dose on a mg/m^2 basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily oral dose on a mg/m^2 basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily oral dose on a mg/m^2 basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

Literature revised October 1, 2007

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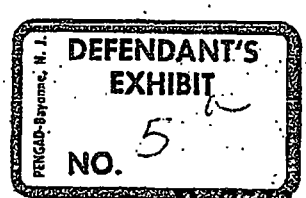
Exhibit 9

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.



Calculation of Net Cost of Risperdal to the State							Calculation of Excess Net Cost of Zyprexa	
[1]	[2] Claims Data	[3] Claims Data	[4] [2]+[3]	[5] Table 1	[6] Table 2	[7] [4]-[5]-[6]	[8] Substituting Zyprexa for Risperal	[9] [8]([7]/[4])
	Risperdal Gross Cost			Federal Medical Assistance Program Payments	Janssen Rebates Retained by the State	Risperdal Net Cost	Excess Gross Cost of Zyprexa	Estimated Excess Net Cost of Zyprexa
Year	Medicaid	SHP	Total					
1994	909,920.53	0	909,920.53	663,784.14	37,960.19	208,176.20		
1995	2,464,295.26	58,679	2,522,974.26	1,883,212.62	106,726.83	533,034.81		
1996	3,631,635.71	104,596	3,736,231.97	2,989,483.63	164,785.66	581,962.69		
1997	4,133,103.64	148,257	4,281,360.74	3,470,174.85	205,364.86	605,821.02	2,507,719.49	354,847.27
1998	5,216,290.22	176,421	5,392,711.03	4,046,014.91	332,369.25	1,014,326.87	4,039,668.57	759,830.14
1999	7,077,269.43	211,590	7,288,858.98	5,170,691.32	576,422.95	1,541,744.70	5,914,418.76	1,251,022.12
2000	9,188,436.03	439,359	9,627,794.87	7,246,807.02	735,346.23	1,645,641.62	8,247,753.57	1,409,756.52
2001	10,201,297.39	609,326	10,810,623.53	7,986,943.83	774,819.96	2,048,859.73	8,762,702.73	1,660,732.03
2002	12,540,200.85	724,184	13,264,384.55	9,418,591.79	1,076,863.99	2,768,928.78	9,302,954.91	1,941,983.77
2003	15,488,264.97	910,361	16,398,625.58	11,833,835.23	1,378,175.47	3,186,614.88	10,389,575.51	2,018,923.83
2004	17,378,038.90	977,449	18,355,488.18	13,273,141.11	1,717,628.71	3,364,718.37	13,327,994.22	2,443,135.62
2005	19,665,137.50	892,784	20,557,921.94	14,666,345.16	2,017,321.25	3,874,255.53	15,468,638.36	2,915,151.53
2006	12,993,892.98	1,077,132	14,071,024.68	10,977,248.26	1,372,479.30	1,721,297.13	8,722,916.65	1,067,067.37
1994-2006			127,217,921 --> *chart 19*		*chart 19* <--	23,095,382		
1994-July 21, 2004			84,126,041 --> *chart 20*		*chart 20* <--	15,948,501		
1994-April 28, 2005			98,779,993 --> *chart 21*		*chart 21* <--	18,666,562		
1997-2006			120,048,794 --> *chart 23*			21,772,209	86,684,343 --> *chart 23*	15,822,450 --> *chart 23*

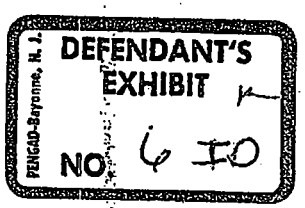


Table 1
Calculation of Federal Medical Assistance Program (FMAP) Payments to South Carolina for Risperdal

[1]	[2] Note 1	[3] Note 1	[4] Note 1	[5] Note 1	[6] Average	[7] Note 2	[8] = [6] [7]
	Federal Medical Assistance Program Contribution Percents to South Carolina					Risperdal Contribution to Cost Basis for Calculation of FMAP Payments to SC	FMAP Payments to SC for Risperdal
Year	Quarter 1	Quarter 2	Quarter 3	Quarter 4	Average		
1993				71.08%			
1994	71.08%	71.08%	71.08%	70.71%	70.99%	935,038.94	663,784.14
1995	70.71%	70.71%	70.71%	70.77%	70.73%	2,662,537.28	1,883,212.62
1996	70.77%	70.77%	70.77%	70.43%	70.69%	4,229,004.99	2,989,483.63
1997	70.43%	70.43%	70.43%	70.23%	70.38%	4,930,626.39	3,470,174.85
1998	70.23%	70.23%	70.23%	69.85%	70.14%	5,768,484.33	4,046,014.91
1999	69.85%	69.85%	69.85%	69.95%	69.88%	7,399,386.55	5,170,691.32
2000	69.95%	69.95%	69.95%	70.44%	70.07%	10,342,239.22	7,246,807.02
2001	70.44%	70.44%	70.44%	69.34%	70.17%	11,382,277.09	7,986,943.83
2002	69.34%	69.34%	69.34%	69.81%	69.46%	13,559,734.79	9,418,591.79
2003	69.81%	72.76%	72.76%	72.81%	72.04%	16,426,756.29	11,833,835.23
2004	72.81%	72.81%	69.86%	69.89%	71.34%	18,605,468.33	13,273,141.11
2005	69.89%	69.89%	69.89%	69.32%	69.75%	21,027,018.15	14,666,345.16
2006	69.32%	69.32%	69.32%	69.54%	69.38%	15,821,920.23	10,977,248.26
2007	69.54%	69.54%	69.54%				

Note 1: South Carolina Department of Health & Human Services, "State Fiscal Year 2007 Annual Report", p. 38 (for 1999q4-2007q3); U.S Dept. of Health & Human Services, "Federal Percentages and Federal Medical Assistance Percentages, FY 1961 - FY 2011", http://aspe.hhs.gov/health/fmapearly.htm (for 1993q4-1999q3).

Note 2: U.S Dept. of Health & Human Services, Centers for Medicare and Medicaid Services, State Drug Utilization Data, South Carolina, 1994-2006.

Table 2
Calculation of Janssen Rebates for Risperdal Retained by South Carolina

[1]	[2] Janssen Compilation	[3] Table 1	[4] = [2] (100%–[3])
Year	Janssen Rebates to State for Risperdal	FMAP Contribution Percentage for South Carolina	Portion of Janssen Rebates for Risperdal Retained by State
1994	130,852.08	70.99%	37,960.19
1995	364,628.74	70.73%	106,726.83
1996	562,216.50	70.69%	164,785.66
1997	693,331.75	70.38%	205,364.86
1998	1,113,091.94	70.14%	332,369.25
1999	1,913,754.83	69.88%	576,422.95
2000	2,456,886.82	70.07%	735,346.23
2001	2,597,452.11	70.17%	774,819.96
2002	3,526,077.24	69.46%	1,076,863.99
2003	4,929,096.80	72.04%	1,378,175.47
2004	5,993,121.79	71.34%	1,717,628.71
2005	6,668,830.59	69.75%	2,017,321.25
2006	4,482,296.86	69.38%	1,372,479.30

South Carolina Risperdal Prescriptions
How much would Zyprexa have cost?

[1]	[2]	[3]	[4]	[5]=[4]/[3]	[6]	[7]	[8]	[9]=[8]/[7]	[10]=[3]x[9]	[11]=[10]-[4]
Year and Month	Risperdal Rx	Risperdal Days Supply	Total Paid: Risperdal	Avg Paid per Day: Risperdal	Zyprexa Rx	Zyprexa Days Supply	Total Paid: Zyprexa	Avg Paid per Day: Zyprexa	Total Paid: Equal Amt of Zyprexa Supply	Excess Cost of Zyprexa
01/1997	1,767	65,258	340,875.53	5.22	649	25,846	191,221.92	7.40	482,812.05	141,936.52
02/1997	1,705	64,598	338,474.21	5.24	865	34,425	262,460.31	7.62	492,502.86	154,028.65
03/1997	1,690	62,450	322,763.42	5.17	1,042	42,819	328,706.63	7.68	479,407.01	156,643.59
04/1997	1,755	66,444	342,065.50	5.15	1,102	45,372	355,506.08	7.84	520,612.85	178,547.35
05/1997	1,840	70,179	357,772.23	5.10	1,256	51,374	404,960.22	7.88	553,192.34	195,420.11
06/1997	1,771	67,577	338,568.89	5.01	1,363	55,179	445,911.36	8.08	546,101.81	207,532.92
07/1997	1,828	70,098	347,078.05	4.95	1,475	60,065	486,127.25	8.09	567,327.86	220,249.81
08/1997	1,850	71,754	352,287.72	4.91	1,511	59,180	484,495.46	8.19	587,436.41	235,148.70
09/1997	1,888	74,026	378,452.09	5.11	1,609	65,114	550,176.38	8.45	625,477.73	247,025.64
10/1997	1,987	78,559	395,254.27	5.03	1,756	72,750	601,701.07	8.27	649,746.18	254,491.91
11/1997	1,870	71,869	364,967.43	5.08	1,699	72,881	624,894.15	8.57	616,217.09	251,249.66
12/1997	2,017	79,912	402,801.41	5.04	1,801	75,481	631,192.80	8.36	668,246.04	265,444.63
01/1998	2,032	82,129	418,800.01	5.10	1,836	79,348	673,682.14	8.49	697,293.45	278,493.44
02/1998	1,945	77,472	385,336.18	4.97	1,771	77,258	682,147.89	8.83	684,037.40	298,701.22
03/1998	2,054	81,773	415,020.81	5.08	1,905	81,877	718,565.78	8.78	717,653.06	302,632.24
04/1998	2,080	84,569	424,016.83	5.01	1,866	80,867	711,798.47	8.80	744,383.80	320,366.97
05/1998	1,998	80,832	417,873.24	5.17	1,841	81,407	725,197.64	8.91	720,075.37	302,202.13
06/1998	2,099	85,986	446,491.08	5.19	1,907	83,340	746,689.37	8.96	770,396.36	323,905.28
07/1998	2,231	90,250	461,284.45	5.11	1,998	86,436	763,772.11	8.84	797,473.66	336,189.21
08/1998	2,246	89,606	461,827.76	5.15	1,982	84,996	767,368.36	9.03	808,988.76	347,161.00
09/1998	2,326	93,481	473,280.53	5.06	1,993	87,667	786,677.93	8.97	838,849.74	365,569.21
10/1998	2,437	97,767	486,625.86	4.98	2,140	94,456	837,020.14	8.86	866,360.50	379,734.64
11/1998	2,391	96,983	488,474.69	5.04	2,058	88,564	789,118.93	8.91	864,133.52	375,658.84
12/1998	2,545	102,162	513,679.61	5.03	2,223	97,095	876,968.51	9.03	922,733.99	409,054.38
01/1999	2,594	105,720	518,767.69	4.91	2,256	100,000	893,328.73	8.93	944,427.13	425,659.44
02/1999	2,611	104,252	535,999.71	5.14	2,192	95,118	873,698.07	9.19	957,597.62	421,597.92
03/1999	2,860	115,951	586,150.65	5.06	2,365	100,670	939,494.86	9.33	1,082,103.59	495,952.94
04/1999	2,773	113,104	573,542.06	5.07	2,333	104,356	969,109.92	9.29	1,050,348.89	476,806.82
05/1999	2,866	117,780	595,897.82	5.06	2,239	97,648	911,138.36	9.33	1,098,986.93	503,089.11
06/1999	2,956	119,666	613,225.52	5.12	2,408	104,467	959,492.07	9.18	1,099,089.45	485,863.93
07/1999	2,920	118,490	593,823.80	5.01	2,483	109,395	1,011,326.44	9.24	1,095,407.20	501,583.40
08/1999	3,073	125,921	645,674.11	5.13	2,496	107,482	997,909.66	9.28	1,169,105.36	523,431.25
09/1999	2,997	122,895	620,830.98	5.05	2,482	104,430	954,965.31	9.14	1,123,819.42	502,988.44
10/1999	3,119	127,256	652,278.87	5.13	2,512	109,926	997,654.46	9.08	1,154,936.20	502,657.33
11/1999	3,200	131,811	659,944.90	5.01	2,551	111,571	986,050.81	8.84	1,164,929.45	504,984.55
12/1999	3,409	140,463	692,722.88	4.93	2,640	113,763	1,022,538.34	8.99	1,262,526.50	569,803.61
01/2000	3,329	137,641	682,129.58	4.96	2,554	112,484	1,002,113.41	8.91	1,226,235.65	544,106.08

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South Carolina Risperdal Prescriptions
How much would Zyprexa have cost?

[1]	[2]	[3]	[4]	[5]=[4]/[3]	[6]	[7]	[8]	[9]=[8]/[7]	[10]=[3]x[9]	[11]=[10]-[4]
Year and Month	Risperdal Rx	Risperdal Days Supply	Total Paid: Risperdal	Avg Paid per Day: Risperdal	Zyprexa Rx	Zyprexa Days Supply	Total Paid: Zyprexa	Avg Paid per Day: Zyprexa	Total Paid: Equal Amt of Zyprexa Supply	Excess Cost of Zyprexa
02/2000	3,507	147,566	736,018.20	4.99	2,602	115,051	1,054,038.72	9.16	1,351,924.61	615,906.42
03/2000	3,736	152,794	750,997.12	4.92	2,802	122,075	1,111,892.72	9.11	1,391,689.83	640,692.72
04/2000	3,446	142,603	692,493.79	4.86	2,626	116,007	1,067,719.18	9.20	1,312,506.65	620,012.86
05/2000	3,813	158,726	794,650.39	5.01	2,796	123,141	1,130,312.68	9.18	1,456,947.81	662,297.42
06/2000	3,750	156,115	775,700.27	4.97	2,862	125,325	1,165,928.76	9.30	1,452,375.57	676,675.29
07/2000	3,734	156,291	779,034.27	4.98	2,758	120,701	1,152,493.30	9.55	1,492,318.46	713,284.20
08/2000	4,026	168,862	858,559.71	5.08	2,941	131,654	1,255,961.99	9.54	1,610,921.46	752,361.75
09/2000	4,016	169,834	852,005.78	5.02	2,884	129,108	1,249,655.90	9.68	1,643,849.03	791,843.25
10/2000	4,015	167,514	867,657.59	5.18	2,923	128,956	1,238,056.64	9.60	1,608,237.08	740,579.49
11/2000	4,148	172,544	913,518.38	5.29	3,007	133,018	1,262,163.35	9.49	1,637,212.36	723,693.97
12/2000	4,127	172,521	925,029.80	5.36	3,006	133,276	1,306,586.95	9.80	1,691,329.92	766,300.12
01/2001	4,111	170,236	922,000.53	5.42	3,144	138,838	1,380,840.52	9.95	1,693,115.47	771,114.95
02/2001	3,656	150,466	806,681.61	5.36	2,834	126,013	1,270,553.55	10.08	1,517,106.26	710,424.65
03/2001	3,921	164,650	885,556.93	5.38	2,935	130,506	1,319,048.99	10.11	1,664,148.90	778,591.97
04/2001	3,972	167,907	914,838.60	5.45	3,045	134,563	1,328,406.15	9.87	1,657,578.17	742,739.57
05/2001	4,174	176,377	970,487.65	5.50	3,158	142,826	1,464,268.37	10.25	1,808,237.03	837,749.38
06/2001	4,000	167,923	917,776.59	5.47	3,093	141,983	1,453,262.46	10.24	1,718,770.50	800,993.91
07/2001	4,202	125,174	688,741.06	5.50	3,220	97,105	969,001.46	9.98	1,249,099.31	560,358.25
08/2001	5,133	153,614	883,169.29	5.75	3,969	119,537	1,195,801.98	10.00	1,536,695.12	653,525.83
09/2001	5,150	153,910	878,844.96	5.71	4,139	124,718	1,256,658.43	10.08	1,550,796.99	671,952.03
10/2001	5,753	172,458	990,665.24	5.74	4,661	141,052	1,430,552.31	10.14	1,749,072.62	758,407.38
11/2001	5,647	169,310	980,801.98	5.79	4,647	140,480	1,424,245.33	10.14	1,716,536.00	735,734.03
12/2001	5,673	169,715	971,059.08	5.72	4,745	143,622	1,448,930.64	10.09	1,712,169.89	741,110.80
01/2002	5,914	176,775	1,003,032.88	5.67	4,893	147,670	1,532,166.48	10.38	1,834,148.64	831,115.77
02/2002	5,222	155,792	880,292.41	5.65	4,389	131,972	1,362,597.59	10.32	1,608,536.69	728,244.27
03/2002	5,403	161,917	931,431.68	5.75	4,542	136,996	1,429,002.96	10.43	1,688,953.49	757,521.80
04/2002	5,718	171,308	1,064,927.26	6.22	4,793	144,488	1,488,726.27	10.30	1,765,065.06	700,137.79
05/2002	5,526	165,030	1,017,187.59	6.16	4,745	143,109	1,487,382.21	10.39	1,715,214.88	698,027.29
06/2002	5,825	174,435	1,088,348.28	6.24	4,968	149,438	1,562,274.09	10.45	1,823,600.97	735,252.69
07/2002	6,374	190,872	1,196,129.36	6.27	5,493	165,058	1,703,028.32	10.32	1,969,370.89	773,241.53
08/2002	6,575	196,259	1,224,374.88	6.24	5,678	170,659	1,741,461.50	10.20	2,002,692.46	778,317.58
09/2002	6,344	189,414	1,167,451.75	6.16	5,500	165,228	1,691,605.26	10.24	1,939,221.68	771,769.93
10/2002	6,786	202,904	1,236,439.70	6.09	5,869	176,575	1,806,355.79	10.23	2,075,700.50	839,260.80
11/2002	6,561	195,595	1,186,838.23	6.07	5,691	171,132	1,762,608.34	10.30	2,014,569.91	827,731.69
12/2002	6,739	201,297	1,267,930.52	6.30	5,852	176,159	1,864,236.57	10.58	2,130,264.30	862,333.78
01/2003	6,945	207,808	1,324,312.45	6.37	6,050	181,908	1,916,024.88	10.53	2,188,827.86	864,515.40
02/2003	6,518	192,777	1,231,652.78	6.39	5,841	174,024	1,823,347.46	10.48	2,019,833.20	788,180.42

South Carolina Risperdal Prescriptions
How much would Zyprexa have cost?

[1]	[2]	[3]	[4]	[5]=[4]/[3]	[6]	[7]	[8]	[9]=[8]/[7]	[10]=[3]x[9]	[11]=[10]-[4]
Year and Month	Risperdal Rx	Risperdal Days Supply	Total Paid: Risperdal	Avg Paid per Day: Risperdal	Zyprexa Rx	Zyprexa Days Supply	Total Paid: Zyprexa	Avg Paid per Day: Zyprexa	Total Paid: Equal Amt of Zyprexa Supply	Excess Cost of Zyprexa
03/2003	7,068	210,054	1,328,810.67	6.33	6,116	182,843	1,899,300.92	10.39	2,181,958.05	853,147.38
04/2003	7,254	215,654	1,360,023.91	6.31	6,111	183,396	1,907,596.30	10.40	2,243,128.38	883,104.46
05/2003	7,199	214,000	1,350,429.84	6.31	6,284	188,532	1,981,333.32	10.51	2,248,983.36	898,553.52
06/2003	6,906	205,268	1,291,854.96	6.29	6,058	181,199	1,882,236.10	10.39	2,132,257.02	840,402.06
07/2003	7,179	213,707	1,378,020.91	6.45	6,316	188,670	1,974,452.91	10.47	2,236,467.95	858,447.04
08/2003	7,111	211,953	1,406,086.03	6.63	6,104	182,926	1,910,698.17	10.45	2,213,890.92	807,804.88
09/2003	7,131	211,197	1,400,973.02	6.63	6,131	183,353	1,903,964.28	10.38	2,193,100.44	792,127.42
10/2003	7,603	225,994	1,488,825.65	6.59	6,359	190,649	1,972,300.54	10.35	2,337,951.35	849,125.70
11/2003	6,809	202,139	1,341,346.71	6.64	5,775	173,412	1,902,260.83	10.97	2,217,384.62	876,037.91
12/2003	7,648	227,878	1,496,288.63	6.57	6,399	191,892	2,167,871.44	11.30	2,574,417.94	1,078,129.31
01/2004	7,073	210,093	1,390,351.02	6.62	5,844	175,357	2,001,730.08	11.42	2,398,242.45	1,007,896.43
02/2004	6,954	206,227	1,341,605.95	6.51	5,599	167,270	1,899,155.84	11.35	2,341,467.16	999,861.21
03/2004	7,811	231,863	1,518,095.77	6.55	6,333	189,275	2,136,631.48	11.29	2,617,386.26	1,099,290.49
04/2004	7,653	227,665	1,500,402.98	6.59	5,910	177,045	1,992,799.07	11.26	2,562,572.22	1,062,169.25
05/2004	7,429	221,244	1,462,141.14	6.61	5,598	167,173	1,895,051.82	11.34	2,507,993.78	1,045,852.64
06/2004	7,884	233,725	1,559,628.93	6.67	5,941	177,238	2,027,500.58	11.44	2,673,679.30	1,114,050.37
07/2004	7,721	229,545	1,537,740.69	6.70	5,609	168,076	1,919,065.96	11.42	2,620,909.56	1,083,168.87
08/2004	7,886	234,610	1,587,667.78	6.77	5,552	166,189	1,904,472.03	11.46	2,688,554.50	1,100,886.71
09/2004	7,764	230,460	1,585,531.63	6.88	5,491	163,826	1,962,357.06	11.98	2,760,519.14	1,174,987.51
10/2004	7,809	230,377	1,571,040.86	6.82	5,321	159,429	1,917,106.98	12.02	2,770,244.78	1,199,203.91
11/2004	8,047	237,217	1,614,989.27	6.81	5,444	161,094	1,928,892.80	11.97	2,840,367.51	1,225,378.24
12/2004	8,090	239,776	1,686,292.16	7.03	5,477	164,354	1,988,855.53	12.10	2,901,540.73	1,215,248.57
01/2005	7,460	222,012	1,555,975.93	7.01	4,983	150,040	1,832,510.28	12.21	2,711,538.74	1,155,562.81
02/2005	7,198	213,501	1,480,216.75	6.93	4,781	143,136	1,730,832.11	12.09	2,581,701.22	1,101,484.47
03/2005	7,974	237,326	1,655,098.12	6.97	5,131	153,560	1,881,166.83	12.25	2,907,331.34	1,252,233.22
04/2005	7,748	230,145	1,592,694.57	6.92	5,057	151,473	1,833,327.41	12.10	2,785,520.43	1,192,825.86
05/2005	7,970	237,758	1,620,546.21	6.82	5,043	151,487	1,840,691.90	12.15	2,888,955.65	1,268,409.44
06/2005	7,918	235,262	1,621,665.77	6.89	5,023	150,525	1,889,684.31	12.55	2,953,468.92	1,331,803.15
07/2005	7,549	224,043	1,571,435.02	7.01	4,759	141,981	1,883,348.55	13.26	2,971,883.98	1,400,448.96
08/2005	8,625	256,222	1,878,424.08	7.33	5,134	153,209	2,002,660.23	13.07	3,349,187.13	1,470,763.05
09/2005	8,204	242,533	1,819,246.67	7.50	4,889	145,061	1,889,448.48	13.03	3,159,040.74	1,339,794.07
10/2005	8,336	245,445	1,874,734.55	7.64	4,833	144,040	1,894,011.25	13.15	3,227,406.22	1,352,671.67
11/2005	8,471	248,819	1,957,450.84	7.87	4,850	143,251	1,862,236.63	13.00	3,234,601.20	1,277,150.36
12/2005	8,227	242,088	1,930,433.43	7.97	4,694	138,155	1,858,094.09	13.45	3,255,924.73	1,325,491.30
01/2006	4,392	129,548	1,049,816.17	8.10	1,848	55,172	750,290.27	13.60	1,761,737.91	711,921.74
02/2006	4,093	120,748	1,007,091.16	8.34	1,730	51,200	720,098.51	14.06	1,698,251.08	691,159.93
03/2006	4,774	140,251	1,217,758.50	8.68	1,891	56,112	812,536.01	14.48	2,030,920.08	813,161.58

R. 7538

South Carolina Risperdal Prescriptions
How much would Zyprexa have cost?

[1]	[2]	[3]	[4]	[5]=[4]/[3]	[6]	[7]	[8]	[9]=[8]/[7]	[10]=[3]x[9]	[11]=[10]-[4]
Year and Month	Risperdal Rx	Risperdal Days Supply	Total Paid: Risperdal	Avg Paid per Day: Risperdal	Zyprexa Rx	Zyprexa Days Supply	Total Paid: Zyprexa	Avg Paid per Day: Zyprexa	Total Paid: Equal Amt of Zyprexa Supply	Excess Cost of Zyprexa
04/2006	4,226	124,102	1,072,526.23	8.64	1,673	49,831	721,677.33	14.48	1,797,306.90	724,780.67
05/2006	4,740	139,217	1,240,080.98	8.91	1,884	55,887	805,763.40	14.42	2,007,192.44	767,111.46
06/2006	4,517	132,136	1,166,325.53	8.83	1,792	53,454	778,463.16	14.56	1,924,327.61	758,002.08
07/2006	4,425	130,000	1,182,184.68	9.09	1,701	50,980	736,274.71	14.44	1,877,514.95	695,330.27
08/2006	4,727	138,680	1,270,791.08	9.16	1,853	54,806	777,873.59	14.19	1,968,315.69	697,524.61
09/2006	4,488	131,802	1,197,700.55	9.09	1,810	53,695	769,653.58	14.33	1,889,223.97	691,523.42
10/2006	4,636	135,709	1,232,800.39	9.08	1,780	53,210	766,116.39	14.40	1,953,935.16	721,134.76
11/2006	4,641	136,230	1,250,566.69	9.18	1,749	51,852	746,192.81	14.39	1,960,461.44	709,894.75
12/2006	4,533	132,365	1,183,382.71	8.94	1,726	51,181	744,236.31	14.54	1,924,754.10	741,371.38
01/2007	4,675	136,929	1,258,141.34	9.19	1,735	52,479	766,510.40	14.61	1,999,990.53	741,849.19
02/2007	4,459	130,677	1,145,216.55	8.76	1,510	44,941	666,048.19	14.82	1,936,698.77	791,482.22
03/2007	4,829	141,872	1,237,123.19	8.72	1,704	49,874	742,125.77	14.88	2,111,057.20	873,934.02
04/2007	4,733	139,203	1,188,348.81	8.54	1,622	48,326	660,193.92	13.66	1,901,688.00	713,339.19
05/2007	4,972	145,350	1,248,699.19	8.59	1,784	53,285	741,700.62	13.92	2,023,199.50	774,500.31
06/2007	4,645	135,895	1,184,767.50	8.72	1,672	49,916	696,186.33	13.95	1,895,349.01	710,581.51
07/2007	4,674	137,625	1,239,157.62	9.00	1,687	50,196	713,356.01	14.21	1,955,845.51	716,687.89
08/2007	4,970	145,987	1,313,277.42	9.00	1,745	52,051	742,948.48	14.27	2,083,741.33	770,463.92
09/2007	4,463	130,358	1,207,351.52	9.26	1,613	47,942	684,533.84	14.28	1,861,300.38	653,948.86
10/2007	4,838	142,046	1,325,945.88	9.33	1,733	51,854	733,849.68	14.15	2,010,267.51	684,321.63
11/2007	4,671	136,848	1,272,574.15	9.30	1,664	49,046	709,863.19	14.47	1,980,658.10	708,083.95
12/2007	4,501	131,412	1,236,522.86	9.41	1,644	49,019	717,021.89	14.63	1,922,219.55	685,696.69
1997-2007	641,550	20,726,767	134,905,920.11		450,759	15,134,503.00	162,249,539.94		230,415,152.24	95,509,232.12
1997-2006	585,120	19,072,565	120,048,794.08		430,646	14,535,574.00	153,675,201.62		206,733,136.85	86,684,342.74

R. 7539

Court Exhibit 2

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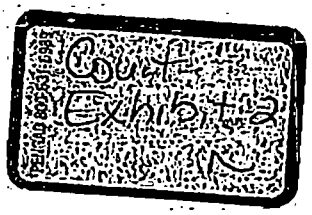

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TITLE 21 – FOOD AND DRUGS
REVISED AS OF APRIL 1, 2002
CHAPTER I -- FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER C -- DRUGS: GENERAL
PART 201 -- LABELING
SUBPART B -- LABELING REQUIREMENTS FOR PRESCRIPTION DRUGS AND/OR INSULIN

21 CFR 201.57

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

Each section heading listed in § 201.56(d), if not omitted under § 201.56(d)(3), shall contain the following information in the following order:

(a) "Description": (1) Under this section heading, the labeling shall contain:

(i) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug;

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

(iii) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for labels;

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

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

(vi) The chemical name and structural formula of the drug;

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

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

(b) "Clinical Pharmacology": (1) Under this section heading, the labeling shall contain a concise factual summary of the clinical pharmacology and actions of the drug in humans. The summary may include information based on in vitro and/or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. Pharmacokinetic information that is important to safe and effective use of the drug is required, if known, e.g., degree and rate of absorption, pathways of biotransformation, percentage of dose as unchanged drug and metabolites, rate or half-time of elimination, concentration in body fluids associated with therapeutic and/or toxic effects, degree of binding to plasma proteins, degree of uptake by a particular organ or in the fetus, and passage across the blood brain barrier. Inclusion of pharmacokinetic information is restricted to that which relates to clinical use of the drug. If the pharmacological mode of action of the drug is unknown or if important metabolic or pharmacokinetic data in humans are unavailable, the labeling shall contain a statement about the lack of information.

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

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

(ii) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled clinical studies, as defined in § 314.126(b) of this chapter, to be pertinent to clinical use may be used only if a waiver is granted under § 201.58 or § 314.126(b) of this chapter.

(c) "Indications and Usage": (1) Under this section heading, the labeling shall state that:

(i) The drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, e.g., penicillin is indicated for the treatment of pneumonia due to susceptible pneumococci; and/or

(ii) The drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, e.g., chlorothiazide is indicated for the treatment of edema in patients with congestive heart failure; and/or

(iii) The drug is indicated for the relief of symptoms associated with a disease or syndrome, e.g., chlorpheniramine is indicated for the symptomatic relief of nasal congestion in patients with vasomotor rhinitis; and/or

(iv) The drug, if used for a particular indication only in conjuction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy.

(2) All indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(3) This section of the labeling shall also contain the following additional information:

(i) If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, syndrome, or symptom under consideration, e.g., patients with mild disease or patients in a special age group, the labeling shall describe the available evidence and state the limitations of usefulness of the drug. The labeling shall also identify specific tests needed for selection or monitoring of the patients who need the drug, e.g., microbe susceptibility tests. Information on the approximate kind, degree, and duration of improvement to be anticipated shall be stated if available and shall be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the "Dosage and Administration" section of the labeling and referenced in this section.

(ii) If safety considerations are such that the drug should be reserved for certain situations, e.g., cases refractory to other drugs, this information shall be stated in this section.

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

(iv) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use or condition.

(v) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication shall be supported by adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(d) "Contraindications": Under this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of the drug to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, e.g., if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state "None known."

(e) "Warnings": Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectivenes for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

(f) "Precautions": Under this section heading, the labeling shall contain the following subsections as appropriate for the drug:

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

(2) Information for patients: This subsection of the labeling shall contain information to be given to patients for safe and effective use of the drug, e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects. Any printed patient information or Medication Guide required under this chapter to be distributed to the patient shall be referred to under the "Precautions" section of the labeling and the full text of such patient information or Medication Guide shall be reprinted at the end of the labeling. The print size requirements for the Medication Guide set forth in § 208.20 of this chapter, however, do not apply to the Medication Guide that is reprinted in the professional labeling.

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

(4)(i) Drug interactions: This subsection of the labeling shall contain specific practical guidance for the physician on preventing clinically significant drug/drug and drug/food interactions that may occur in vivo in patients taking the drug. Specific drugs or classes of drugs with which the drug to which the labeling applies may interact in vivo shall be identified, and the mechanism(s) of the interaction shall be briefly described. Information in this subsection of the labeling shall be limited to that pertaining to clinical use of the drug in patients. Drug interactions supported only by animal or in vitro experiments may not ordinarily be included, but animal or in vitro data may be used if shown to be clinically relevant. Drug incompatibilities, i.e., drug interactions that may occur when drugs are mixed in vitro, as in a solution for intravenous administration, shall be discussed under the "Dosage and Administration" section of the labeling rather than under this subsection of the labeling.

(ii) Drug/laboratory test interactions: This subsection of the labeling shall contain practical guidance on known interference of the drug with laboratory tests.

(5) Carcinogenesis, mutagenesis, impairment of fertility: This subsection of the labeling shall state whether long-term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If reproduction studies or other data in animals reveal a problem or potential problem concerning mutagenesis or impairment of fertility in either males or females, the information shall be described. Any precautionary statement on these topics shall include practical, relevant advice to the physician on the significance of these animal findings. If there is evidence from human data that the drug may be carcinogenic or mutagenic or that it impairs fertility, this information shall be included under the "Warnings" section of the labeling. Also, under "Precautions," the labeling shall state "See 'Warnings' section for information on carcinogenesis, mutagenesis, and impairment of fertility."

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

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

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

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

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

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

(e) Pregnancy category X. If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling shall state: "Pregnancy Category X. See 'Contraindications' section."

Under "Contraindications," the labeling shall state: "(Name of drug) may (can) cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinant animal data.) (Name of drug) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

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

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

(8) Nursing mothers: (i) If a drug is absorbed systemically, this subsection of the labeling shall contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring shall be described.

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

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

(9) Pediatric use: (i) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (f)(9)(ii) through (f)(9)(viii) of this setion, the terms "pediatric population(s)" and "pediatric patient(s)" are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

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

(iii) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they shall be summarized in the "Pediatric

use" subsection of the labeling and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage shall be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection of the labeling shall also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information shall also be contained in the "Contraindications," "Warnings," and elsewhere in the "Precautions" sections.

(iv) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the "Pediatric use" subsection of the labeling shall contain either the following statement, or a reasonable alternative: "The safety and effectiveness of (drug name) have been established in the age groups - to - (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (drug name) in these age groups is supported by evidence from adequate and well-controlled studies of (drug name) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population)." Data summarized in the preceding prescribed statement in this subsection of the labeling shall be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or the "Clinical Studies" section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the "Clinical Pharmacology" section. Pediatric dosing instructions shall be included in the "Dosage and Administration" section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients shall be cited briefly in the "Pediatric use" subsection and, as appropriate, in the "Contraindications," "Warnings," "Precautions," and "Dosage and Administration" sections.

(v) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the "Pediatric use" subsection of the labeling shall contain an appropriate statement such as "Safety and effectiveness in pediatric patients below the age of (-) have not been established." If use of the drug in this pediatric population is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.

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

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

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

(10) Geriatric use. (i) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population shall be described under the "Indications and Usage" section of the labeling, and appropriate geriatric dosage shall be stated under the "Dosage and Administration" section of the labeling. The "Geriatric use"

subsection shall cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the "Geriatric use" subsection of the labeling shall pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection of the labeling shall be discussed in more detail, if appropriate, under "Clinical Pharmacology" or the "Clinical Studies" section. As appropriate, this information shall also be contained in "Contraindications," "Warnings," and elsewhere in "Precautions."

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

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

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

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

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

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

(iii)(A) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they shall be described briefly in the "Geriatric use" subsection of the labeling and in detail under the "Clinical Pharmacology" section. The "Clinical Pharmacology" section and "Drug interactions" subsection of the "Precautions" section ordinarily contain information on drug-disease and drug-drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to utilize concomitant drugs.

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

"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."

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

(v) Labeling under paragraphs (f)(10)(i) through (f)(10)(iii) of this section may include statements, if they would be useful in enhancing safe use of the drug, that reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that:

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

(vi) If the sponsor believes that none of the requirements described in paragraphs (f)(10)(i) through (f)(10)(v) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

(g) "Adverse Reactions": An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

(1) This section of the labeling shall list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable.

(2) In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies is available, the categories and the adverse reactions within each category shall be listed in decreasing order of frequency. An adverse reaction that is significantly more severe than the other reactions listed in a category, however, shall be listed before those reactions, regardless of its frequency. If frequency information from adequate clinical studies is not available, the categories and adverse reactions within each category shall be listed in decreasing order of severity. The approximate frequency of each adverse reaction shall be expressed in rough estimates or orders of magnitude essentially as follows: "The most frequent adverse reaction(s) to (name of drug) is (are) (list reactions). This (these) occur(s) in about (e.g., one-third of patients; one in 30 patients; less than one-tenth of patients). Less frequent adverse reactions are (list reactions), which occur in approximately (e.g., one in 100 patients). Other adverse reactions, which occur rarely, in approximately (e.g., one in 1,000 patients), are (list reactions)." Percent figures may not ordinarily be used unless they are documented by adequate and well-controlled studies as defined in § 314.126(b) of this chapter, they are shown to reflect general experience, and they do not falsely imply a greater degree of accuracy than actually exists.

(3) The "Warnings" section of the labeling or, if appropriate, the "Contraindications" section of the labeling shall identify any potentially fatal adverse reaction.

(4) Any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions shall be based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(h) "Drug Abuse and Dependence": Under this section heading, the labeling shall contain the following subsections, as appropriate for the drug:

(1) Controlled Substance: If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled shall be stated.

(2) Abuse: This subsection of the labeling shall be based primarily on human data and human experience, but pertinent animal data may also be used. This subsection shall state the types of abuse that can occur with the drug and the adverse reactions pertinent to them. Particularly susceptible patient populations shall be identified.

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

(i) "Overdosage": Under this section heading, the labeling shall describe the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment. This section shall be based on human data, when available. If human data are unavailable, appropriate animal and in vitro data may be used. Specific information shall be provided about the following:

(1) Signs, symptoms, and laboratory findings associated with an overdosage of the drug.

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

(3) Oral LD[50] of the drug in animals; concentrations of the drug in biologic fluids associated with toxicity and/or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the "Clinical Pharmacology" section also may be referenced here, if applicable to overdoses.

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

(5) Whether the drug is dialyzable.

(6) Recommended general treatment procedures and specific measures for support of vital functions, such as proven antidotes, induced emesis, gastric lavage, and forced diuresis. Unqualified recommendations for which data are lacking with the specific drug or class of drugs, especially treatment using another drug (for example, central nervous system stimulants, respiratory stimulants) may not be stated unless specific data or scientific rationale exists to support safe and effective use.

(j) "Dosage and Administration": This section of the labeling shall state the recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established; dosages shall be stated for each indication when appropriate. This section shall also state the intervals recommended between doses, the optimal method of titrating dosage, the usual duration of treatment, and any modification of dosage needed in special patient populations, e.g., in children, in geriatric age groups, or in patients with renal or hepatic disease. Specific tables or monographs may be included to clarify dosage schedules. Radiation dosimetry information shall be stated for both the patient receiving a radioactive drug and the person administering it. This section shall also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed, e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the drug or reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs; and the following statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."

(k) "How Supplied": This section of the labeling shall contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information shall ordinarily include:

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

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

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

(4) Special handling and storage conditions.

(l) "Animal Pharmacology and/or Animal Toxicology": In most cases, the labeling need not include this section. Significant animal data necessary for safe and effective use of the drug in humans shall ordinarily be included in one or more of the other sections of the labeling, as appropriate. Commonly for a drug that has been marketed for a long time, and in rare cases for a new drug, chronic animal toxicity studies have not been performed or completed for a drug that is administered over prolonged periods or is implanted in the body. The unavailability of such data shall be stated in the appropriate section of the labeling for the drug. If the pertinent animal data cannot be appropriately incorporated into other sections of the labeling, this section may be used.

(m) "Clinical Studies" and "References": These sections may appear in labeling in the place of a detailed discussion of a subject that is of limited interest but nonetheless important. A reference to a specific important clinical study may be made in any section of the format required under §§ 201.56 and 201.57 if the study is essential to an understandable presentation of the available information. References may appear in sections of the labeling format, other than the "Clinical Studies" or "References" section, in rare circumstances only. A clinical study or reference may be cited in prescription drug labeling only under the following conditions:

(1) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning an indication for use of the drug, the reference shall be based upon, or the clinical study shall constitute, an adequate and well-controlled clinical investigation under § 314.126(b) of this chapter.

(2) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning a risk or risks from the use of the drug, the risk or risks shall also be identified or discussed in the appropriate section of the labeling for the drug.

HISTORY: [44 FR 37462, June 26, 1979, as amended at 55 FR 11576, March 29, 1990, 59 FR 64249, Dec. 13, 1994; 62 FR 45313, 45325, Aug. 27, 1997; 63 FR 66378, 66396, Dec. 1, 1998]

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NOTES: NOTES APPLICABLE TO ENTIRE TITLE:
Cross References: Food Safety and Inspection Services, Department of Agriculture: See Meat and Poultry Inspection, 9 CFR CHAPTER III.
Federal Trade Commission: See Commercial Practices, 16 CFR chapter I.
U.S. Customs Service, Department of the Treasury: See Customs Duties, 19 CFR chapter I.
Internal Revenue Service, Department of the Treasury: See Internal Revenue, 26 CFR chapter I.
Bureau of Alcohol, Tobacco, and Firearms, Department of the Treasury: See Alcohol, Tobacco Production and Firearms, 27 CFR chapter I.

NOTES APPLICABLE TO ENTIRE CHAPTER:
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TITLE 21 -- FOOD AND DRUGS
REVISED AS OF JANUARY 1, 2004
CHAPTER I -- FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER C -- DRUGS: GENERAL
PART 201 -- LABELING
SUBPART B -- LABELING REQUIREMENTS FOR PRESCRIPTION DRUGS AND/OR INSULIN

21 CFR 201.57

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

Each section heading listed in § 201.56(d), if not omitted under § 201.56(d)(3), shall contain the following information in the following order:

(a) "Description": (1) Under this section heading, the labeling shall contain:

(i) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug;

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

(iii) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for labels;

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

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

(vi) The chemical name and structural formula of the drug;

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

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

(b) "Clinical Pharmacology": (1) Under this section heading, the labeling shall contain a concise factual summary of the clinical pharmacology and actions of the drug in humans. The summary may include information based on in vitro and/or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. Pharmacokinetic information that is important to safe and effective use of the drug is required, if known, e.g., degree and rate of absorption, pathways of biotransformation, percentage of dose as unchanged drug and metabolites, rate or half-time of elimination, concentration in body fluids associated with therapeutic and/or toxic effects, degree of binding to plasma proteins, degree of uptake by a particular organ or in the fetus, and passage across the blood brain barrier. Inclusion of pharmacokinetic information is restricted to that which relates to clinical use of the drug. If the pharmacological mode of action of the drug is unknown or if important metabolic or pharmacokinetic data in humans are unavailable, the labeling shall contain a statement about the lack of information.

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

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

(ii) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled clinical studies, as defined in § 314.126(b) of this chapter, to be pertinent to clinical use may be used only if a waiver is granted under § 201.58 or § 314.126(b) of this chapter.

(c) "Indications and Usage": (1) Under this section heading, the labeling shall state that:

(i) The drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, e.g., penicillin is indicated for the treatment of pneumonia due to susceptible pneumococci; and/or

(ii) The drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, e.g., chlorothiazide is indicated for the treatment of edema in patients with congestive heart failure; and/or

(iii) The drug is indicated for the relief of symptoms associated with a disease or syndrome, e.g., chlorpheniramine is indicated for the symptomatic relief of nasal congestion in patients with vasomotor rhinitis; and/or

(iv) The drug, if used for a particular indication only in conjuction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy.

(2) All indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(3) This section of the labeling shall also contain the following additional information:

(i) If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, syndrome, or symptom under consideration, e.g., patients with mild disease or patients in a special age group, the labeling shall describe the available evidence and state the limitations of usefulness of the drug. The labeling shall also identify specific tests needed for selection or monitoring of the patients who need the drug, e.g., microbe susceptibility tests. Information on the approximate kind, degree, and duration of improvement to be anticipated shall be stated if available and shall be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the "Dosage and Administration" section of the labeling and referenced in this section.

(ii) If safety considerations are such that the drug should be reserved for certain situations, e.g., cases refractory to other drugs, this information shall be stated in this section.

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

(iv) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use or condition.

(v) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication shall be supported by adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(d) "Contraindications": Under this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of the drug to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, e.g., if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state "None known."

(e) "Warnings": Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectivenes for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

(f) "Precautions": Under this section heading, the labeling shall contain the following subsections as appropriate for the drug:

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

(2) Information for patients: This subsection of the labeling shall contain information to be given to patients for safe and effective use of the drug, e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects. Any printed patient information or Medication Guide required under this chapter to be distributed to the patient shall be referred to under the "Precautions" section of the labeling and the full text of such patient information or Medication Guide shall be reprinted at the end of the labeling. The print size requirements for the Medication Guide set forth in § 208.20 of this chapter, however, do not apply to the Medication Guide that is reprinted in the professional labeling.

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

(4)(i) Drug interactions: This subsection of the labeling shall contain specific practical guidance for the physician on preventing clinically significant drug/drug and drug/food interactions that may occur in vivo in patients taking the drug. Specific drugs or classes of drugs with which the drug to which the labeling applies may interact in vivo shall be identified, and the mechanism(s) of the interaction shall be briefly described. Information in this subsection of the labeling shall be limited to that pertaining to clinical use of the drug in patients. Drug interactions supported only by animal or in vitro experiments may not ordinarily be included, but animal or in vitro data may be used if shown to be clinically relevant. Drug incompatibilities, i.e., drug interactions that may occur when drugs are mixed in vitro, as in a solution for intravenous administration, shall be discussed under the "Dosage and Administration" section of the labeling rather than under this subsection of the labeling.

(ii) Drug/laboratory test interactions: This subsection of the labeling shall contain practical guidance on known interference of the drug with laboratory tests.

(5) Carcinogenesis, mutagenesis, impairment of fertility: This subsection of the labeling shall state whether long-term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If reproduction studies or other data in animals reveal a problem or potential problem concerning mutagenesis or impairment of fertility in either males or females, the information shall be described. Any precautionary statement on these topics shall include practical, relevant advice to the physician on the significance of these animal findings. If there is evidence from human data that the drug may be carcinogenic or mutagenic or that it impairs fertility, this information shall be included under the "Warnings" section of the labeling. Also, under "Precautions," the labeling shall state: "See 'Warnings' section for information on carcinogenesis, mutagenesis, and impairment of fertility."

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

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

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

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

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

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

(e) Pregnancy category X. If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling shall state: "Pregnancy Category X. See 'Contraindications' section."

Under "Contraindications," the labeling shall state: "(Name of drug) may (can) cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinant animal data.) (Name of drug) is contraindicated in women who are or may become pregnant.If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

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

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

(8) Nursing mothers: (i) If a drug is absorbed systemically, this subsection of the labeling shall contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring shall be described.

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

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

(9) Pediatric use: (i) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (f)(9)(ii) through (f)(9)(viii) of this setion, the terms "pediatric population(s)" and "pediatric patient(s)" are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

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

(iii) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they shall be summarized in the "Pediatric

use" subsection of the labeling and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage shall be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection of the labeling shall also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information shall also be contained in the "Contraindications," "Warnings," and elsewhere in the "Precautions" sections.

(iv) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the "Pediatric use" subsection of the labeling shall contain either the following statement, or a reasonable alternative: "The safety and effectiveness of (drug name) have been established in the age groups - to - (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (drug name) in these age groups is supported by evidence from adequate and well-controlled studies of (drug name) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population)." Data summarized in the preceding prescribed statement in this subsection of the labeling shall be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or the "Clinical Studies" section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the "Clinical Pharmacology" section. Pediatric dosing instructions shall be included in the "Dosage and Administration" section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients shall be cited briefly in the "Pediatric use" subsection and, as appropriate, in the "Contraindications," "Warnings," "Precautions," and "Dosage and Administration" sections.

(v) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the "Pediatric use" subsection of the labeling shall contain an appropriate statement such as "Safety and effectiveness in pediatric patients below the age of (-) have not been established." If use of the drug in this pediatric population is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.

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

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

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

(10) Geriatric use. (i) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population shall be described under the "Indications and Usage" section of the labeling, and appropriate geriatric dosage shall be stated under the "Dosage and Administration" section of the labeling. The "Geriatric use"

subsection shall cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the "Geriatric use" subsection of the labeling shall pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection of the labeling shall be discussed in more detail, if appropriate, under "Clinical Pharmacology" or the "Clinical Studies" section. As appropriate, this information shall also be contained in "Contraindications," "Warnings," and elsewhere in "Precautions."

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

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

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

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

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

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

(iii)(A) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they shall be described briefly in the "Geriatric use" subsection of the labeling and in detail under the "Clinical Pharmacology" section. The "Clinical Pharmacology" section and "Drug interactions" subsection of the "Precautions" section ordinarily contain information on drug-disease and drug-drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to utilize concomitant drugs.

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

"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."

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

(v) Labeling under paragraphs (f)(10)(i) through (f)(10)(iii) of this section may include statements, if they would be useful in enhancing safe use of the drug, that reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that:

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

(vi) If the sponsor believes that none of the requirements described in paragraphs (f)(10)(i) through (f)(10)(v) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

(g) "Adverse Reactions": An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

(1) This section of the labeling shall list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable.

(2) In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies is available, the categories and the adverse reactions within each category shall be listed in decreasing order of frequency. An adverse reaction that is significantly more severe than the other reactions listed in a category, however, shall be listed before those reactions, regardless of its frequency. If frequency information from adequate clinical studies is not available, the categories and adverse reactions within each category shall be listed in decreasing order of severity. The approximate frequency of each adverse reaction shall be expressed in rough estimates or orders of magnitude essentially as follows: "The most frequent adverse reaction(s) to (name of drug) is (are) (list reactions). This (these) occur(s) in about (e.g., one-third of patients; one in 30 patients; less than one-tenth of patients). Less frequent adverse reactions are (list reactions), which occur in approximately (e.g., one in 100 patients). Other adverse reactions, which occur rarely, in approximately (e.g., one in 1,000 patients), are (list reactions)." Percent figures may not ordinarily be used unless they are documented by adequate and well-controlled studies as defined in § 314.126(b) of this chapter, they are shown to reflect general experience, and they do not falsely imply a greater degree of accuracy than actually exists.

(3) The "Warnings" section of the labeling or, if appropriate, the "Contraindications" section of the labeling shall identify any potentially fatal adverse reaction.

(4) Any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions shall be based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(h) "Drug Abuse and Dependence": Under this section heading, the labeling shall contain the following subsections, as appropriate for the drug:

(1) Controlled Substance: If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled shall be stated.

(2) Abuse: This subsection of the labeling shall be based primarily on human data and human experience, but pertinent animal data may also be used. This subsection shall state the types of abuse that can occur with the drug and the adverse reactions pertinent to them. Particularly susceptible patient populations shall be identified.

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

(i) "Overdosage": Under this section heading, the labeling shall describe the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment. This section shall be based on human data, when available. If human data are unavailable, appropriate animal and in vitro data may be used. Specific information shall be provided about the following:

(1) Signs, symptoms, and laboratory findings associated with an overdosage of the drug.

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

(3) Oral LD[50] of the drug in animals; concentrations of the drug in biologic fluids associated with toxicity and/or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the "Clinical Pharmacology" section also may be referenced here, if applicable to overdoses.

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

(5) Whether the drug is dialyzable.

(6) Recommended general treatment procedures and specific measures for support of vital functions, such as proven antidotes, induced emesis, gastric lavage, and forced diuresis. Unqualified recommendations for which data are lacking with the specific drug or class of drugs, especially treatment using another drug (for example, central nervous system stimulants, respiratory stimulants) may not be stated unless specific data or scientific rationale exists to support safe and effective use.

(j) "Dosage and Administration": This section of the labeling shall state the recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established; dosages shall be stated for each indication when appropriate. This section shall also state the intervals recommended between doses, the optimal method of titrating dosage, the usual duration of treatment, and any modification of dosage needed in special patient populations, e.g., in children, in geriatric age groups, or in patients with renal or hepatic disease. Specific tables or monographs may be included to clarify dosage schedules. Radiation dosimetry information shall be stated for both the patient receiving a radioactive drug and the person administering it. This section shall also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed, e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the drug or reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs; and the following statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."

(k) "How Supplied": This section of the labeling shall contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information shall ordinarily include:

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

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

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

(4) Special handling and storage conditions.

(l) "Animal Pharmacology and/or Animal Toxicology": In most cases, the labeling need not include this section. Significant animal data necessary for safe and effective use of the drug in humans shall ordinarily be included in one or more of the other sections of the labeling, as appropriate. Commonly for a drug that has been marketed for a long time, and in rare cases for a new drug, chronic animal toxicity studies have not been performed or completed for a drug that is administered over prolonged periods or is implanted in the body. The unavailability of such data shall be stated in the appropriate section of the labeling for the drug. If the pertinent animal data cannot be appropriately incorporated into other sections of the labeling, this section may be used.

(m) "Clinical Studies" and "References": These sections may appear in labeling in the place of a detailed discussion of a subject that is of limited interest but nonetheless important. A reference to a specific important clinical study may be made in any section of the format required under §§ 201.56 and 201.57 if the study is essential to an understandable presentation of the available information. References may appear in sections of the labeling format, other than the "Clinical Studies" or "References" section, in rare circumstances only. A clinical study or reference may be cited in prescription drug labeling only under the following conditions:

(1) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning an indication for use of the drug, the reference shall be based upon, or the clinical study shall constitute, an adequate and well-controlled clinical investigation under § 314.126(b) of this chapter.

(2) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning a risk or risks from the use of the drug, the risk or risks shall also be identified or discussed in the appropriate section of the labeling for the drug.

HISTORY: [44 FR 37462, June 26, 1979, as amended at 55 FR 11576, March 29, 1990, 59 FR 64249, Dec. 13, 1994; 62 FR 45313, 45325, Aug. 27, 1997; 63 FR 66378, 66396, Dec. 1, 1998]

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

NOTES: NOTES APPLICABLE TO ENTIRE TITLE:
Cross References: Food Safety and Inspection Services, Department of Agriculture: See Meat and Poultry Inspection, 9 CFR CHAPTER III.
Federal Trade Commission: See Commercial Practices, 16 CFR chapter I.
U.S. Customs Service, Department of the Treasury: See Customs Duties, 19 CFR chapter I.
Internal Revenue Service, Department of theTreasury: See Internal Revenue, 26 CFR chapter I.
Bureau of Alcohol, Tobacco, and Firearms, Department of the Treasury: See Alcohol, Tobacco Production and Firearms, 27 CFR chapter I.

NOTES APPLICABLE TO ENTIRE CHAPTER:
[EDITORIAL NOTE: For nomenclature changes to chapter I see 59 FR 14366, Mar. 28, 1994.]
[PUBLISHER'S NOTE: For the uniform compliance date for food labeling regulations under Chapter 1, see 61 FR 67710, Dec. 24, 1996; 61 FR 68145, Dec. 27, 1996; 62 FR 49881, Sept. 23, 1997.]

NOTES APPLICABLE TO ENTIRE PART:
[PUBLISHER'S NOTE: Nomenclature changes affecting part 201 appear at 68 FR 24879, May 9, 2003; 69 FR 13716, 13717, Mar. 24, 2004.]

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LEXISNEXIS' CODE OF FEDERAL REGULATIONS
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TITLE 21 – FOOD AND DRUGS
REVISED AS OF APRIL 1, 2008
CHAPTER I – FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER C -- DRUGS: GENERAL
PART 201 -- LABELING
SUBPART B -- LABELING REQUIREMENTS FOR PRESCRIPTION DRUGS AND/OR INSULIN

21 CFR 201.57

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

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

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

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

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

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

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

(5) Recent major changes. A list of the section(s) of the full prescribing information, limited to the labeling sections described in paragraphs (c)(1), (c)(2), (c)(3), (c)(5), and (c)(6) of this section, that contain(s) substantive labeling changes that have been approved by FDA or authorized under § 314.70(c)(6) or (d)(2), or § 601.12(f)(1) through (f)(3) of this chapter. The heading(s) and, if appropriate, the subheading(s) of the labeling section(s) affected by the change

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(3) 2 Dosage and administration. (i) This section must state the recommended dose and, as appropriate:

(A) The dosage range,

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

(C) Dosages for each indication and subpopulation,

(D) The intervals recommended between doses,

(E) The optimal method of titrating dosage,

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

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

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

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

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

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

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

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

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

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

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

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

(6) 5 Warnings and precautions. (i) General. This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically signifi-

cant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

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

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

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

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

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

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

(A) Clinical trials experience. This section must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse reactions that occurred below the specified rate are included, they must be included in a separate listing. If comparative rates of occurrence cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), adverse reactions must be grouped within specified frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified, if frequency ranges cannot be determined. For adverse reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.

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

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

(8) 7 Drug interactions. (i) This section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them. The mechanism(s) of the interaction, if known, must be briefly described. Interactions that are described in the "Contraindications" or "Warnings and Precautions" sections must be discussed in more detail under this section. Details of drug interaction pharmacokinetic studies that are included in the "Clinical Pharmacology" section that are pertinent to clinical use of the drug must not be repeated in this section.

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

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

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

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

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

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

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

needed." The labeling must contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

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

(5) Pregnancy category X. If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling must state: "Pregnancy Category X. See 'Contraindications' section." Under "Contraindications," the labeling must state: "(Name of drug) may (can) cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) (Name of drug) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus."

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

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

(iii) 8.3 Nursing mothers. (A) If a drug is absorbed systemically, this subsection must contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring must be described.

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

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

(iv) 8.4 Pediatric use. (A) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(H) ofthis section, the terms pediatric population(s) and pediatric patient(s) are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates; infants, children, and adolescents.

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

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

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

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

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

(E) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the "Pediatric use" subsection must contain an appropriate statement such as "Safety and effectiveness in pediatric patients below the age of (--) have not been established." If use of the drug in this pediatric population is associated with a specific hazard, the hazard must be described in this subsection, or, if appropriate, the hazard must be stated in the "Contraindications" or "Warnings and Precautions" section and this subsection must refer to it.

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

(G) If the sponsor believes that none of the statements described in paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(F) of this section are appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if

FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

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

(v) 8.5 Geriatric use. (A) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population must be described under the "Indications and Usage" section, and appropriate geriatric dosage must be stated under the "Dosage and Administration" section. The "Geriatric use" subsection must cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the "Geriatric use" subsection must pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection must be discussed in more detail, if appropriate, under "Clinical Pharmacology" or the "Clinical Studies" section. As appropriate, this information must also be contained in the "Warnings and Precautions" and/or "Contraindications" section(s).

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

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

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

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

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

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

(C)(1) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they must be described briefly in the "Geriatric use" subsection and in detail under the "Clinical Pharmacology" section. The "Clinical Pharmacology" and "Drug Interactions" sections ordinarily contain information on drug/disease and drug/drug inte-

ractions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to use concomitant drugs.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(v) Whether the drug is dialyzable; and

(vi) Recommended general treatment procedures and specific measures for support of vital functions (e.g., proven antidotes, gastric lavage, forced diuresis, or as per Poison Control Center). Such recommendations must be based on

data available for the specific drug or experience with pharmacologically related drugs. Unqualified recommendations for which data are lacking for the specific drug or class of drugs must not be stated.

(12) 11 Description. (i) This section must contain:

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

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

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

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

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

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

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

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

(13) 12 Clinical pharmacology. (i) This section must contain information relating to the human clinical pharmacology and actions of the drug in humans. Pharmacologic information based on in vitro data using human biomaterials or pharmacologic animal models, or relevant details about in vivo study designs or results (e.g., drug interaction studies), may be included in this section if essential to understand dosing or drug interaction information presented in other sections of the labeling. This section must include the following subsections:

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

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

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

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

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

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

(14) 13 Nonclinical toxicology. This section must contain the following subsections as appropriate:

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

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

(15) 14 Clinical studies. This section must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively. Ordinarily, this section will describe the studies that support effectiveness for the labeled indication(s), including discussion of study design, population, endpoints, and results, but must not include an encyclopedic listing of all, or even most, studies performed as part of the product's clinical development program. If a specific important clinical study is mentioned in any section of the labeling required under §§ 201.56 and 201.57 because the study is essential to an understandable presentation of the information in that section of the labeling, any detailed discussion of the study must appear in this section.

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

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

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

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

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

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

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

(iv) Special handling and storage conditions.

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

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

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

(2) A horizontal line must separate the information required by paragraphs (a), (b), and (c) of this section.

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

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

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

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

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

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

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

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

HISTORY: *[71 FR 3922, 3988,* Jan. 24, 2006]

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

NOTES: [EFFECTIVE DATE NOTE: *71 FR 3922, 3988,* Jan. 24, 2006, added this section, effective June 30, 2006.]
NOTES APPLICABLE TO ENTIRE TITLE:
Cross References: Food Safety and Inspection Services, Department of Agriculture: See Meat and Poultry Inspection, 9 CFR CHAPTER III.
Federal Trade Commission: See Commercial Practices, 16 CFR chapter I.
U.S. Customs Service, Department of the Treasury: See Customs Duties, 19 CFR chapter I.
Internal Revenue Service, Department of the Treasury: See Internal Revenue, 26 CFR chapter I.

Bureau of Alcohol, Tobacco, and Firearms, Department of the Treasury: See Alcohol, Tobacco Production and Firearms, 27 CFR chapter I.

NOTES APPLICABLE TO ENTIRE CHAPTER:
[PUBLISHER'S NOTE NOTE: Nomenclature changes affecting chapter I appear at: *70 FR 40880,* July 15, 2005; *70 FR 67650,* Nov. 8, 2005.]
[PUBLISHER'S NOTE: For the uniform compliance date for food labeling regulations under Chapter 1, see *61 FR 67710,* Dec. 24, 1996; *61 FR 68145,* Dec. 27, 1996; *62 FR 49881,* Sept. 23, 1997.]

NOTES APPLICABLE TO ENTIRE PART:
[PUBLISHER'S NOTE: Nomenclature changes affecting part 201 appear at *68 FR 24879,* May 9, 2003; *69 FR 13716, 13717,* Mar. 24, 2004.]
[PUBLISHER'S NOTE: For Federal Register citations concerning Part 201 Notice of availability of additional questions and answers incorporated into Guidance for Industry: Bar Code Label Requirements, see: *71 FR 58739,* Oct. 5, 2006.]

NOTES TO DECISIONS: COURT AND ADMINISTRATIVE DECISIONS SIGNIFICANTLY DISCUSSING SECTION --
McNellis v Pfizer, Inc. (2005, DC NJ) *CCH Prod Liab Rep P17351* (criticized in Ackermann v Wyeth Pharms. (2006, ED Tex) *CCH Prod Liab Rep P17563)* and reconsideration den, Certificate of appealability granted, stay gr (2006, DC NJ) *CCH Prod Liab Rep P17585*
McNellis v Pfizer, Inc. (2006, DC NJ) *CCH Prod Liab Rep P17585*
Motus v Pfizer Inc. (2000, CD Cal) 127 F Supp 2d 1085, CCH Prod Liab Rep P15976 (criticized in *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig. (2006, ND Cal) 2006 US Dist LEXIS 95500)*

1 of 2 DOCUMENTS

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TITLE 21 -- FOOD AND DRUGS
REVISED AS OF APRIL 1, 2006
CHAPTER I – FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER C -- DRUGS: GENERAL
PART 201 – LABELING
SUBPART B -- LABELING REQUIREMENTS FOR PRESCRIPTION DRUGS AND/OR INSULIN

21 CFR 201.57

THERE ARE MULTIPLE VERSIONS OF THIS DOCUMENT.

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs. [This section was redesignated as § 201.80, effective June 30, 2006. See 71 FR 3922, 3988, Jan. 24, 2006.]

[PUBLISHER'S NOTE: This section was formerly § 201.57 and was redesignated as § 201.80 at *71 FR 3922, 3988*, Jan. 24, 2006, effective June 30, 2006.]

Each section heading listed in § 201.56(d), if not omitted under § 201.56(d)(3), shall contain the following information in the following order:

Each section heading listed in § 201.56(d), if not omitted under § 201.56(d)(3), shall contain the following information in the following order:

(a) Description: (1) Under this section heading, the labeling shall contain:

(i) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug;

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

(iii) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for labels;

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

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

(vi) The chemical name and structural formula of the drug;

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

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

(b) Clinical Pharmacology: (1) Under this section heading, the labeling shall contain a concise factual summary of the clinical pharmacology and actions of the drug in humans. The summary may include information based on in vitro and/or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. Pharmacokinetic information that is important to safe and effective use of the drug is required, if known, e.g., degree and rate of absorption, pathways of biotransformation, per-

centage of dose as unchanged drug and metabolites, rate or half-time of elimination, concentration in body fluids associated with therapeutic and/or toxic effects, degree of binding to plasma proteins, degree of uptake by a particular organ or in the fetus, and passage across the blood brain barrier. Inclusion of pharmacokinetic information is restricted to that which relates to clinical use of the drug. If the pharmacological mode of action of the drug is unknown or if important metabolic or pharmacokinetic data in humans are unavailable, the labeling shall contain a statement about the lack of information.

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

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

(ii) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled clinical studies, as defined in § 314.126(b) of this chapter, to be pertinent to clinical use may be used only if a waiver is granted under § 201.58 or § 314.126(b) of this chapter.

(c) Indications and Usage: (1) Under this section heading, the labeling shall state that:

(i) The drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, e.g., penicillin is indicated for the treatment of pneumonia due to susceptible pneumococci; and/or

(ii) The drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, e.g., chlorothiazide is indicated for the treatment of edema in patients with congestive heart failure; and/or

(iii) The drug is indicated for the relief of symptoms associated with a disease or syndrome, e.g., chlorpheniramine is indicated for the symptomatic relief of nasal congestion in patients with vasomotor rhinitis; and/or

(iv) The drug, if used for a particular indication only in conjuction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy.

(2) All indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(3) This section of the labeling shall also contain the following additional information:

(i) If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, syndrome, or symptom under consideration, e.g., patients with mild disease or patients in a special age group, the labeling shall describe the available evidence and state the limitations of usefulness of the drug. The labeling shall also identify specific tests needed for selection or monitoring of the patients who need the drug, e.g., microbe susceptibility tests. Information on the approximate kind, degree, and duration of improvement to be anticipated shall be stated if available and shall be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the "Dosage and Administration" section of the labeling and referenced in this section.

(ii) If safety considerations are such that the drug should be reserved for certain situations, e.g., cases refractory to other drugs, this information shall be stated in this section.

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

(iv) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use or condition.

(v) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication shall be supported by adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(d) Contraindications: Under this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of the drug to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, e.g., if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state "None known."

(e) Warnings: Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectivenes for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

(f) Precautions: Under this section heading, the labeling shall contain the following subsections as appropriate for the drug:

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

(2) Information for patients: This subsection of the labeling shall contain information to be given to patients for safe and effective use of the drug, e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects. Any printed patient information or Medication Guide required under this chapter to be distributed to the patient shall be referred to under the "Precautions" section of the labeling and the full text of such patient information or Medication Guide shall be reprinted at the end of the labeling. The print size requirements for the Medication Guide set forth in § 208.20 of this chapter, however, do not apply to the Medication Guide that is reprinted in the professional labeling.

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

(4)(i) Drug interactions: This subsection of the labeling shall contain specific practical guidance for the physician on preventing clinically significant drug/drug and drug/food interactions that may occur in vivo in patients taking the drug. Specific drugs or classes of drugs with which the drug to which the labeling applies may interact in vivo shall be identified, and the mechanism(s) of the interaction shall be briefly described. Information in this subsection of the labeling shall be limited to that pertaining to clinical use of the drug in patients. Drug interactions supported only by animal or in vitro experiments may not ordinarily be included, but animal or in vitro data may be used if shown to be clinically relevant. Drug incompatibilities, i.e., drug interactions that may occur when drugs are mixed in vitro, as in a solution for intravenous administration, shall be discussed under the "Dosage and Administration" section of the labeling rather than under this subsection of the labeling.

(ii) Drug/laboratory test interactions: This subsection of the labeling shall contain practical guidance on known interference of the drug with laboratory tests.

(5) Carcinogenesis, mutagenesis, impairment of fertility: This subsection of the labeling shall state whether long-term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If reproduction studies or other data in animals reveal a problem or potential problem concerning mutagenesis or impairment of fertility in either males or females, the information shall be described. Any precautionary statement on these topics shall include practical, relevant advice to the physician on the significance of these animal findings. If there is evidence from human data that the drug may be carcinogenic or mutagenic or that it impairs fertility, this information shall be included under the "Warnings" section of the labeling. Also, under "Precautions," the labeling shall state: "See 'Warnings' section for information on carcinogenesis, mutagenesis, and impairment of fertility."

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

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

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

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

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

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

(e) Pregnancy category X. If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling shall state: "Pregnancy Category X. See 'Contraindications' section." Under "Contraindications," the labeling shall state: "(Name of drug) may (can) cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinant animal data.) (Name of drug) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

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

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

(8) Nursing mothers: (i) If a drug is absorbed systemically, this subsection of the labeling shall contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring shall be described.

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

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

(9) Pediatric use: (i) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (f)(9)(ii) through (f)(9)(viii) of this setion, the terms "pediatric population(s)" and "pediatric patient(s)" are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

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

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

(iv) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the "Pediatric use" subsection of the labeling shall contain either the following statement, or a reasonable alternative: "The safety and effectiveness of (drug name) have been established in the age groups - to - (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (drug name) in these age groups is supported by evidence from adequate and well-controlled studies of (drug name) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population)." Data summarized in the preceding prescribed statement in this subsection of the labeling shall be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or the "Clinical Studies" section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the "Clinical Pharmacology" section. Pediatric dosing instructions shall be included in the "Dosage and Administration" section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients shall be cited briefly in the "Pediatric use" subsection and, as appropriate, in the "Contraindications," "Warnings," "Precautions," and "Dosage and Administration" sections.

(v) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the "Pediatric use" subsection of the labeling shall contain an appropriate statement such as "Safety and effectiveness in pediatric patients below the age of (-) have not been established." If use of the drug in this pediatric population is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.

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

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

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

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

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

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

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

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

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

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

(iii)(A) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they shall be described briefly in the "Geriatric use" subsection of the labeling and in detail under the "Clinical Pharmacology" section. The "Clinical Pharmacology" section and "Drug interactions" subsection of the "Precautions" section ordinarily contain information on drug-disease and drug-drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to utilize concomitant drugs.

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

"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."

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

(v) Labeling under paragraphs (f)(10)(i) through (f)(10)(iii) of this section may include statements, if they would be useful in enhancing safe use of the drug, that reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that:

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

(vi) If the sponsor believes that none of the requirements described in paragraphs (f)(10)(i) through (f)(10)(v) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

(g) Adverse Reactions: An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

(1) This section of the labeling shall list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable.

(2) In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies is available, the categories and the adverse reactions within each category shall be listed in decreasing order of frequency. An adverse reaction that is significantly more severe than the other reactions listed in a category, however, shall be listed before those reactions, regardless of its frequency. If frequency information from adequate clinical studies is not available, the categories and adverse reactions within each category shall be listed in decreasing order of severity. The approximate frequency of each adverse reaction shall be expressed in rough estimates or orders of magnitude essentially as follows: "The most frequent adverse reaction(s) to (name of drug) is (are) (list reactions). This (these) occur(s) in about (e.g., one-third of patients; one in 30 patients; less than one-tenth of patients). Less frequent adverse reactions are (list reactions), which occur in approximately (e.g., one in 100 patients). Other adverse reactions, which occur rarely, in approximately (e.g., one in 1,000 patients), are (list reactions)." Percent figures may not ordinarily be used unless they are documented by adequate and well-controlled studies as defined in § 314.126(b) of this chapter, they are shown to reflect general experience, and they do not falsely imply a greater degree of accuracy than actually exists.

(3) The "Warnings" section of the labeling or, if appropriate, the "Contraindications" section of the labeling shall identify any potentially fatal adverse reaction.

(4) Any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions shall be based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(h) Drug Abuse and Dependence: Under this section heading, the labeling shall contain the following subsections, as appropriate for the drug:

(1) Controlled Substance: If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled shall be stated.

(2) Abuse: This subsection of the labeling shall be based primarily on human data and human experience, but pertinent animal data may also be used. This subsection shall state the types of abuse that can occur with the drug and the adverse reactions pertinent to them. Particularly susceptible patient populations shall be identified.

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

(i) Overdosage: Under this section heading, the labeling shall describe the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment. This section shall be based on human data, when available. If human data are unavailable, appropriate animal and in vitro data may be used. Specific information shall be provided about the following:

(1) Signs, symptoms, and laboratory findings associated with an overdosage of the drug.

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

(3) Oral LD[50] of the drug in animals; concentrations of the drug in biologic fluids associated with toxicity and/or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the "Clinical Pharmacology" section also may be referenced here, if applicable to overdoses.

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

(5) Whether the drug is dialyzable.

(6) Recommended general treatment procedures and specific measures for support of vital functions, such as proven antidotes, induced emesis, gastric lavage, and forced diuresis. Unqualified recommendations for which data are lacking with the specific drug or class of drugs, especially treatment using another drug (for example, central nervous system stimulants, respiratory stimulants) may not be stated unless specific data or scientific rationale exists to support safe and effective use.

(j) Dosage and Administration: This section of the labeling shall state the recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established; dosages shall be stated for each indication when appropriate. This section shall also state the intervals recommended between doses, the optimal method of titrating dosage, the usual duration of treatment, and any modification of dosage needed in special patient populations, e.g., in children, in geriatric age groups, or in patients with renal or hepatic disease. Specific tables or monographs may be included to clarify dosage schedules. Radiation dosimetry information shall be stated for both the patient receiving a radioactive drug and the person administering it. This section shall also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed, e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the drug or reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs; and the following statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."

(k) How Supplied: This section of the labeling shall contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information shall ordinarily include:

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

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

Court EXHIBIT –

P's objections to D's Opening Statement

1. Label was amended several times for new indications or additional warnings but the FDA only approved the NEW drug once.
2. Agree with Plaintiff's position. Label is drafted by the company but the FDA can insist on certain language.
3. Objection Denied. Statement is OK.
4. Objection to statement upheld.
5. Objection Denied. D counsel should be allowed to make such inference.
6. Agree with P's position.
   a. P's have right to argue broader audience than Doctors.
   b. D can't argue that audience is strictly Doctors.
   c. However, D can argue the sophistication of the audience.
7. Included in Charge on Law.
8. Will include charge stating that a finding of "fraud" is not required.
9. Instruct defense counsel not to misquote the 1999 warning.
10. Require proper quoting of materials.
11. Will not prevent them from talking about what was known.
12. Will not prevent them from talking about what was known.
13. Will not allow argument concerning fact that DMH did not want to sue.
14. Will allow the use of the actual testimony of a witness who was present.
15. Agree that the video clip of deposition of a witness who was present and testifying should not be used.
16. Require in closing that any reference to SCDUP be accurate.
17. Will require that the Board be referred to by its proper name. I will also charge that Common Law Fraud is not required to be proved and will go over the elements.
18. Confine arguments to the Proof.
19. Statement is Ok.
20. I will instruct the jury on the law: specifically 39-5-110 provides that the attorney is the only state officer or agency which has the right or duty to bring an action under that code section.
21. Evidence regarding SCORE has been ruled inadmissible.
22. I will not prevent reference to that issue…it could go to the weight. Basis of their opinion.

D's objections to P's Opening Statement

1. I will instruct the jury on the law that what attorneys say in both closing and opening statements is evidence and cannot be used by them as such in reaching a verdict.
2. Denied. The duty is to communicate through its label which may be to Doctors or Patients.
3. I will instruct the jury that the issue before the court is a violation of SCUPTA not FDA Regulations or Federal Law.
4. While this is not a "fraud on the FDA" case the failure to disclose information would be evidence of willfulness.
5. Objection Denied.
6. D has made case that the statement when made was true, the fact that it did not avail itself of the mechanism of appeal to the FDA could be taken as an admission as to the truth or falsity of the statement.
7. Need Oral Argument.
8. The word "prosecuted" should not be used.
9. Could go to willfulness.

Court Exhibit 4

STATE OF SOUTH CAROLINA)	IN THE COURT OF COMMON PLEAS
)	FOR THE SEVENTH JUDICIAL CIRCUIT
COUNTY OF SPARTANBURG)	
STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina,)	Civil Action No. 2007-CP-42-1438
Plaintiff,)	
v.)	**DEFENDANTS' OFFER OF PROOF FOR THE POST-2007 FDA-APPROVED PACKAGE INSERT FOR ZYPREXA AND THE 2010 FDA-APPROVED PACKAGE INSERT FOR LATUDA**
ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA INC., and/or JANSSEN, L.P. and JOHNSON & JOHNSON, INC.,)	
Defendants.)	

Defendants, Ortho-McNeil-Janssen Pharmaceuticals, Inc. and Johnson & Johnson (erroneously named as Johnson & Johnson, Inc.), by and through their undersigned counsel, hereby submit this Offer of Proof in response to the Court's Order of March 7, 2011 and pursuant to South Carolina Rule of Evidence 103. The Court's Order excluded post-2004 evidence relating to weight gain, diabetes, and other metabolic risks associated with Risperdal® and other atypical antipsychotics. If Defendants had been allowed to offer post-2004 evidence related to weight gain, diabetes, and other metabolic risks associated with atypical antipsychotics, Defendants would have offered evidence that the U.S. Food and Drug Administration ("FDA") has acknowledged there are differences in the diabetes-related side effects associated with the various atypical antipsychotics. Specifically, Defendants would have offered evidence that the FDA has required Eli Lilly & Co., Inc., which manufactures Zyprexa®,

and Sunovion Pharmaceuticals Inc., which manufactures Latuda®, to add language to the warning sections of their package inserts acknowledging these differences.

The Zyprexa Package Insert

In 2007, the FDA required Eli Lilly to add a stronger diabetes-related warning to the Zyprexa package insert. Specifically, the Warnings and Precautions section of the post-2007 Zyprexa label provides:

> Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. 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. Epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics. **While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.**

D4011 at 8 (2009 Zyprexa Package Insert) (emphasis added), attached as Ex. A.

The Latuda Package Insert

Similarly, in October 2010, when the FDA approved a new atypical antipsychotic, Latuda, the FDA required Sunovion to include language in the Warnings and Precautions section of the Latuda label that recognized the differences in the metabolic-related side effects associated with the various atypical antipsychotics:

> Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. **While all of the drugs in the class have been**

shown to produce some metabolic changes, each drug has its own specific risk profile.

D6367 at 5 (2010 Latuda Package Insert) (emphasis added), attached as Ex. B.

Respectfully submitted,

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ATTORNEYS FOR DEFENDANTS

March 21, 2011.

CERTIFICATE OF SERVICE

I, Steven J. Pugh, a shareholder of Richardson Plowden & Robinson, P.A., do hereby certify that I served the foregoing DEFENDANTS' OFFER OF PROOF FOR THE POST-2007 FDA-APPROVED PACKAGE INSERT FOR ZYPREXA AND THE 2010 FDA-APPROVED PACKAGE INSERT FOR LATUDA to be served upon the following counsel of record by causing a copy of same to be e-mailed and/or mailed by United States Mail, Postage Prepaid, First Class, as noted below addressed as follows:

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Steven J. Pugh

March 21, 2011.

EXHIBIT A

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ZYPREXA (olanzapine) Tablet for Oral use
ZYPREXA ZYDIS (olanzapine) Tablet, Orally Disintegrating for Oral use
ZYPREXA IntraMuscular (olanzapine) Injection, Powder, For Solution for Intramuscular use

Initial U.S. Approval: 1996

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

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis. (5.1, 5.14, 17.2)

When using ZYPREXA and fluoxetine in combination, also refer to the Boxed Warning section of the package insert for Symbyax.

RECENT MAJOR CHANGES

Indications and Usage:	
Schizophrenia (1.1)	MM/2009
Bipolar I Disorder (Manic or Mixed Episodes) (1.2)	MM/2009
Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder (1.3)	MM/2009
ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania (1.4)	MM/2009
Indications and Usage, *ZYPREXA and Fluoxetine in Combination:*	
Depressive Episodes Associated with Bipolar I Disorder (1.5)	03/2009
Treatment Resistant Depression (1.6)	03/2009
Dosage and Administration:	
Schizophrenia (2.1)	MM/2009
Bipolar I Disorder (Manic or Mixed Episodes) (2.2)	MM/2009
Dosage and Administration, *ZYPREXA and Fluoxetine in Combination:*	
Depressive Episodes Associated with Bipolar I Disorder (2.5)	03/2009
Treatment Resistant Depression (2.6)	03/2009
Warnings and Precautions:	
Hyperglycemia (5.4)	03/2009
Hyperlipidemia (5.5)	03/2009
Weight Gain (5.6)	03/2009
Leukopenia, Neutropenia, and Agranulocytosis (5.9)	08/2009
Use in Patients with Concomitant Illness (5.14)	03/2009
Hyperprolactinemia (5.15)	03/2009
Use in Combination with Fluoxetine, Lithium, or Valproate (5.16)	03/2009
Laboratory Tests (5.17)	03/2009

INDICATIONS AND USAGE

ZYPREXA® (olanzapine) is an atypical antipsychotic indicated:

As oral formulation for the:

- Treatment of schizophrenia. (1.1)
  - Adults: Efficacy was established in three clinical trials in patients with schizophrenia: two 6-week trials and one maintenance trial. (14.1)
  - Adolescents (ages 13-17): Efficacy was established in one 6-week trial in patients with schizophrenia (14.1). The increased potential (in adolescents compared with adults) for weight gain and hyperlipidemia may lead clinicians to consider prescribing other drugs first in adolescents. (1.1)
- Acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. (1.2)
  - Adults: Efficacy was established in three clinical trials in patients with manic or mixed episodes of bipolar I disorder: two 3- to 4-week trials and one maintenance trial. (14.2)
  - Adolescents (ages 13-17): Efficacy was established in one 3-week trial in patients with manic or mixed episodes associated with bipolar I disorder (14.2). The increased potential (in adolescents compared with adults) for weight gain and hyperlipidemia may lead clinicians to consider prescribing other drugs first in adolescents. (1.2)
- Medication therapy for pediatric patients with schizophrenia or bipolar I disorder should be undertaken only after a thorough diagnostic evaluation and with careful consideration of the potential risks. (1.3)
- Adjunct to valproate or lithium in the treatment of manic or mixed episodes associated with bipolar I disorder. (1.2)
  - Efficacy was established in two 6-week clinical trials in adults (14.2). Maintenance efficacy has not been systematically evaluated.

As ZYPREXA IntraMuscular for the:

- Treatment of acute agitation associated with schizophrenia and bipolar I mania. (1.4)
  - Efficacy was established in three 1-day trials in adults. (14.3)

As ZYPREXA and Fluoxetine in Combination for the:

- Treatment of depressive episodes associated with bipolar I disorder. (1.5)
  - Efficacy was established with Symbyax (olanzapine and fluoxetine in combination) in adults; refer to the product label for Symbyax.
- Treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode). (1.6)
  - Efficacy was established with Symbyax (olanzapine and fluoxetine in combination) in adults; refer to the product label for Symbyax.

DOSAGE AND ADMINISTRATION

Schizophrenia in adults (2.1)	Oral: Start at 5-10 mg once daily; Target: 10 mg/day within several days
Schizophrenia in adolescents (2.1)	Oral: Start at 2.5-5 mg once daily; Target: 10 mg/day
Bipolar I Disorder (manic or mixed episodes) in adults (2.2)	Oral: Start at 10 or 15 mg once daily
Bipolar I Disorder (manic or mixed episodes) in adolescents (2.2)	Oral: Start at 2.5-5 mg once daily; Target: 10 mg/day
Bipolar I Disorder (manic or mixed episodes) with lithium or valproate in adults (2.2)	Oral: Start at 10 mg once daily
Agitation associated with Schizophrenia and Bipolar I Mania in adults (2.4)	IM: 10 mg (5 mg or 7.5 mg when clinically warranted) Assess for orthostatic hypotension prior to subsequent dosing (max. 3 doses 2-4 hrs apart)
Depressive Episodes associated with Bipolar I Disorder in adults (2.5)	Oral in combination with fluoxetine: Start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily
Treatment Resistant Depression in adults (2.6)	Oral in combination with fluoxetine: Start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily

- Lower starting dose recommended in debilitated or pharmacodynamically sensitive patients or patients with predisposition to hypotensive reactions, or with potential for slowed metabolism. (2.1)
- Olanzapine may be given without regard to meals. (2.1)

ZYPREXA and Fluoxetine in Combination:

- Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability. (2.5, 2.6)
- Olanzapine monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder or treatment resistant depression. (2.5, 2.6)
- Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated. (2.5, 2.6)

DOSAGE FORMS AND STRENGTHS

- Tablets (not scored): 2.5, 5, 7.5, 10, 15, 20 mg (3)
- Orally Disintegrating Tablets (not scored): 5, 10, 15, 20 mg (3)

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- Intramuscular Injection: 10 mg vial (3)

CONTRAINDICATIONS

- None with ZYPREXA monotherapy.
- When using ZYPREXA and fluoxetine in combination, also refer to the Contraindications section of the package insert for Symbyax®. (4)
- When using ZYPREXA in combination with lithium or valproate, refer to the Contraindications section of the package inserts for those products. (4)

WARNINGS AND PRECAUTIONS

- *Elderly Patients with Dementia-Related Psychosis:* Increased risk of death and increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack). (5.1)
- *Suicide:* The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy; when using in combination with fluoxetine, also refer to the Boxed Warning and Warnings and Precautions sections of the package insert for Symbyax. (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring. (5.3)
- *Hyperglycemia:* In some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking olanzapine. Patients taking olanzapine should be monitored for symptoms of hyperglycemia and undergo fasting blood glucose testing at the beginning of, and periodically during, treatment. (5.4)
- *Hyperlipidemia:* Undesirable alterations in lipids have been observed. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically during, treatment. (5.5)
- *Weight Gain:* Potential consequences of weight gain should be considered. Patients should receive regular monitoring of weight. (5.6)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate. (5.7)
- *Orthostatic Hypotension:* Orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, may occur especially during initial dose titration. Use caution in patients with cardiovascular disease, cerebrovascular disease, and those conditions that could affect hemodynamic responses. (5.8)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Has been reported with antipsychotics, including ZYPREXA. Patients with a history of a clinically significant low white blood cell count (WBC) or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.9)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.11)
- *Potential for Cognitive and Motor Impairment:* Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery. (5.12)
- *Hyperprolactinemia:* May elevate prolactin levels. (5.15)
- *Use in Combination with Fluoxetine, Lithium or Valproate:* Also refer to the package inserts for Symbyax, lithium, or valproate. (5.16)
- *Laboratory Tests:* Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment. (5.17)

ADVERSE REACTIONS

Most common adverse reactions (≥5% and at least twice that for placebo) associated with:

Oral Olanzapine Monotherapy:

- Schizophrenia (Adults) – postural hypotension, constipation, weight gain, dizziness, personality disorder, akathisia (6.1)
- Schizophrenia (Adolescents) – sedation, weight increased, headache, increased appetite, dizziness, abdominal pain, pain in extremity, fatigue, dry mouth (6.1)
- Manic or Mixed Episodes, Bipolar I Disorder (Adults) – asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor (6.1)
- Manic or Mixed Episodes, Bipolar I Disorder (Adolescents) – sedation, weight increased, increased appetite, headache, fatigue, dizziness, dry mouth, abdominal pain, pain in extremity (6.1)

Combination of ZYPREXA and Lithium or Valproate:

- Manic or Mixed Episodes, Bipolar I Disorder (Adults) – dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia (6.1)

ZYPREXA and Fluoxetine in Combination: Also refer to the Adverse Reactions section of the package insert for Symbyax. (6)

ZYPREXA IntraMuscular for Injection:

- Agitation with Schizophrenia and Bipolar I Mania (Adults) – somnolence (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- *Diazepam:* May potentiate orthostatic hypotension. (7.1, 7.2)
- *Alcohol:* May potentiate orthostatic hypotension. (7.1)
- *Carbamazepine:* Increased clearance of olanzapine. (7.1)
- *Fluvoxamine:* May increase olanzapine levels. (7.1)
- *ZYPREXA and Fluoxetine in Combination:* Also refer to the Drug Interactions section of the package insert for Symbyax. (7.1)
- *CNS Acting Drugs:* Caution should be used when taken in combination with other centrally acting drugs and alcohol. (7.2)
- *Antihypertensive Agents:* Enhanced antihypertensive effect. (7.2)
- *Levodopa and Dopamine Agonists:* May antagonize levodopa/dopamine agonists. (7.2)
- *Lorazepam (IM):* Increased somnolence with IM olanzapine. (7.2)
- *Other Concomitant Drug Therapy:* When using olanzapine in combination with lithium or valproate, refer to the Drug Interactions sections of the package insert for those products. (7.2)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* ZYPREXA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- *Nursing Mothers:* Breast-feeding is not recommended. (8.3)
- *Pediatric Use:* Safety and effectiveness of ZYPREXA in children <13 years of age have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

Revised: MM/2009

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FULL PRESCRIBING INFORMATION

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1, 5.14) and Patient Counseling Information (17.2)]*.

When using ZYPREXA and fluoxetine in combination, also refer to the Boxed Warning section of the package insert for Symbyax.

1 INDICATIONS AND USAGE

1.1 Schizophrenia

Oral ZYPREXA is indicated for the treatment of schizophrenia. Efficacy was established in three clinical trials in adult patients with schizophrenia: two 6-week trials and one maintenance trial. In adolescent patients with schizophrenia (ages 13-17), efficacy was established in one 6-week trial *[see Clinical Studies (14.1)]*.

When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Warnings and Precautions (5.5, 5.6)]*.

1.2 Bipolar I Disorder (Manic or Mixed Episodes)

Monotherapy — Oral ZYPREXA is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. Efficacy was established in three clinical trials in adult patients with manic or mixed episodes of bipolar I disorder: two 3- to 4-week trials and one monotherapy maintenance trial. In adolescent patients with manic or mixed episodes associated with bipolar I disorder (ages 13-17), efficacy was established in one 3-week trial *[see Clinical Studies (14.2)]*.

When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Warnings and Precautions (5.5, 5.6)]*.

Adjunctive Therapy to Lithium or Valproate — Oral ZYPREXA is indicated for the treatment of manic or mixed episodes associated with bipolar I disorder as an adjunct to lithium or valproate. Efficacy was established in two 6-week clinical trials in adults. The effectiveness of adjunctive therapy for longer-term use has not been systematically evaluated in controlled trials *[see Clinical Studies (14.2)]*.

1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder

Pediatric schizophrenia and bipolar I disorder are serious mental disorders; however, diagnosis can be challenging. For pediatric schizophrenia, symptom profiles can be variable, and for bipolar I disorder, pediatric patients may have variable patterns of periodicity of manic or mixed symptoms. It is recommended that medication therapy for pediatric schizophrenia and bipolar I disorder be initiated only after a thorough diagnostic evaluation has been performed and careful consideration given to the risks associated with medication treatment. Medication treatment for both pediatric schizophrenia and bipolar I disorder should be part of a total treatment program that often includes psychological, educational and social interventions.

1.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania

ZYPREXA IntraMuscular is indicated for the treatment of acute agitation associated with schizophrenia and bipolar I mania.

Efficacy was demonstrated in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients with: schizophrenia or bipolar I disorder (manic or mixed episodes) *[see Clinical Studies (14.3)]*.

"Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation.

1.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder

Oral ZYPREXA and fluoxetine in combination is indicated for the treatment of depressive episodes associated with bipolar I disorder, based on clinical studies in adult patients. When using ZYPREXA and fluoxetine in combination, refer to the Clinical Studies section of the package insert for Symbyax. ,

ZYPREXA monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.

1.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

Oral ZYPREXA and fluoxetine in combination is indicated for the treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode), based on clinical studies in adult patients. When using ZYPREXA and fluoxetine in combination, refer to the Clinical Studies section of the package insert for Symbyax.

ZYPREXA monotherapy is not indicated for the treatment of treatment resistant depression.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of 15 mg/day or greater) is recommended only after clinical assessment. Olanzapine is not indicated for use in doses above 20 mg/day.

Dosing in Special Populations — The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*. When indicated, dose escalation should be performed with caution in these patients.

Maintenance Treatment — The effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for relapse has been

demonstrated in a placebo-controlled trial *[see Clinical Studies (14.1)]*. The physician who elects to use ZYPREXA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Adolescents

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg, with a target dose of 10 mg/day. Efficacy in adolescents with schizophrenia was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 12.5 mg/day (mean dose of 11.1 mg/day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended.

The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials *[see Clinical Studies (14.1)]*.

Maintenance Treatment — The efficacy of ZYPREXA for the maintenance treatment of schizophrenia in the adolescent population has not been systematically evaluated; however, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.2 Bipolar I Disorder (Manic or Mixed Episodes)

Adults

Dose Selection for Monotherapy — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials *[see Clinical Studies (14.2)]*.

Maintenance Monotherapy — The benefit of maintaining bipolar I patients on monotherapy with oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of 2 weeks, was demonstrated in a controlled trial *[see Clinical Studies (14.2)]*. The physician who elects to use ZYPREXA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Dose Selection for Adjunctive Treatment — When administered as adjunctive treatment to lithium or valproate, oral olanzapine dosing should generally begin with 10 mg once-a-day without regard to meals.

Antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials *[see Clinical Studies (14.2)]*. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Adolescents

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg, with a target dose of 10 mg/day. Efficacy in adolescents with bipolar I disorder (manic or mixed episodes) was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 10.7 mg/day (mean dose of 8.9 mg/day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended.

The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials *[see Clinical Studies (14.2)]*.

Maintenance Treatment — The efficacy of ZYPREXA for the maintenance treatment of bipolar I disorder in the adolescent population has not been evaluated; however, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.3 Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)

After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without liquid.

2.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania

Dose Selection for Agitated Adult Patients with Schizophrenia and Bipolar I Mania — The efficacy of intramuscular olanzapine for injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant *[see Clinical Studies (14.3)]*. If agitation warranting additional intramuscular doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for injection in agitated patients has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (e.g., 3 doses of 10 mg administered 2-4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension *[see Warnings and Precautions (5.8)]*. Thus, it is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended.

If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate *[see Dosage and Administration (2.1, 2.2)]*.

Intramuscular Dosing in Special Populations — A dose of 5 mg/injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg/injection should be considered for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

Administration of ZYPREXA IntraMuscular — ZYPREXA IntraMuscular is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for Preparation of ZYPREXA IntraMuscular with Sterile Water for Injection — Dissolve the contents of the vial using 2.1 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow. ZYPREXA IntraMuscular reconstituted with Sterile Water for Injection should be used immediately (within 1 hour) after reconstitution. *Discard any unused portion.*

The following table provides injection volumes for delivering various doses of intramuscular olanzapine for injection reconstituted with Sterile Water for Injection.

Dose, mg Olanzapine	Volume of Injection, mL
10	Withdraw total contents of vial
7.5	1.5
5	1
2.5	0.5

Physical Incompatibility Information — ZYPREXA IntraMuscular should be reconstituted only with Sterile Water for Injection. ZYPREXA IntraMuscular should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed. Lorazepam injection should not be used to reconstitute ZYPREXA IntraMuscular as this combination results in a delayed reconstitution time. ZYPREXA IntraMuscular should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

2.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of oral olanzapine 5 to 12.5 mg and fluoxetine 20 to 50 mg. Antidepressant efficacy was demonstrated with ZYPREXA and fluoxetine in combination in adult patients with a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg.

Safety and efficacy of ZYPREXA and fluoxetine in combination was determined in clinical trials supporting approval of Symbyax (fixed dose combination of ZYPREXA and fluoxetine). Symbyax is dosed between 3 mg/25 mg (olanzapine/fluoxetine) per day and 12 mg/50 mg (olanzapine/fluoxetine) per day. The following table demonstrates the appropriate individual component doses of ZYPREXA and fluoxetine versus Symbyax. Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability.

Table 1: Approximate Dose Correspondence Between Symbyax[a] and the Combination of ZYPREXA and Fluoxetine

For Symbyax (mg/day)	Use in Combination	
	ZYPREXA (mg/day)	Fluoxetine (mg/day)
3 mg olanzapine/25 mg fluoxetine	2.5	20
6 mg olanzapine/25 mg fluoxetine	5	20
12 mg olanzapine/25 mg fluoxetine	10+2.5	20
6 mg olanzapine/50 mg fluoxetine	5	40+10
12 mg olanzapine/50 mg fluoxetine	10+2.5	40+10

[a] Symbyax (olanzapine/fluoxetine HCl) is a fixed-dose combination of ZYPREXA and fluoxetine.

While there is no body of evidence to answer the question of how long a patient treated with ZYPREXA and fluoxetine in combination should remain on it, it is generally accepted that bipolar I disorder, including the depressive episodes associated with bipolar I disorder, is a chronic illness requiring chronic treatment. The physician should periodically reexamine the need for continued pharmacotherapy.

Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies.

ZYPREXA monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.

2.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of oral olanzapine 5 to 20 mg and fluoxetine 20 to 50 mg. Antidepressant efficacy was demonstrated with olanzapine and fluoxetine in combination in adult patients with a dose range of olanzapine 6 to 18 mg and fluoxetine 25 to 50 mg.

Safety and efficacy of olanzapine in combination with fluoxetine was determined in clinical trials supporting approval of Symbyax (fixed dose combination of olanzapine and fluoxetine). Symbyax is dosed between 3 mg/25 mg (olanzapine/fluoxetine) per day and 12 mg/50 mg (olanzapine/fluoxetine) per day. Table 1 above demonstrates the appropriate individual component doses of ZYPREXA and fluoxetine versus Symbyax. Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability.

While there is no body of evidence to answer the question of how long a patient treated with ZYPREXA and fluoxetine in combination should remain on it, it is generally accepted that treatment resistant depression (major depressive disorder in adult patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode) is a chronic illness requiring chronic treatment. The physician should periodically reexamine the need for continued pharmacotherapy.

Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies.

ZYPREXA monotherapy is not indicated for treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 antidepressants of adequate dose and duration in the current episode).

2.7 ZYPREXA and Fluoxetine in Combination: Dosing in Special Populations

The starting dose of oral olanzapine 2.5-5 mg with fluoxetine 20 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine or fluoxetine in combination (female gender, geriatric age, nonsmoking status), or those patients who may be pharmacodynamically sensitive to olanzapine. Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism. When indicated, dose escalation should be performed with caution in these patients. ZYPREXA and fluoxetine in combination have not been systematically studied in patients over 65 years of age or in patients <18 years of age *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. Tablets are not scored. The tablets are available as follows:

	TABLET STRENGTH					
	2.5 mg	5 mg	7.5 mg	10 mg	15 mg	20 mg
Tablet No. Identification	4112 LILLY 4112	4115 LILLY 4115	4116 LILLY 4116	4117 LILLY 4117	4415 LILLY 4415	4420 LILLY 4420

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. Tablets are not scored. The tablets are available as follows:

	TABLET STRENGTH			
ZYPREXA ZYDIS Tablets	5 mg	10 mg	15 mg	20 mg
Tablet No.	4453	4454	4455	4456
Debossed	5	10	15	20

ZYPREXA IntraMuscular is available in 10 mg vial (1s).

4 CONTRAINDICATIONS

- None with ZYPREXA monotherapy.
- When using ZYPREXA and fluoxetine in combination, also refer to the Contraindications section of the package insert for Symbyax.
- For specific information about the contraindications of lithium or valproate, refer to the Contraindications section of the package inserts for these other products.

5 WARNINGS AND PRECAUTIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Warnings and Precautions section of the package insert for Symbyax.

5.1 Elderly Patients with Dementia-Related Psychosis

Increased Mortality — Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.14), and Patient Counseling Information (17.2)]*.

In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively).

Cerebrovascular Adverse Events (CVAE), Including Stroke — Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Patient Counseling Information (17.2)]*.

5.2 Suicide

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

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including olanzapine. 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 exclude 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 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 *[see Patient Counseling Information (17.3)]*.

5.4 Hyperglycemia

Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100-126 mg/dL, nonfasting 140-200 mg/dL). Patients taking olanzapine should be monitored regularly for worsening of glucose control. Patients starting treatment with olanzapine should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug *[see Patient Counseling Information (17.4)]*.

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. 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. Epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the 2 highest serum concentrations was 15.0 mg/dL.

In a study of healthy volunteers, subjects who received olanzapine (N=22) for 3 weeks had a mean increase compared to baseline in fasting blood glucose of 2.3 mg/dL. Placebo-treated subjects (N=19) had a mean increase in fasting blood glucose compared to baseline of 0.34 mg/dL.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with a median treatment duration of approximately 3 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (patients diagnosed with diabetes mellitus or related adverse reactions, patients treated with anti-diabetic agents, patients with a baseline random glucose level ≥200 mg/dL, and/or a baseline fasting glucose

level ≥126 mg/dL). Olanzapine-treated patients had a greater mean HbA1c increase from baseline of 0.04% (median exposure 21 days), compared to a mean HbA1c decrease of 0.06% in placebo-treated subjects (median exposure 17 days).

In an analysis of 8 placebo-controlled studies (median treatment exposure 4-5 weeks), 6.1% of olanzapine-treated subjects (N=855) had treatment-emergent glycosuria compared to 2.8% of placebo-treated subjects (N=599). Table 2 shows short-term and long-term changes in fasting glucose levels from adult olanzapine monotherapy studies.

Table 2: Changes in Fasting Glucose Levels from Adult Olanzapine Monotherapy Studies

			Up to 12 weeks exposure		At least 48 weeks exposure	
Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	N	Patients	N	Patients
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Olanzapine	543	2.2%	345	12.8%
		Placebo	293	3.4%	NA[a]	NA[a]
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Olanzapine	178	17.4%	127	26.0%
		Placebo	96	11.5%	NA[a]	NA[a]

[a] Not Applicable.

The mean change in fasting glucose for patients exposed at least 48 weeks was 4.2 mg/dL (N=487). In analyses of patients who completed 9-12 months of olanzapine therapy, mean change in fasting and nonfasting glucose levels continued to increase over time.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a greater mean change from baseline in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). The mean change in fasting glucose for adolescents exposed at least 24 weeks was 3.1 mg/dL (N=121). Table 3 shows short-term and long-term changes in fasting blood glucose from adolescent olanzapine monotherapy studies.

Table 3: Changes in Fasting Glucose Levels from Adolescent Olanzapine Monotherapy Studies

			Up to 12 weeks exposure		At least 24 weeks exposure	
Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	N	Patients	N	Patients
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Olanzapine	124	0%	108	0.9%
		Placebo	53	1.9%	NA[a]	NA[a]
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Olanzapine	14	14.3%	13	23.1%
		Placebo	13	0%	NA[a]	NA[a]

[a] Not Applicable.

5.5 Hyperlipidemia

Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using olanzapine, is recommended *[see Patient Counseling Information (17.5)]*.

Clinically significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no clinically meaningful differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse reactions, patients treated with lipid lowering agents, or patients with high baseline lipid levels.

In long-term studies (at least 48 weeks), patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.6 mg/dL, 2.5 mg/dL, and 18.7 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 0.16 mg/dL. In an analysis of patients who completed 12 months of therapy, the mean nonfasting total cholesterol did not increase further after approximately 4-6 months.

The proportion of patients who had changes (at least once) in total cholesterol, LDL cholesterol or triglycerides from normal or borderline to high, or changes in HDL cholesterol from normal or borderline to low, was greater in long-term studies (at least 48 weeks) as compared with short-term studies. Table 4 shows categorical changes in fasting lipids values.

Table 4: Changes in Fasting Lipids Values from Adult Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure N	Up to 12 weeks exposure Patients	At least 48 weeks exposure N	At least 48 weeks exposure Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	745	39.6%	487	61.4%
		Placebo	402	26.1%	NA[a]	NA[a]
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Olanzapine	457	9.2%	293	32.4%
		Placebo	251	4.4%	NA[a]	NA[a]
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	135	39.3%	75	70.7%
		Placebo	65	20.0%	NA[a]	NA[a]
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	745	21.6%	489	32.9%
		Placebo	402	9.5%	NA[a]	NA[a]
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Olanzapine	392	2.8%	283	14.8%
		Placebo	207	2.4%	NA[a]	NA[a]
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Olanzapine	222	23.0%	125	55.2%
		Placebo	112	12.5%	NA[a]	NA[a]
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	536	23.7%	483	39.8%
		Placebo	304	14.1%	NA[a]	NA[a]
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Olanzapine	154	0%	123	7.3%
		Placebo	82	1.2%	NA[a]	NA[a]
	Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL)	Olanzapine	302	10.6%	284	31.0%
		Placebo	173	8.1%	NA[a]	NA[a]

[a] Not Applicable.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the mean increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescents, including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine-treated adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 12.9 mg/dL, 6.5 mg/dL, and 28.4 mg/dL, respectively, compared to increases from baseline in mean fasting total cholesterol and LDL cholesterol of 1.3 mg/dL and 1.0 mg/dL, and a decrease in triglycerides of 1.1 mg/dL for placebo-treated adolescents. For fasting HDL cholesterol, no clinically meaningful differences were observed between olanzapine-treated adolescents and placebo-treated adolescents.

In long-term studies (at least 24 weeks), adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.5 mg/dL, 5.4 mg/dL, and 20.5 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 4.5 mg/dL. Table 5 shows categorical changes in fasting lipids values in adolescents.

Table 5: Changes in Fasting Lipids Values from Adolescent Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 6 weeks exposure N	Up to 6 weeks exposure Patients	At least 24 weeks exposure N	At least 24 weeks exposure Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	138	37.0%	122	45.9%
		Placebo	66	15.2%	NA[a]	NA[a]
	Normal to High (<90 mg/dL to >130 mg/dL)	Olanzapine	67	26.9%	66	36.4%
		Placebo	28	10.7%	NA[a]	NA[a]
	Borderline to High (≥90 mg/dL and ≤130 mg/dL to >130 mg/dL)	Olanzapine	37	59.5%	31	64.5%
		Placebo	17	35.3%	NA[a]	NA[a]
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	138	14.5%	122	14.8%
		Placebo	66	4.5%	NA[a]	NA[a]
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	87	6.9%	78	7.7%
		Placebo	43	2.3%	NA[a]	NA[a]
	Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	36	38.9%	33	57.6%
		Placebo	13	7.7%	NA[a]	NA[a]

Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	137	17.5%	121	22.3%
		Placebo	63	11.1%	NA[a]	NA[a]
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	98	5.1%	92	10.9%
		Placebo	44	4.5%	NA[a]	NA[a]
	Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	29	48.3%	21	47.6%
		Placebo	9	0%	NA[a]	NA[a]

[a] Not Applicable.

5.6 Weight Gain

Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight *[see Patient Counseling Information (17.6)]*.

Olanzapine Monotherapy in Adults — In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg (5.7 lb) compared to an average 0.3 kg (0.6 lb) weight loss in placebo-treated patients with a median exposure of 6 weeks; 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight, compared to 3% of placebo-treated patients, with a median exposure of 8 weeks; 4.2% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 0.3% of placebo-treated patients, with a median exposure of 12 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients and in 0% of placebo-treated patients.

In long-term studies (at least 48 weeks), the mean weight gain was 5.6 kg (12.3 lb) (median exposure of 573 days, N=2021). The percentages of patients who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 64%, 32%, and 12%, respectively. Discontinuation due to weight gain occurred in 0.4% of olanzapine-treated patients following at least 48 weeks of exposure.

Table 6 includes data on adult weight gain with olanzapine pooled from 86 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 6: Weight Gain with Olanzapine Use in Adults

Amount Gained kg (lb)	6 Weeks (N=7465) (%)	6 Months (N=4162) (%)	12 Months (N=1345) (%)	24 Months (N=474) (%)	36 Months (N=147) (%)
≤0	26.2	24.3	20.8	23.2	17.0
0 to ≤5 (0-11 lb)	57.0	36.0	26.0	23.4	25.2
>5 to ≤10 (11-22 lb)	14.9	24.6	24.2	24.1	18.4
>10 to ≤15 (22-33 lb)	1.8	10.9	14.9	11.4	17.0
>15 to ≤20 (33-44 lb)	0.1	3.1	8.6	9.3	11.6
>20 to ≤25 (44-55 lb)	0	0.9	3.3	5.1	4.1
>25 to ≤30 (55-66 lb)	0	0.2	1.4	2.3	4.8
>30 (>66 lb)	0	0.1	0.8	1.2	2

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. Mean increase in weight in adolescents was greater than in adults. In 4 placebo-controlled trials, discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to 0% of placebo-treated patients.

Table 7: Weight Gain with Olanzapine Use in Adolescents from 4 Placebo-Controlled Trials

	Olanzapine-treated patients	Placebo-treated patients
Mean change in body weight from baseline (median exposure = 3 weeks)	4.6 kg (10.1 lb)	0.3 kg (0.7 lb)
Percentage of patients who gained at least 7% of baseline body weight	40.6% (median exposure to 7% = 4 weeks)	9.8% (median exposure to 7% = 8 weeks)
Percentage of patients who gained at least 15% of baseline body weight	7.1% (median exposure to 15% = 19 weeks)	2.7% (median exposure to 15% = 8 weeks)

In long-term studies (at least 24 weeks), the mean weight gain was 11.2 kg (24.6 lb); (median exposure of 201 days, N=179). The percentages of adolescents who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 89%, 55%, and 29%, respectively. Among adolescent patients, mean weight gain by baseline BMI category was 11.5 kg (25.3 lb), 12.1 kg (26.6 lb), and 12.7 kg (27.9 lb), respectively, for normal (N=106), overweight (N=26) and obese (N=17). Discontinuation due to weight gain occurred in 2.2% of olanzapine-treated patients following at least 24 weeks of exposure.

Table 8 shows data on adolescent weight gain with olanzapine pooled from 6 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified. Little clinical trial data is available on weight gain in adolescents with olanzapine beyond 6 months of treatment.

Table 8: Weight Gain with Olanzapine Use in Adolescents

Amount Gained kg (lb)	6 Weeks (N=243) (%)	6 Months (N=191) (%)
≤0	2.9	2.1
0 to ≤5 (0-11 lb)	47.3	24.6
>5 to ≤10 (11-22 lb)	42.4	26.7
>10 to ≤15 (22-33 lb)	5.8	22.0
>15 to ≤20 (33-44 lb)	0.8	12.6
>20 to ≤25 (44-55 lb)	0.8	9.4
>25 to ≤30 (55-66 lb)	0	2.1
>30 to ≤35 (66-77 lb)	0	0
>35 to ≤40 (77-88 lb)	0	0
>40 (>88 lb)	0	0.5

5.7 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 or may even arise after discontinuation of treatment.

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, olanzapine 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 (1) who suffer from a chronic illness that 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 olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

For specific information about the warnings of lithium or valproate, refer to the Warnings section of the package inserts for these other products.

5.8 Orthostatic Hypotension

Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonistic properties *[see Patient Counseling Information (17.7)]*.

For oral olanzapine therapy, the risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD *[see Dosage and Administration (2)]*. A more gradual titration to the target dose should be considered if hypotension occurs.

Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in nonagitated patients with schizophrenia in which the safety and tolerability of intramuscular olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (i.e., decrease ≥30 mmHg) *[see Dosage and Administration (2.4)]*. Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the reactions occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. For intramuscular olanzapine for injection therapy, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation.

Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression *[see Drug Interactions (7)]*. Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine has not been studied and is therefore not recommended. If use of intramuscular olanzapine in combination with parenteral benzodiazepines is considered, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

5.9 Leukopenia, Neutropenia, and Agranulocytosis

Class Effect — In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including ZYPREXA. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue ZYPREXA and have their WBC followed until recovery.

5.10 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine is not approved for the treatment of patients with Alzheimer's disease.

5.11 Seizures

During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Olanzapine is not approved for the treatment of patients with Alzheimer's disease. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.12 Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse reaction associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse reaction was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

Since olanzapine 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 olanzapine therapy does not affect them adversely *[see Patient Counseling Information (17.8)]*.

5.13 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration *[see Patient Counseling Information (17.9)]*.

5.14 Use in Patients with Concomitant Illness

Clinical experience with olanzapine in patients with certain concomitant systemic illnesses is limited *[see Clinical Pharmacology (12.3)]*.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with olanzapine, olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse reactions possibly related to cholinergic antagonism. Such adverse reactions were not often the basis for discontinuations from olanzapine, but olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus or related conditions.

In 5 placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse reactions were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse reactions was greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1), and Patient Counseling Information (17.2)]*.

Olanzapine 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 premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients *[see Warnings and Precautions (5.8)]*.

5.15 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, olanzapine elevates prolactin levels, and a modest elevation persists during chronic administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

In clinical studies, elevated plasma prolactin concentrations were observed in 34% of adults treated with olanzapine compared to 13.1% of placebo-treated patients. In a pooled analysis from clinical studies including 8136 adults treated with olanzapine, potentially associated clinical manifestations such as galactorrhea (14/8136; 0.2%), gynecomastia (8/4896; 0.2% of males), and breast enlargement (2/3240; 0.06% of females) were reported.

In placebo-controlled olanzapine monotherapy studies in adolescent patients with schizophrenia or bipolar I disorder (manic or mixed episodes), elevated prolactin concentrations compared to baseline occurred in 47.4% of olanzapine-treated patients compared to 6.8% of placebo-treated patients. In long-term clinical trials of olanzapine in adolescents, gynecomastia occurred in 2.4% of males (7/286) and galactorrhea occurred in 1.8% of females (3/168) *[see Use in Specific Populations (8.4)]*.

5.16 Use in Combination with Fluoxetine, Lithium, or Valproate

When using ZYPREXA and fluoxetine in combination, the prescriber should also refer to the Warnings and Precautions section of the package insert for Symbyax. When using ZYPREXA in combination with lithium or valproate, the prescriber should refer to the Warnings and Precautions sections of the package inserts for lithium or valproate *[see Drug Interactions (7)]*.

5.17 Laboratory Tests

Fasting blood glucose testing and lipid profile at the beginning of, and periodically during, treatment is recommended *[see Warnings and Precautions (5.4, 5.5) and Patient Counseling Information (17.4, 17.5)]*.

6 ADVERSE REACTIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Adverse Reactions section of the package insert for Symbyax.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect or predict the rates observed in practice.

Clinical Trials in Adults

The information below for olanzapine is derived from a clinical trial database for olanzapine consisting of 8661 adult patients with approximately 4165 patient-years of exposure to oral olanzapine and 722 patients with exposure to intramuscular olanzapine for injection. This database includes: (1) 2500 patients who participated in multiple-dose oral olanzapine premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in oral olanzapine premarketing bipolar I disorder (manic or mixed episodes) trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in an oral olanzapine trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; (4) 5788 patients from 88 additional oral olanzapine clinical trials as of December 31, 2001; and (5) 722 patients who participated in intramuscular olanzapine for injection premarketing trials in agitated patients with schizophrenia, bipolar I disorder (manic or mixed episodes), or dementia. In addition, information from the premarketing 6-week clinical study database for olanzapine in combination with lithium or valproate, consisting of 224 patients who participated in bipolar I disorder (manic or mixed episodes) trials with approximately 22 patient-years of exposure, is included below.

The conditions and duration of treatment with olanzapine varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, weights, laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely, dose-dependent adverse reactions, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar I disorder (manic or mixed episodes) or agitation. However, this information is also generally applicable to bipolar I disorder (manic or mixed episodes) and agitation.

Adverse reactions during 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 reactions without first grouping similar types of reactions into a smaller number of standardized reaction categories. In the tables and tabulations that follow, MedDRA and COSTART Dictionary terminology has been used to classify reported adverse reactions.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The reported reactions do not include those reaction terms that were so general as to be uninformative. Reactions listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the reactions occurred during treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

The prescriber should be aware that the figures in the tables and tabulations 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 that prevailed in the clinical trials. 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 adverse reactions incidence in the population studied.

Incidence of Adverse Reactions in Short-Term, Placebo-Controlled and Combination Trials

The following findings are based on premarketing trials of (1) oral olanzapine for schizophrenia, bipolar I disorder (manic or mixed episodes), a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease, and premarketing combination trials, and (2) intramuscular olanzapine for injection in agitated patients with schizophrenia or bipolar I mania.

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Schizophrenia — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (5% for oral olanzapine vs 6% for placebo). However, discontinuations due to increases in ALT were considered to be drug related (2% for oral olanzapine vs 0% for placebo).

Bipolar I Disorder (Manic or Mixed Episodes) Monotherapy — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (2% for oral olanzapine vs 2% for placebo).

Agitation — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (0.4% for intramuscular olanzapine for injection vs 0% for placebo).

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term Combination Trials

Bipolar I Disorder (Manic or Mixed Episodes), Olanzapine as Adjunct to Lithium or Valproate — In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse reactions were 11% for the combination of oral olanzapine with lithium or valproate compared to 2% for patients who remained on lithium or valproate monotherapy. Discontinuations with the combination of oral olanzapine and lithium or valproate that occurred in more than 1 patient were: somnolence (3%), weight gain (1%), and peripheral edema (1%).

Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials

The most commonly observed adverse reactions associated with the use of oral olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

Table 9: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Trials — SCHIZOPHRENIA

	Percentage of Patients Reporting Event	
Adverse Reaction	Olanzapine (N=248)	Placebo (N=118)
Postural hypotension	5	2
Constipation	9	3
Weight gain	6	1
Dizziness	11	4
Personality disorder[a]	8	4
Akathisia	5	1

[a] Personality disorder is the COSTART term for designating nonaggressive objectionable behavior.

Table 10: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 3-Week and 4-Week Trials — Bipolar I Disorder (Manic or Mixed Episodes)

	Percentage of Patients Reporting Event	
Adverse Reaction	Olanzapine (N=125)	Placebo (N=129)
Asthenia	15	6
Dry mouth	22	7
Constipation	11	5
Dyspepsia	11	5
Increased appetite	6	3

16		
Somnolence	35	13
Dizziness	18	6
Tremor	6	3

Olanzapine Intramuscular — There was 1 adverse reaction (somnolence) observed at an incidence of 5% or greater among intramuscular olanzapine for injection-treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) during the placebo-controlled premarketing studies. The incidence of somnolence during the 24 hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar I mania was 6% for intramuscular olanzapine for injection and 3% for placebo.

Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term, Placebo-Controlled Trials

Table 11 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with oral olanzapine (doses ≥2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of placebo-controlled trials.

Table 11: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials with Oral Olanzapine

	Percentage of Patients Reporting Event	
Body System/Adverse Reaction	Olanzapine (N=532)	Placebo (N=294)
Body as a Whole		
Accidental injury	12	8
Asthenia	10	9
Fever	6	2
Back pain	5	2
Chest pain	3	1
Cardiovascular System		
Postural hypotension	3	1
Tachycardia	3	1
Hypertension	2	1
Digestive System		
Dry mouth	9	5
Constipation	9	4
Dyspepsia	7	5
Vomiting	4	3
Increased appetite	3	2
Hemic and Lymphatic System		
Ecchymosis	5	3
Metabolic and Nutritional Disorders		
Weight gain	5	3
Peripheral edema	3	1
Musculoskeletal System		
Extremity pain (other than joint)	5	3
Joint pain	5	3
Nervous System		
Somnolence	29	13
Insomnia	12	11
Dizziness	11	4
Abnormal gait	6	1
Tremor	4	3
Akathisia	3	2
Hypertonia	3	2
Articulation impairment	2	1
Respiratory System		
Rhinitis	7	6
Cough increased	6	3
Pharyngitis	4	3
Special Senses		
Amblyopia	3	2
Urogenital System		

17		
Urinary incontinence	2	1
Urinary tract infection	2	1

Commonly Observed Adverse Reactions in Short-Term Trials of Oral Olanzapine as Adjunct to Lithium or Valproate

In the bipolar I disorder (manic or mixed episodes) adjunct placebo-controlled trials, the most commonly observed adverse reactions associated with the combination of olanzapine and lithium or valproate (incidence of ≥5% and at least twice placebo) were:

Table 12: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Adjunct to Lithium or Valproate Trials — Bipolar I Disorder (Manic or Mixed Episodes)

	Percentage of Patients Reporting Event	
Adverse Reaction	Olanzapine with lithium or valproate (N=229)	Placebo with lithium or valproate (N=115)
Dry mouth	32	9
Weight gain	26	7
Increased appetite	24	8
Dizziness	14	7
Back pain	8	4
Constipation	8	4
Speech disorder	7	1
Increased salivation	6	2
Amnesia	5	2
Paresthesia	5	2

Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term Trials of Olanzapine as Adjunct to Lithium or Valproate

Table 13 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with the combination of olanzapine (doses ≥5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials.

Table 13: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials of Oral Olanzapine as Adjunct to Lithium or Valproate

	Percentage of Patients Reporting Event	
Body System/Adverse Reaction	Olanzapine with lithium or valproate (N=229)	Placebo with lithium or valproate (N=115)
Body as a Whole		
Asthenia	18	13
Back pain	8	4
Accidental injury	4	2
Chest pain	3	2
Cardiovascular System		
Hypertension	2	1
Digestive System		
Dry mouth	32	9
Increased appetite	24	8
Thirst	10	6
Constipation	8	4
Increased salivation	6	2
Metabolic and Nutritional Disorders		
Weight gain	26	7
Peripheral edema	6	4
Edema	2	1
Nervous System		
Somnolence	52	27
Tremor	23	13
Depression	18	17
Dizziness	14	7
Speech disorder	7	1
Amnesia	5	2
Paresthesia	5	2

18		
Apathy	4	3
Confusion	4	1
Euphoria	3	2
Incoordination	2	0
Respiratory System		
Pharyngitis	4	1
Dyspnea	3	1
Skin and Appendages		
Sweating	3	1
Acne	2	0
Dry skin	2	0
Special Senses		
Amblyopia	9	5
Abnormal vision	2	0
Urogenital System		
Dysmenorrhea[a]	2	0
Vaginitis[a]	2	0

[a] Denominator used was for females only (olanzapine, N=128; placebo, N=51).

For specific information about the adverse reactions observed with lithium or valproate, refer to the Adverse Reactions section of the package inserts for these other products.

Adverse Reactions Occurring at an Incidence of 1% or More among Intramuscular Olanzapine for Injection-Treated Patients in Short-Term, Placebo-Controlled Trials

Table 14 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 1% or more of patients treated with intramuscular olanzapine for injection (dose range of 2.5-10 mg/injection) and with incidence greater than placebo who participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar I mania.

Table 14: Treatment-Emergent Adverse Reactions: Incidence in Short-Term (24 Hour), Placebo-Controlled Clinical Trials with Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia or Bipolar I Mania

	Percentage of Patients Reporting Event	
Body System/Adverse Reaction	Olanzapine (N=415)	Placebo (N=150)
Body as a Whole		
Asthenia	2	1
Cardiovascular System		
Hypotension	2	0
Postural hypotension	1	0
Nervous System		
Somnolence	6	3
Dizziness	4	2
Tremor	1	0

Additional Findings Observed in Clinical Trials

Dose Dependency of Adverse Reactions in Short-Term, Placebo-Controlled Trials

Extrapyramidal Symptoms: The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during acute therapy in a controlled clinical trial comparing oral olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

Table 15: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase

	Percentage of Patients Reporting Event			
	Placebo	Olanzapine 5 ± 2.5 mg/day	Olanzapine 10 ± 2.5 mg/day	Olanzapine 15 ± 2.5 mg/day
Parkinsonism[a]	15	14	12	14
Akathisia[b]	23	16	19	27

[a] Percentage of patients with a Simpson-Angus Scale total score >3.

[b] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

Table 16: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase

	Percentage of Patients Reporting Event			
	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Dystonic events[a]	1	3	2	3
Parkinsonism events[b]	10	8	14	20
Akathisia events[c]	1	5	11	10
Dyskinetic events[d]	4	0	2	1
Residual events[e]	1	2	5	1
Any extrapyramidal event	16	15	25	32

[a] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

[b] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

[c] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

[d] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

[e] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

The following table enumerates the percentage of adolescent patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy (dose range: 2.5 to 20 mg/day).

Table 17: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in Placebo-Controlled Clinical Trials of Oral Olanzapine in Schizophrenia and Bipolar I Disorder — Adolescents

	Percentage of Patients Reporting Event	
Categories[a]	Placebo (N=89)	Olanzapine (N=179)
Dystonic events	0	1
Parkinsonism events	2	1
Akathisia events	4	6
Dyskinetic events	0	1
Nonspecific events	0	4
Any extrapyramidal event	6	10

[a] Categories are based on Standard MedDRA Queries (SMQ) for extrapyramidal symptoms as defined in MedDRA version 12.0.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during controlled clinical trials comparing fixed doses of intramuscular olanzapine for injection with placebo in agitation. Patients in each dose group could receive up to 3 injections during the trials *(see Clinical Studies (14.3))*. Patient assessments were conducted during the 24 hours following the initial dose of intramuscular olanzapine for injection.

Table 18: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia

	Percentage of Patients Reporting Event				
	Placebo	Olanzapine IM 2.5 mg	Olanzapine IM 5 mg	Olanzapine IM 7.5 mg	Olanzapine IM 10 mg
Parkinsonism[a]	0	0	0	0	3
Akathisia[b]	0	0	5	0	0

[a] Percentage of patients with a Simpson-Angus Scale total score >3.

[b] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions in the same controlled clinical trial comparing fixed doses of intramuscular olanzapine for injection with placebo in agitated patients with schizophrenia.

Table 19: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia

	Percentage of Patients Reporting Event				
	Placebo (N=45)	Olanzapine IM 2.5 mg (N=48)	Olanzapine IM 5 mg (N=45)	Olanzapine IM 7.5 mg (N=46)	Olanzapine IM 10 mg (N=46)
Dystonic events[a]	0	0	0	0	0
Parkinsonism events[b]	0	4	2	0	0
Akathisia events[c]	0	2	0	0	0
Dyskinetic events[d]	0	0	0	0	0
Residual events[e]	0	0	0	0	0
Any extrapyramidal events	0	4	2	0	0

[a] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

[b] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

[c] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

[d] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

[e] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

Dystonia, Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, the frequency and severity are greater with high potency and at higher doses of first generation antipsychotic drugs. In general, an elevated risk of acute dystonia may be observed in males and younger age groups receiving antipsychotics; however, events of dystonia have been reported infrequently (<1%) with olanzapine use.

Other Adverse Reactions: The following table addresses dose relatedness for other adverse reactions using data from a schizophrenia trial involving fixed dosage ranges of oral olanzapine. It enumerates the percentage of patients with treatment-emergent adverse reactions for the 3 fixed-dose range groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and the table includes only those adverse reactions for which there was a trend.

Table 20: Percentage of Patients from a Schizophrenia Trial with Treatment-Emergent Adverse Reactions for the 3 Dose Range Groups and Placebo

	Percentage of Patients Reporting Event			
Adverse Reaction	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Asthenia	15	8	9	20
Dry mouth	4	3	5	13
Nausea	9	0	2	9
Somnolence	16	20	30	39
Tremor	3	0	5	7

Differences among Fixed-Dose Groups Observed in Other Olanzapine Clinical Trials

In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of oral olanzapine in patients with schizophrenia or schizoaffective disorder, differences among 3 dose groups were observed for the following safety outcomes: weight gain, prolactin elevation, fatigue and dizziness. Mean baseline to endpoint increase in weight (10 mg/day: 1.9 kg; 20 mg/day: 2.3 kg; 40 mg/day: 3 kg) was observed with significant differences between 10 vs 40 mg/day. Incidence of treatment-emergent prolactin elevation >24.2 ng/mL (female) or >18.77 ng/mL (male) at any time during the trial (10 mg/day: 31.2%; 20 mg/day: 42.7%; 40 mg/day: 61.1%) with significant differences between 10 vs 40 mg/day and 20 vs 40 mg/day; fatigue (10 mg/day: 1.5%; 20 mg/day: 2.1%; 40 mg/day: 6.6%) with significant differences between 10 vs 40 and 20 vs 40 mg/day; and dizziness (10 mg/day: 2.6%; 20 mg/day: 1.6%; 40 mg/day: 6.6%) with significant differences between 20 vs 40 mg, was observed.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Oral Olanzapine

Following is a list of treatment-emergent adverse reactions reported by patients treated with oral olanzapine (at multiple doses ≥1 mg/day) in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo. Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

Body as a Whole — *Infrequent:* chills, face edema, photosensitivity reaction, suicide attempt[1]; *Rare:* chills and fever, hangover effect, sudden death[1].

Cardiovascular System — *Infrequent:* cerebrovascular accident, vasodilatation.

Digestive System — *Infrequent:* nausea and vomiting, tongue edema; *Rare:* ileus, intestinal obstruction, liver fatty deposit.

Hemic and Lymphatic System — *Infrequent:* leukopenia, thrombocytopenia.

Metabolic and Nutritional Disorders — *Infrequent:* alkaline phosphatase increased, bilirubinemia, hypoproteinemia.

Musculoskeletal System — *Rare:* osteoporosis.

Nervous System — *Infrequent:* ataxia, dysarthria, libido decreased, stupor; *Rare:* coma.

Respiratory System — *Infrequent:* epistaxis; *Rare:* lung edema.

Skin and Appendages — *Infrequent:* alopecia.

Special Senses — *Infrequent:* abnormality of accommodation, dry eyes; *Rare:* mydriasis.

Urogenital System — *Infrequent:* amenorrhea[2], breast pain, decreased menstruation, impotence[2], increased menstruation[2], menorrhagia[2], metrorrhagia[2], polyuria[2], urinary frequency, urinary retention, urinary urgency, urination impaired.

[1] These terms represent serious adverse events but do not meet the definition for adverse drug reactions. They are included here because of their seriousness.

[2] Adjusted for gender.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Intramuscular Olanzapine for Injection

Following is a list of treatment-emergent adverse reactions reported by patients treated with intramuscular olanzapine for injection (at 1 or more doses ≥2.5 mg/injection) in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) for which occurred at a rate equal to or less than placebo. Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients.

Body as a Whole — *Frequent:* injection site pain.

Cardiovascular System — *Infrequent:* syncope.

Digestive System — *Infrequent:* nausea.

Metabolic and Nutritional Disorders — *Infrequent:* creatine phosphokinase increased.

Clinical Trials in Adolescent Patients (age 13 to 17 years)

Commonly Observed Adverse Reactions in Oral Olanzapine Short-Term, Placebo-Controlled Trials

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥2.5 mg) reported with an incidence of 5% or more and reported at least twice as frequently as placebo-treated patients are listed in Table 21.

Table 21: Treatment-Emergent Adverse Reactions of ≥5% Incidence among Adolescents (13-17 Years Old) with Schizophrenia or Bipolar I Disorder (Manic or Mixed Episodes)

	Percentage of Patients Reporting Event			
	6 Week Trial % Schizophrenia Patients		3 Week Trial % Bipolar Patients	
Adverse Reactions	Olanzapine (N=72)	Placebo (N=35)	Olanzapine (N=107)	Placebo (N=54)
Sedation[a]	39	9	48	9
Weight increased	31	9	29	4
Headache	17	6	17	17
Increased appetite	17	9	29	4
Dizziness	8	3	7	2
Abdominal pain[b]	6	3	6	7
Pain in extremity	6	3	5	0
Fatigue	3	3	14	6
Dry mouth	4	0	7	0

[a] Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.

[b] Patients with the following MedDRA terms were counted in this category: abdominal pain, abdominal pain lower, abdominal pain upper.

Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term (3-6 weeks), Placebo-Controlled Trials

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥2.5 mg) reported with an incidence of 2% or more and greater than placebo are listed in Table 22.

Table 22: Treatment-Emergent Adverse Reactions of ≥2% Incidence among Adolescents (13-17 Years Old) (Combined Incidence from Short-Term, Placebo-Controlled Clinical Trials of Schizophrenia or Bipolar I Disorder [Manic or Mixed Episodes])

	Percentage of Patients Reporting Event	
Adverse Reaction	Olanzapine (N=179)	Placebo (N=89)
Sedation[a]	44	9
Weight increased	30	6
Increased appetite	24	6
Headache	17	12
Fatigue	9	4
Dizziness	7	2
Dry mouth	6	0
Pain in extremity	5	1
Constipation	4	0
Nasopharyngitis	4	2
Diarrhea	3	0
Restlessness	3	2
Liver enzymes increased[b]	8	1
Dyspepsia	3	1
Epistaxis	3	0
Respiratory tract infection[c]	3	2
Sinusitis	3	0
Arthralgia	2	0
Musculoskeletal stiffness	2	0

[a] Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.

[b] The terms alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hepatic enzyme were combined under liver enzymes.

[c] Patients with the following MedDRA terms were counted in this category: lower respiratory tract infection, respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection, viral upper respiratory tract infection.

6.2 Vital Signs and Laboratory Studies

Vital Sign Changes — Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials *[see Warnings and Precautions (5)]*.

Laboratory Changes — An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in ALT, AST, and GGT. In placebo-controlled olanzapine monotherapy studies in adults, clinically significant ALT elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. In 2 of these patients, liver enzymes decreased toward normal despite continued treatment and, in 2 others, enzymes decreased upon discontinuation of olanzapine. In the remaining 2 patients, 1, seropositive for hepatitis C, had persistent enzyme elevations for 4 months after discontinuation, and the other had insufficient follow-up to determine if enzymes normalized.

Within the larger premarketing database of about 2400 adult patients with baseline ALT ≤90 IU/L, the incidence of ALT elevation to >200 IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued.

Among 2500 adult patients in oral olanzapine clinical trials, about 1% (23/2500) discontinued treatment due to transaminase increases.

In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from <3 times the upper limit of normal at baseline to ≥3 times the upper limit of the normal range) were observed in 12% (21/174) of patients exposed to olanzapine compared to 2% (2/87) of the placebo-treated patients. Discontinuation due to transaminase increases occurred in 3.4% (6/179) of patients exposed to olanzapine.

Rare postmarketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the postmarketing period.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs.

Olanzapine administration was also associated with increases in serum prolactin *[see Warnings and Precautions (5.15)]*, with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

Given the concern about neutropenia associated with other psychotropic compounds and the finding of leukopenia associated with the administration of olanzapine in several animal models *[see Nonclinical Toxicology (13.2)]*, careful attention was given to examination of hematologic parameters in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

Olanzapine Monotherapy in Adolescents: In placebo-controlled clinical trials of adolescent patients with schizophrenia or bipolar I disorder (manic or mixed episodes), greater frequencies for the following treatment-emergent findings, at anytime, were observed in laboratory analytes compared to placebo: elevated ALT (≥3 X ULN in patients with ALT at baseline <3 X ULN), (12.1% vs 2.3%); elevated AST (27.6% vs 3.8%); low total bilirubin (22.1% vs 6.7%); elevated GGT (10.1% vs 1.2%); and elevated prolactin (47.4% vs 6.8%).

ECG Changes — In pooled studies of adults as well as pooled studies of adolescents, there were no significant differences between olanzapine and placebo in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc (Fridericia corrected), and PR intervals. Olanzapine use was associated with a mean increase in heart rate compared to placebo (adults: +2.4 beats per minute vs no change with placebo; adolescents: +6.3 beats per minute vs -5.1 beats per minute with placebo). This increase in heart rate may be related to olanzapine's potential for inducing orthostatic changes *[see Warnings and Precautions (5.8)]*.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ZYPREXA. Because these reactions are reported voluntarily from a population of uncertain size, it is difficult to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

Adverse reactions reported since market introduction that were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, diabetic ketoacidosis, discontinuation reaction (diaphoresis, nausea or vomiting), jaundice, neutropenia, pancreatitis, priapism, rash, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

7 DRUG INTERACTIONS

The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies.

7.1 Potential for Other Drugs to Affect Olanzapine

Diazepam — The co-administration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine *[see Drug Interactions (7.2)]*.

Cimetidine and Antacids — Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

Inducers of CYP1A2 — Carbamazepine therapy (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Alcohol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The co-administration of alcohol (i.e., ethanol) with olanzapine potentiated the orthostatic hypotension observed with olanzapine *[see Drug Interactions (7.2)]*.

Inhibitors of CYP1A2

Fluvoxamine: Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine Cmax following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

Inhibitors of CYP2D6

Fluoxetine: Fluoxetine (60 mg single dose or 60 mg daily dose for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended. When using ZYPREXA and fluoxetine in combination, also refer to the Drug Interactions section of the package insert for Symbyax.

Warfarin — Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics *[see Drug Interactions (7.2)]*.

Inducers of CYP1A2 or Glucuronyl Transferase — Omeprazole and rifampin may cause an increase in olanzapine clearance.

Charcoal — The administration of activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

7.2 Potential for Olanzapine to Affect Other Drugs

CNS Acting Drugs — Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Antihypertensive Agents — Olanzapine, because of its potential for inducing hypotension, may enhance the effects of certain antihypertensive agents.

Levodopa and Dopamine Agonists — Olanzapine may antagonize the effects of levodopa and dopamine agonists.

Lorazepam (IM) — Administration of intramuscular lorazepam (2 mg) 1 hour after intramuscular olanzapine for injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone *[see Warnings and Precautions (5.8)]*.

Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium *[see Warnings and Precautions (5.16)]*.

Valproate — Olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate *[see Warnings and Precautions (5.16)]*.

Effect of Olanzapine on Drug Metabolizing Enzymes — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Imipramine — Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

Warfarin — Single doses of olanzapine did not affect the pharmacokinetics of warfarin *[see Drug Interactions (7.1)]*.

Diazepam — Olanzapine did not influence the pharmacokinetics of diazepam or its active metabolite N-desmethyldiazepam. However, diazepam co-administered with olanzapine increased the orthostatic hypotension observed with either drug given alone *[see Drug Interactions (7.1)]*.

Alcohol — Multiple doses of olanzapine did not influence the kinetics of ethanol *[see Drug Interactions (7.1)]*.

Biperiden — Multiple doses of olanzapine did not influence the kinetics of biperiden.

Theophylline — Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

8 USE IN SPECIFIC POPULATIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Use in Specific Populations section of the package insert for Symbyax.

8.1 Pregnancy

Teratogenic Effects, Pregnancy Category C — In oral reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily oral dose on a mg/m^2 basis, respectively) no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the maximum recommended human daily oral dose on a mg/m^2 basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily oral dose on a mg/m^2 basis). In an oral rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the maximum recommended human daily oral dose on a mg/m^2 basis). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled trials with olanzapine in pregnant females. Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion.

8.2 Labor and Delivery

The effect of olanzapine on labor and delivery in humans is unknown. Parturition in rats was not affected by olanzapine.

8.3 Nursing Mothers

In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose. It is recommended that women receiving olanzapine should not breast-feed.

8.4 Pediatric Use

The safety and effectiveness of oral ZYPREXA in the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder were established in short-term studies in adolescents (ages 13 to 17 years). Use of ZYPREXA in adolescents is supported by evidence from adequate and well-controlled studies of ZYPREXA in which 268 adolescents received ZYPREXA in a range of 2.5 to 20 mg/day *[see Clinical Studies (14.1, 14.2)]*. Recommended starting dose for adolescents is lower than that for adults *[see Dosage and Administration (2.1, 2.2)]*. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic transaminase levels *[see Warnings and Precautions (5.5, 5.6, 5.15, 5.17) and Adverse Reactions (6.2)]*. When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Indications and Usage (1.1, 1.2)]*.

Safety and effectiveness of olanzapine in children <13 years of age have not been established *[see Patient Counseling Information (17.13)]*.

Safety and effectiveness of ZYPREXA and fluoxetine in combination in children and adolescents <18 years of age have not been established.

8.5 Geriatric Use

Of the 2500 patients in premarketing clinical studies with oral olanzapine, 11% (263) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient *[see Boxed Warning, Dosage and Administration (2.1), and Warnings and Precautions (5.1)]*.

Clinical studies of ZYPREXA and fluoxetine in combination did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients.

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily oral dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily oral dose on a mg/m^2 basis.

Olanzapine has not been systematically studied in 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 misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs were usually within normal limits following overdoses.

In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious reactions: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and 1 patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg of oral olanzapine; however, in another case, a patient was reported to survive an acute olanzapine ingestion of approximately 2 g of oral olanzapine.

10.2 Management of Overdose

The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The administration of activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

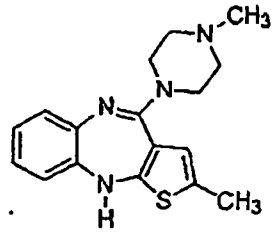
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. (Do not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring should continue until the patient recovers.

For specific information about overdosage with lithium or valproate, refer to the Overdosage section of the package inserts for these products. For specific information about overdosage with olanzapine and fluoxetine in combination, refer to the Overdosage section of the Symbyax package insert.

11 DESCRIPTION

ZYPREXA (olanzapine) is an atypical antipsychotic that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44. The chemical structure is:



Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8 µmol), 5 mg (16 µmol), 7.5 mg (24 µmol), 10 mg (32 µmol), 15 mg (48 µmol), or 20 mg (64 µmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5, 7.5, and 10 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 µmol), 10 mg (32 µmol), 15 mg (48 µmol) or 20 mg (64 µmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben.

ZYPREXA IntraMuscular (olanzapine for injection) is intended for intramuscular use only.

Each vial provides for the administration of 10 mg (32 µmol) olanzapine with inactive ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT2) antagonism. The mechanism of action of olanzapine in the treatment of acute manic or mixed episodes associated with bipolar I disorder is unknown.

12.2 Pharmacodynamics

Olanzapine binds with high affinity to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_6$ (K_i=4, 11, and 5 nM, respectively), dopamine D_{1-4} (K_i=11-31 nM), histamine H_1 (K_i=7 nM), and adrenergic α_1 receptors (K_i=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ (K_i=57 nM) and muscarinic M_{1-5} (K_i=73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds weakly to $GABA_A$, BZD, and β-adrenergic receptors (K_i>10 µM).

Antagonism at receptors other than dopamine and $5HT_2$ may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic-like effects. Olanzapine's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

12.3 Pharmacokinetics

Oral Administration, Monotherapy — Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age.

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α_1-acid glycoprotein.

Metabolism and Elimination — Following a single oral dose of ^{14}C labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Intramuscular Administration — ZYPREXA IntraMuscular results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a 5 mg dose of intramuscular olanzapine for injection produces, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5 mg dose of oral olanzapine. Area under the curve achieved after an intramuscular dose is similar to that achieved after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are qualitatively similar to metabolic profiles after oral administration.

Specific Populations

Renal Impairment — Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment — Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Geriatric — In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (≥65 years) than in nonelderly subjects (<65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity *[see Dosage and Administration (2)]*.

Gender — Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status — Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Race — In vivo studies have shown that exposures are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine *[see Dosage and Administration (2)]*.

Adolescents (ages 13 to 17 years) — In clinical studies, most adolescents were nonsmokers and this population had a lower average body weight, which resulted in higher average olanzapine exposure compared to adults.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8-5 times the maximum recommended human daily oral dose on a mg/m^2 basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily oral dose on a mg/m^2 basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human daily oral dose on a mg/m^2 basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in 1 mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily oral dose on a mg/m^2 basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the maximum recommended human daily oral dose on a mg/m^2 basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the maximum recommended human daily oral dose on a mg/m^2 basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland 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 finding of prolactin mediated endocrine tumors in rodents is unknown *(see Warnings and Precautions (5.15))*.

Mutagenesis — No evidence of genotoxic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Impairment of Fertility — In an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the maximum recommended human daily oral dose on a mg/m^2 basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the maximum recommended human daily oral dose on a mg/m^2 basis). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a mg/m^2 basis); therefore olanzapine may produce a delay in ovulation.

13.2 Animal Toxicology and/or Pharmacology

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily oral dose on a mg/m^2 basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily oral dose on a mg/m^2 basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily oral dose on a mg/m^2 basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily oral dose on a mg/m^2 basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

14 CLINICAL STUDIES

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

14.1 Schizophrenia

Adults

The efficacy of oral olanzapine in the treatment of schizophrenia was established in 2 short-term (6-week) controlled trials of adult inpatients who met DSM III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in 1 of the 2 trials, but this trial did not compare these 2 drugs on the full range of clinically relevant doses for both.

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, 2 more recently developed scales were employed; these included the 30-item Positive and Negative Symptoms Scale (PANSS), in which are embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative subscale or SANS; and CGI Severity. The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=149) involving 2 fixed olanzapine doses of 1 and 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis cluster, on the PANSS Negative subscale, and on CGI Severity.

(2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine (5 ± 2.5 mg/day, 10 ± 2.5 mg/day, and 15 ± 2.5 mg/day) on a once daily schedule, the 2 highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest olanzapine dose group was superior to placebo on the SANS. There was no clear advantage for the high-dose group over the medium-dose group.

(3) In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine during open-label treatment for at least 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms of increases in BPRS positive symptoms or hospitalization, was planned for 12 months, however, criteria were met for stopping the trial early due to an excess of placebo relapses compared to olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in patients stabilized for approximately 8 weeks and followed for an observation period of up to 8 months.

Examination of population subsets (race and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

Adolescents

The efficacy of oral olanzapine in the acute treatment of schizophrenia in adolescents (ages 13 to 17 years) was established in a 6-week double-blind, placebo-controlled, randomized trial of inpatients and outpatients with schizophrenia (n=107) who met diagnostic criteria according to DSM-IV-TR and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL).

The primary rating instrument used for assessing psychiatric signs and symptoms in this trial was the Anchored Version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score.

In this flexible-dose trial, olanzapine 2.5 to 20 mg/day (mean modal dose 12.5 mg/day, mean dose of 11.1 mg/day) was more effective than placebo in the treatment of adolescents diagnosed with schizophrenia, as supported by the statistically significantly greater mean reduction in BPRS-C total score for patients in the olanzapine treatment group than in the placebo group.

While there is no body of evidence available to answer the question of how long the adolescent patient treated with ZYPREXA should be maintained, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

14.2 Bipolar I Disorder (Manic or Mixed Episodes)

Adults

Monotherapy — The efficacy of oral olanzapine in the treatment of manic or mixed episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials in adult patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome.

(2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar I disorder who had responded during an initial open-label treatment phase for about 2 weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response during the open-label phase was defined by having a decrease of the Y-MRS total score to ≤12 and HAM-D 21 to ≤8. Relapse during the double-blind phase was defined as an increase of the Y-MRS or HAM-D 21 total score to ≥15, or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

Adjunct to Lithium or Valproate — The efficacy of oral olanzapine with concomitant lithium or valproate in the treatment of manic or mixed episodes was established in 2 controlled trials in patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course. The results of the trials follow:

(1) In one 6-week placebo-controlled combination trial, 175 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 6-week placebo-controlled combination trial, 169 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

Adolescents

Acute Monotherapy — The efficacy of oral olanzapine in the treatment of acute manic or mixed episodes in adolescents (ages 13 to 17 years) was established in a 3-week, double-blind, placebo-controlled, randomized trial of adolescent inpatients and outpatients who met the diagnostic criteria for manic or mixed episodes associated with bipolar I disorder (with or without psychotic features) according to the DSM-IV-TR (n=161). Diagnosis was confirmed by the K-SADS-PL.

The primary rating instrument used for assessing manic symptoms in this trial was the Adolescent Structured Young-Mania Rating Scale (Y-MRS) total score.

In this flexible-dose trial, olanzapine 2.5 to 20 mg/day (mean modal dose 10.7 mg/day, mean dose of 8.9 mg/day) was more effective than placebo in the treatment of adolescents with manic or mixed episodes associated with bipolar I disorder, as supported by the statistically significantly greater mean reduction in Y-MRS total score for patients in the olanzapine treatment group than in the placebo group.

While there is no body of evidence available to answer the question of how long the adolescent patient treated with ZYPREXA should be maintained, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

14.3 Agitation Associated with Schizophrenia and Bipolar I Mania

The efficacy of intramuscular olanzapine for injection for the treatment of agitation was established in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients from 2 diagnostic groups: schizophrenia and bipolar I disorder (manic or mixed episodes). Each of the trials included a single active comparator treatment arm of either haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar I mania study). Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of ≥14 on the 5 items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness and excitement items) with at least 1 individual item score ≥4 using a 1-7 scoring system (1=absent, 4=moderate, 7=extreme). In the studies, the mean baseline PANSS Excited Component score was 18.4, with scores ranging from 13 to 32 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to 3 injections during the 24 hour IM treatment periods; however, patients could not receive the second injection until after the initial 2 hour period when the primary efficacy measure was assessed. The results of the trials follow:

(1) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=270), 4 fixed intramuscular olanzapine for injection doses of 2.5 mg, 5 mg, 7.5 mg and 10 mg were evaluated. All doses were statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consistent for the 3 highest doses. There were no significant pairwise differences for the 7.5 and 10 mg doses over the 5 mg dose.

(2) In a second placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=311), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

(3) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for bipolar I disorder (and currently displaying an acute manic or mixed episode with or without psychotic features) (n=201), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. The tablets are available as follows:

	TABLET STRENGTH					
	2.5 mg	5 mg	7.5 mg	10 mg	15 mg	20 mg
Tablet No.	4112	4115	4116	4117	4415	4420
Identification	LILLY 4112	LILLY 4115	LILLY 4116	LILLY 4117	LILLY 4415	LILLY 4420
NDC Codes:						
Bottles 30	NDC 0002-4112-30	NDC 0002-4115-30	NDC 0002-4116-30	NDC 0002-4117-30	NDC 0002-4415-30	NDC 0002-4420-30
Blisters – ID[a] 100	NDC 0002-4112-33	NDC 0002-4115-33	NDC 0002-4116-33	NDC 0002-4117-33	NDC 0002-4415-33	NDC 0002-4420-33
Bottles 1000	NDC 0002-4112-04	NDC 0002-4115-04	NDC 0002-4116-04	NDC 0002-4117-04	NDC 0002-4415-04	NDC 0002-4420-04

[a] Identi-Dose® (unit dose medication, Lilly).

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. The tablets are available as follows:

	TABLET STRENGTH			
ZYPREXA ZYDIS Tablets[a]	5 mg	10 mg	15 mg	20 mg
Tablet No.	4453	4454	4455	4456
Debossed	5	10	15	20
NDC Codes:				
Dose Pack 30 (Child Resistant)	NDC 0002-4453-85	NDC 0002-4454-85	NDC 0002-4455-85	NDC 0002-4456-85

ZYPREXA is a registered trademark of Eli Lilly and Company.

ZYDIS is a registered trademark of Catalent Pharma Solutions.

[a] ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and Company by Catalent Pharma Solutions, United Kingdom. SN5 8RU.

ZYPREXA IntraMuscular is available in:

NDC 0002-7597-01 (No. VL7597) – 10 mg vial (1s)

16.2 Storage and Handling

Store ZYPREXA tablets, ZYPREXA ZYDIS, and ZYPREXA IntraMuscular vials (before reconstitution) at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP]. Reconstituted ZYPREXA IntraMuscular may be stored at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP] for up to 1 hour if necessary. *Discard any unused portion of reconstituted ZYPREXA IntraMuscular.* The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Protect ZYPREXA tablets and ZYPREXA ZYDIS from light and moisture. Protect ZYPREXA IntraMuscular from light, do not freeze.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide for the oral formulations.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking ZYPREXA as monotherapy or in combination with fluoxetine. If you do not think you are getting better or have any concerns about your condition while taking ZYPREXA, call your doctor. When using ZYPREXA and fluoxetine in combination, also refer to the Patient Counseling Information section of the package insert for Symbyax.

17.1 Information on Medication Guide

Prescribers or other health professionals should inform patients, their families, and their caregivers about the potential benefits and potential risks associated with treatment with ZYPREXA, and should counsel them in its appropriate use. A patient Medication Guide is available for ZYPREXA. Prescribers or other health professionals should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. When using ZYPREXA and fluoxetine in combination, also refer to the Medication Guide for Symbyax.

17.2 Elderly Patients with Dementia-Related Psychosis; Increased Mortality and Cerebrovascular Adverse Events (CVAE), Including Stroke

Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with ZYPREXA had a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) compared with placebo.

ZYPREXA is not approved for elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*.

17.3 Neuroleptic Malignant Syndrome (NMS)

Patients and caregivers should be counseled that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including ZYPREXA. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) *[see Warnings and Precautions (5.3)]*.

17.4 Hyperglycemia

Patients should be advised of the potential risk of hyperglycemia-related adverse reactions. Patients should be monitored regularly for worsening of glucose control. Patients who have diabetes should follow their doctor's instructions about how often to check their blood sugar while taking ZYPREXA *[see Warnings and Precautions (5.4)]*.

17.5 Hyperlipidemia

Patients should be counseled that hyperlipidemia has occurred during treatment with ZYPREXA. Patients should have their lipid profile monitored regularly *[see Warnings and Precautions (5.5)]*.

17.6 Weight Gain

Patients should be counseled that weight gain has occurred during treatment with ZYPREXA. Patients should have their weight monitored regularly *[see Warnings and Precautions (5.6)]*.

17.7 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of ZYPREXA, e.g., diazepam or alcohol *[see Warnings and Precautions (5.8) and Drug Interactions (7)]*. Patients should be advised to change positions carefully to help prevent orthostatic hypotension, and to lie down if they feel dizzy or faint, until they feel better. Patients should be advised to call their doctor if they experience any of the following signs and symptoms associated with orthostatic hypotension: dizziness, fast or slow heart beat, or fainting.

17.8 Potential for Cognitive and Motor Impairment

Because ZYPREXA 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 ZYPREXA therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

17.9 Body Temperature Regulation

Patients should be advised regarding appropriate care in avoiding overheating and dehydration. Patients should be advised to call their doctor right away if they become severely ill and have some or all of these symptoms of dehydration: sweating too much or not at all, dry mouth, feeling very hot, feeling thirsty, not able to produce urine *[see Warnings and Precautions (5.13)]*.

17.10 Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, Symbyax. Patients should also be advised to inform their physicians if they are taking, plan to take, or have stopped taking any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions *[see Drug Interactions (7)]*.

17.11 Alcohol

Patients should be advised to avoid alcohol while taking ZYPREXA *[see Drug Interactions (7)]*.

17.12 Phenylketonurics

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5, 10, 15, or 20 mg tablet, respectively) *[see Description (11)]*.

17.13 Use in Specific Populations

Pregnancy — Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with ZYPREXA *[see Use in Specific Populations (8.1)]*.

Nursing Mothers — Patients should be advised not to breast-feed an infant if they are taking ZYPREXA *[see Use in Specific Populations (8.3)]*.

Pediatric Use — ZYPREXA is indicated for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adolescents 13 to 17 years of age. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin, and hepatic transaminase levels. Patients should be counseled about the potential long-term risks associated with ZYPREXA and advised that these risks may lead them to consider other drugs first *[see Indications and Usage (1.1, 1.2)]*. Safety and effectiveness of ZYPREXA in patients under 13 years of age have not been established. Safety and effectiveness of ZYPREXA and fluoxetine in combination in patients <18 years of age have not been established *[see Warnings and Precautions (5.5, 5.6) and Use in Specific Populations (8.4)]*.

17.14 Need for Comprehensive Treatment Program in Pediatric Patients

ZYPREXA is indicated as an integral part of a total treatment program for pediatric patients with schizophrenia and bipolar disorder that may include other measures (psychological, educational, social) for patients with the disorder. Effectiveness and safety of ZYPREXA have not been established in pediatric patients less than 13 years of age. Atypical antipsychotics are not intended for use in the pediatric patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders. Appropriate educational placement is essential and psychosocial intervention is often helpful. The decision to prescribe atypical antipsychotic medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms *[see Indications and Usage (1.3)]*.

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Eli Lilly and Company, Indianapolis, IN 46285, USA

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Medication Guide

ZYPREXA® (zy-PREX-a)

(olanzapine)

Tablet

ZYPREXA® ZYDIS® (zy-PREX-a ZY-dis)

(olanzapine)

Tablet, Orally Disintegrating

Read the Medication Guide that comes with ZYPREXA before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or treatment. Talk with your doctor or pharmacist if there is something you do not understand or you want to learn more about ZYPREXA.

What is the most important information I should know about ZYPREXA?

Serious side effects may happen when you take ZYPREXA, including:

Increased risk of death in elderly patients with dementia-related psychosis: Medicines like ZYPREXA can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). ZYPREXA is not approved for treating psychosis in the elderly with dementia.

High blood sugar (hyperglycemia): High blood sugar can happen if you have diabetes already or even if you have never had diabetes. In rare cases, this could lead to ketoacidosis (build up of acid in the blood due to ketones), coma, or death. Your doctor should do lab tests to check your blood sugar before you start taking ZYPREXA and during treatment. In people who do not have diabetes, sometimes high blood sugar goes away when ZYPREXA is stopped. People with diabetes and some people who did not have diabetes before taking ZYPREXA need to take medicine for high blood sugar even after they stop taking ZYPREXA.

If you have diabetes, follow your doctor's instructions about how often to check your blood sugar while taking ZYPREXA.

Call your doctor if you have any of these symptoms of high blood sugar (hyperglycemia) while taking ZYPREXA:

- feel very thirsty
- need to urinate more than usual
- feel very hungry
- feel weak or tired
- feel sick to your stomach
- feel confused, or your breath smells fruity.

High cholesterol and triglyceride levels in the blood (fat in the blood) may happen in people treated with ZYPREXA, especially in teenagers (13-17 years old). You may not have any symptoms, so your doctor should do blood tests to check your cholesterol and triglyceride levels before you start taking ZYPREXA and during treatment.

Increase in weight (weight gain): Weight gain is very common in people who take ZYPREXA. Teenagers (13-17 years old) are more likely to gain weight and to gain more weight than adults. Some people may gain a lot of weight while taking ZYPREXA, so you and your doctor should check your weight regularly. Talk to your doctor about ways to control weight gain, such as eating a healthy, balanced diet, and exercising.

Increased risk in teenagers (13-17 years old): Possible serious risks of weight gain and increases in cholesterol and triglycerides are more common in teenagers than in adults. You and your doctor should decide if other available treatments should be used first. Before your teenager takes ZYPREXA, talk with your doctor about the possible long-term risks of teenagers taking ZYPREXA.

What is ZYPREXA?

ZYPREXA is a prescription medicine used to treat:

- schizophrenia in people age 13 or older.
- bipolar disorder, including:
  - manic or mixed episodes that happen with bipolar I disorder in people age 13 or older.
  - manic or mixed episodes that happen with bipolar I disorder, when used with the medicine lithium or valproate, in adults.
  - long-term treatment of bipolar I disorder in adults.
- episodes of depression that happen with bipolar I disorder, when used with the medicine fluoxetine (Prozac®), in adults.
- episodes of depression that do not get better after 2 other medicines, also called treatment resistant depression, when used with the medicine fluoxetine (Prozac), in adults.

ZYPREXA has not been approved for use in children under 13 years of age.

The symptoms of schizophrenia include hearing voices, seeing things that are not there, having beliefs that are not true, and being suspicious or withdrawn.

The symptoms of bipolar I disorder include alternating periods of depression and high or irritable mood, increased activity and restlessness, racing thoughts, talking fast, impulsive behavior, and a decreased need for sleep.

The symptoms of treatment resistant depression include decreased mood, decreased interest, increased guilty feelings, decreased energy, decreased concentration, changes in appetite, and suicidal thoughts or behavior.

Some of your symptoms may improve with treatment. If you do not think you are getting better, call your doctor.

What should I tell my doctor before taking ZYPREXA?

ZYPREXA may not be right for you. Before starting ZYPREXA, tell your doctor if you have or had:

- heart problems
- seizures
- diabetes or high blood sugar levels (hyperglycemia)
- high cholesterol or triglyceride levels in your blood
- liver problems
- low or high blood pressure
- strokes or "mini-strokes" also called transient ischemic attacks (TIAs)
- Alzheimer's disease
- narrow-angle glaucoma
- enlarged prostate in men
- bowel obstruction
- phenylketonuria, because ZYPREXA ZYDIS contains phenylalanine

- breast cancer
- thoughts of suicide or hurting yourself
- any other medical condition
- are pregnant or plan to become pregnant. It is not known if ZYPREXA will harm your unborn baby.
- are breast-feeding or plan to breast-feed. ZYPREXA can pass into your breast milk and may harm your baby. You should not breast-feed while taking ZYPREXA. Talk to your doctor about the best way to feed your baby if you take ZYPREXA.

Tell your doctor if you exercise a lot or are in hot places often.

The symptoms of bipolar I disorder, treatment resistant depression, or schizophrenia may include thoughts of suicide or of hurting yourself or others. If you have these thoughts at any time, tell your doctor or go to an emergency room right away.

Tell your doctor about all the medicines that you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. ZYPREXA and some medicines may interact with each other and may not work as well, or cause possible serious side effects. Your doctor can tell you if it is safe to take ZYPREXA with your other medicines. Do not start or stop any medicine while taking ZYPREXA without talking to your doctor first.

How should I take ZYPREXA?

- Take ZYPREXA exactly as prescribed. Your doctor may need to change (adjust) the dose of ZYPREXA until it is right for you.
- If you miss a dose of ZYPREXA, take the missed dose as soon as you remember. If it is almost time for the next dose, just skip the missed dose and take your next dose at the regular time. Do not take two doses of ZYPREXA at the same time.
- **To prevent serious side effects, do not stop taking ZYPREXA suddenly. If you need to stop taking ZYPREXA, your doctor can tell you how to safely stop taking it.**
- **If you take too much ZYPREXA, call your doctor or poison control center at 1-800-222-1212 right away, or get emergency treatment.**
- ZYPREXA can be taken with or without food.
- ZYPREXA is usually taken one time each day.
- Take ZYPREXA ZYDIS as follows:
  - Be sure that your hands are dry.
  - Open the sachet and peel back the foil on the blister. Do not push the tablet through the foil.
  - As soon as you open the blister, remove the tablet and put it into your mouth.
  - The tablet will disintegrate quickly in your saliva so that you can easily swallow it with or without drinking liquid.
- Call your doctor if you do not think you are getting better or have any concerns about your condition while taking ZYPREXA.

What should I avoid while taking ZYPREXA?

- ZYPREXA can cause sleepiness and may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how ZYPREXA affects you.
- Avoid drinking alcohol while taking ZYPREXA. Drinking alcohol while you take ZYPREXA may make you sleepier than if you take ZYPREXA alone.

What are the possible side effects of ZYPREXA?

Serious side effects may happen when you take ZYPREXA, including:

- See "What is the most important information I should know about ZYPREXA?", which describes the increased risk of death in elderly people with dementia-related psychosis and the risks of high blood sugar, high cholesterol and triglyceride levels, and weight gain.
- Increased incidence of stroke or "mini-strokes" called transient ischemic attacks (TIAs) in elderly people with dementia-related psychosis (elderly people who have lost touch with reality due to confusion and memory loss). ZYPREXA is not approved for these patients.
- Neuroleptic Malignant Syndrome (NMS): NMS is a rare but very serious condition that can happen in people who take antipsychotic medicines, including ZYPREXA. NMS can cause death and must be treated in a hospital. Call your doctor right away if you become severely ill and have any of these symptoms:
  - high fever
  - excessive sweating
  - rigid muscles
  - confusion
  - changes in your breathing, heartbeat, and blood pressure.
- Tardive Dyskinesia: This condition causes body movements that keep happening and that you can not control. These movements usually affect the face and tongue. Tardive dyskinesia may not go away, even if you stop taking ZYPREXA. It may also start after you stop taking ZYPREXA. Tell your doctor if you get any body movements that you can not control.
- Decreased blood pressure when you change positions, with symptoms of dizziness, fast or slow heartbeat, or fainting.
- Difficulty swallowing, that can cause food or liquid to get into your lungs.
- Seizures: Tell your doctor if you have a seizure during treatment with ZYPREXA.
- Problems with control of body temperature: You could become very hot, for instance when you exercise a lot or stay in an area that is very hot. It is important for you to drink water to avoid dehydration. Call your doctor right away if you become severely ill and have any of these symptoms of dehydration:
  - sweating too much or not at all
  - dry mouth
  - feeling very hot
  - feeling thirsty
  - not able to produce urine.

Common side effects of ZYPREXA include: lack of energy, dry mouth, increased appetite, sleepiness, tremor (shakes), having hard or infrequent stools, dizziness, changes in behavior, or restlessness.

Other common side effects in teenagers (13-17 years old) include: headache, stomach-area (abdominal) pain, pain in your arms or legs, or tiredness. Teenagers experienced greater increases in prolactin, liver enzymes, and sleepiness, as compared with adults.

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the possible side effects with ZYPREXA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZYPREXA?

- Store ZYPREXA at room temperature, between 68°F to 77°F (20°C to 25°C).

D4011.36

- Keep ZYPREXA away from light.
- Keep ZYPREXA dry and away from moisture.

Keep ZYPREXA and all medicines out of the reach of children.

General Information about ZYPREXA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ZYPREXA for a condition for which it was not prescribed. Do not give ZYPREXA to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about ZYPREXA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ZYPREXA that was written for healthcare professionals. For more information about ZYPREXA call 1-800-Lilly-Rx (1-800-545-5979) or visit www.zyprexa.com.

What are the ingredients in ZYPREXA?

Active ingredient: olanzapine

Inactive ingredients:

Tablets — carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains: Titanium Dioxide, FD&C Blue No. 2 Aluminum Lake, or Synthetic Red Iron Oxide.

ZYDIS — gelatin, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Medication Guide revised Month dd, 2009

Eli Lilly and Company
Indianapolis, IN 46285, USA

www.zyprexa.com

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EXHIBIT B

LATUDA® (lurasidone HCl) Tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LATUDA safely and effectively. See full prescribing information (FPI) for LATUDA.

LATUDA (LURASIDONE HCL) tablets for oral administration,
Initial U.S. Approval: 2010

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

See full prescribing information for complete boxed warning.
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for the treatment of patients with dementia-related psychosis. *(5.1)*

INDICATIONS AND USAGE

LATUDA is an atypical antipsychotic agent indicated for the treatment of patients with schizophrenia *(1)*. Efficacy was established in four 6-week controlled studies of adult patients with schizophrenia *(14.1)*.

DOSAGE AND ADMINISTRATION

The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. The maximum recommended dose is 80 mg once daily. LATUDA should be taken with food *(2.2)*.

DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg and 80 mg *(3)*

CONTRAINDICATIONS

Any known hypersensitivity to LATUDA or any components in the formulation *(4)*. Coadministration with a strong CYP3A4 inhibitor (e.g., ketoconazole) and inducer (e.g.,rifampin) *(4)*.

WARNINGS AND PRECAUTIONS

- **Cerebrovascular Adverse Reactions:** An increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) has been seen in elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs. *(5.2)*.
- **Neuroleptic Malignant Syndrome:** Manage with immediate discontinuation and close monitoring *(5.3)*.
- **Tardive Dyskinesia:** Discontinue if clinically appropriate *(5.4)*.
- **Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain *(5.5)*.
  - **Hyperglycemia and Diabetes Mellitus:** Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes.
  - **Dyslipidemia:** Undesirable alterations have been observed in patients treated with atypical antipsychotics.
  - **Weight Gain:** Gain in body weight has been observed, clinical monitoring of weight is recommended.
- **Hyperprolactinemia:** Prolactin elevations may occur *(5.6)*.
- **Leukopenia, Neutropenia, and Agranulocytosis** have been reported with antipsychotics. Patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and LATUDA should be discontinued at the first sign of a decline in WBC in the absence of other causative factors *(5.7)*.
- **Orthostatic Hypotension and Syncope:** Dizziness, tachycardia or bradycardia, and syncope may occur, especially early in treatment. Use with caution in patients with known cardiovascular or cerebrovascular disease, and in antipsychotic-naive patients *(5.8)*.
- **Seizures:** Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold *(5.9)*.
- **Potential for Cognitive and Motor Impairment:** Use caution when operating machinery *(5.10)*.
- **Suicide:** The possibility of a suicide attempt is inherent in schizophrenia. Closely supervise high-risk patients *(5.12)*.
- See Full Prescribing Information for additional WARNINGS and PRECAUTIONS

ADVERSE REACTIONS

Commonly observed adverse reactions (incidence ≥5% and at least twice the rate for placebo) included somnolence, akathisia, nausea, parkinsonism and agitation *(6.2)*.

To report SUSPECTED ADVERSE REACTIONS, contact Sunovion Pharmaceuticals Inc. at 877-737-7226 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- LATUDA is not recommended to be used in combination with strong CYP3A4 inhibitors, e.g., ketoconazole. *(4 and 7.1)*
- Dose adjustment is recommended for moderate CYP3A4 inhibitors (e.g. diltiazem) *(7.1)*
- LATUDA is not recommended to be used in combination with strong CYP3A4 inducers, e.g., rifampin. *(4 and 7.1)*

USE IN SPECIFIC POPULATIONS

- **Geriatric Use:** No dose adjustments required. *(8.5)*
- **Pregnancy:** Use LATUDA during pregnancy only if the potential benefit justifies the potential risk. *(8.1)*
- **Nursing Mothers:** Breast feeding is not recommended. *(8.3)*
- **Pediatric Use:** Safety and effectiveness have not been established. *(8.4)*
- **Renal Impairment:** Dose adjustment is recommended. *(8.6)*
- **Hepatic Impairment:** Dose adjustment is recommended. *(8.7)*

Revised: October 2010

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INCREASED MORTALITY IN
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FULL PRESCRIBING INFORMATION

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

LATUDA is not approved for the treatment of patients with dementia-related psychosis. *[see Warnings and Precautions (5.1)]*.

1. INDICATIONS AND USAGE

LATUDA is indicated for the treatment of patients with schizophrenia.

The efficacy of LATUDA in schizophrenia was established in four 6-week controlled studies of adult patients with schizophrenia *[see Clinical Studies (14.1)]*.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[see Dosage and Administration (2)]*.

2. DOSAGE AND ADMINISTRATION

2.1. Schizophrenia

The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 40 mg/day to 120 mg/day *[see Clinical Studies (14.1)]*. In the 6-week controlled trials, there was no suggestion of added benefit with the 120 mg/day dose, but there was a dose-related increase in certain adverse reactions. Therefore, the maximum recommended dose is 80 mg/day.

2.2. Administration Instructions

LATUDA should be taken with food (at least 350 calories) *[see Clinical Pharmacology (12)]*.

2.3. Dosage in Special Populations

Dosage adjustments are not recommended on the basis of age, gender, and race *[see Use in Specific Populations (8)]*.

Dose adjustment is recommended in moderate and severe renal impairment patients. The dose in these patients should not exceed 40 mg/day *[see Use in Specific Populations (8)]*.

Dose adjustment is recommended in moderate and severe hepatic impairment patients. The dose in these patients should not exceed 40 mg/day *[see Use in Specific Populations (8)]*.

Dosing recommendation for patients taking LATUDA concomitantly with potential CYP3A4 inhibitors: When coadministration of LATUDA with a moderate CYP3A4 inhibitor such as diltiazem is considered, the dose should not exceed 40 mg/day. LATUDA should not be used in combination with a strong CYP3A4 inhibitor (e.g., ketoconazole) *[see Contraindications (4); Drug Interactions (7.1)]*.

Dosing recommendation for patients taking LATUDA concomitantly with potential CYP3A4 inducers: LATUDA should not be used in combination with a strong CYP3A4 inducer (e.g., rifampin) *[see Contraindications (4); Drug Interactions (7.1)]*.

3. DOSAGE FORMS AND STRENGTHS

LATUDA tablets are available in the following shape and color (Table 1) with respective one-sided debossing: 40 mg (white to off-white, round, "L40"), or 80 mg (pale green, oval, "L80").

Table 1: LATUDA Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings
40 mg	white to off-white round	"L40"
80 mg	pale green oval	"L80"

4. CONTRAINDICATIONS

LATUDA is contraindicated in any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone [*see Adverse Reactions (6.6)*].

LATUDA is contraindicated with strong CYP3A4 inhibitors (e.g., ketoconazole) and strong CYP3A4 inducers (e.g., rifampin) [*see Drug Interactions (7.1)*].

5. WARNINGS AND PRECAUTIONS

5.1. Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

5.2. Cerebrovascular Adverse Reactions, Including Stroke

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see also Boxed Warning and Warnings and Precautions (5.1)]*.

5.3. Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including LATUDA.

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. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g. pneumonia, systemic infection) 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 NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored, since recurrences of NMS have been reported.

5.4. Tardive Dyskinesia

Tardive Dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can 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, LATUDA 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 LATUDA, drug discontinuation should be considered. However, some patients may require treatment with LATUDA despite the presence of the syndrome.

5.5. Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

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. 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. Because LATUDA was not marketed at the time these studies were performed, it is not known if LATUDA is associated with this increased risk.

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

Pooled data from short-term, placebo-controlled studies are presented in Table 2.

Table 2: Change in Fasting Glucose

	Placebo	LATUDA 20 mg/day	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day
			Mean Change from Baseline (mg/dL)		
	n=438	n=71	n=352	n=270	n=283
Serum Glucose	-0.7	-0.6	2.5	-0.9	2.5
			Proportion of Patients with Shifts to ≥ 126 mg/dL		
Serum Glucose (≥ 126 mg/dL)	8.6% (34/397)	11.7% (7/60)	14.3% (47/328)	10.0% (24/241)	10.0% (26/260)

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.6 mg/dL at week 24 (n = 186), +0.3 mg/dL at week 36 (n = 236) and +1.2 mg/dL at week 52 (n = 244).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Pooled data from short-term, placebo-controlled studies are presented in Table 3.

Table 3: Change in Fasting Lipids

	Placebo	LATUDA 20 mg/day	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day
			Mean Change from Baseline (mg/dL)		
	n=418	n=71	n=341	n=263	n=268
Total cholesterol	-8.5	-12.3	-9.4	-9.8	-3.8
Triglycerides	-15.7	-29.1	-6.2	-14.2	-3.1
			Proportion of Patients with Shifts		
Total Cholesterol (≥ 240 mg/dL)	6.6% (23/350)	13.8% (8/58)	7.3% (21/287)	6.9% (15/216)	3.8% (9/238)
Triglycerides (≥ 200 mg/dL)	12.5% (39/312)	14.3% (7/49)	14.0% (37/264)	8.7% (17/196)	10.5% (22/209)

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of -4.2 (n=186) and -13.6 (n=187) mg/dL at week 24, -1.9 (n = 238) and -3.5 (n = 238) mg/dL at week 36 and -3.6 (n=243) and -6.5 (n=243) mg/dL at week 52, respectively.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Pooled data from short-term, placebo-controlled studies are presented in Table 4. The mean weight gain was 0.75 kg for LATUDA-treated patients compared to 0.26 kg for placebo-treated patients. In study 3 [*see Clinical Studies (14.1)*] change in weight from baseline for olanzapine was 4.15 kg. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 5.6% for LATUDA-treated patients versus 4.0% for placebo-treated patients.

Table 4: Mean Change in Weight (kg) from Baseline

	Placebo (n=450)	LATUDA 20 mg/day (n=71)	LATUDA 40 mg/day (n= 358)	LATUDA 80 mg/day (n= 279)	LATUDA 120 mg/day (n=291)
All Patients	0.26	-0.15	0.67	1.14	0.68

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.38 kg at week 24 (n = 531), -0.47 kg at week 36 (n = 303) and -0.71 kg at week 52 (n = 244).

5.6. Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, LATUDA elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male patients *[see Adverse Reactions (6)]*.

In short-term placebo-controlled studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was 1.1 ng/mL and was - 0.6 ng/mL in the placebo-treated patients. The increase in prolactin was greater in female patients; the median change from baseline to endpoint for females was 1.5 ng/mL and was 1.1 ng/mL in males. The increase in prolactin concentrations was dose-dependent (Table 5).

Table 5: Median Change in Prolactin (ng/mL) from Baseline

	Placebo	LATUDA 20 mg/day	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day
All Patients	-0.6 (n=430)	-1.1 (n=70)	0.3 (n=351)	1.1 (n=259)	3.3 (n=284)
Females	-1.5 (n=102)	-0.7 (n=19)	-0.9 (n=99)	2.0 (n=78)	6.7 (n=70)
Males	-0.5 (n=328)	-1.2 (n=51)	0.5 (n=252)	0.9 (n=181)	3.1 (n=214)

The proportion of patients with prolactin elevations ≥ 5x ULN was 3.6% for LATUDA-treated patients versus 0.7% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 8.3% for LATUDA-treated patients versus 1% for placebo-treated female patients. The proportion of male patients with prolactin elevations > 5x ULN was 1.9% versus 0.6% for placebo-treated male patients.

In the uncontrolled longer-term studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of -1.9 ng/mL at week 24 (n = 188), -5.4 ng/mL at week 36 (n=189) and -3.3 ng/mL at week 52 (n = 243).

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 considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a LATUDA carcinogenicity study conducted in rats and mice *[see Nonclinical Toxicology (13)]*. 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, but the available evidence is too limited to be conclusive.

5.7. Leukopenia, Neutropenia and Agranulocytosis

Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and LATUDA should be discontinued at the first sign of decline in WBC, in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1000/mm^3) should discontinue LATUDA and have their WBC followed until recovery.

5.8. Orthostatic Hypotension and Syncope

LATUDA may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. The incidence of orthostatic hypotension and syncope events from short-term, placebo-controlled studies was (LATUDA incidence, placebo incidence): orthostatic hypotension [0.4% (4/1004), 0.2 % (1/455)] and syncope [< 0.1% (1/1004), 0%]. Assessment of orthostatic hypotension defined by vital sign changes (≥ 20 mm Hg decrease in systolic blood pressure and ≥ 10 bpm increase in pulse from sitting to standing or supine to standing positions). In short-term clinical trials orthostatic hypotension occurred with a frequency of 0.8% with LATUDA 40 mg, 1.4% with LATUDA 80 mg and 1.7% with LATUDA 120 mg compared to 0.9% with placebo.

LATUDA should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

5.9. Seizures

As with other antipsychotic drugs, LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

In short-term placebo-controlled trials, seizures/convulsions occurred in < 0.1% (1/1004) of patients treated with LATUDA compared to 0.2% (1/455) placebo-treated patients.

5.10. Potential for Cognitive and Motor Impairment

LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills.

In short-term, placebo-controlled trials, somnolence was reported in 22.3% (224/1004) of patients treated with LATUDA compared to 9.9% (45/455) of placebo patients, respectively. The frequency of somnolence increases with dose; somnolence was reported in 26.5% (77/291) of patients receiving LATUDA 120 mg/day. In these short-term trials, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

5.11. Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration *[see Patient Counseling Information (17.9)]*.

5.12. Suicide

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

In short-term, placebo-controlled studies in patients with schizophrenia, the incidence of treatment-emergent suicidal ideation was 0.6% (6/1004) for LATUDA treated patients compared to 0.4% (2/455) on placebo. No suicide attempts or completed suicides were reported in these studies.

5.13. Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. LATUDA is not indicated for the treatment of dementia-related psychosis, and should not be used in patients at risk for aspiration pneumonia.

5.14. Use in Patients with Concomitant Illness

Clinical experience with LATUDA in patients with certain concomitant systemic illnesses is limited *[see Use in Specific Populations (8.6, 8.7)]*. LATUDA 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 premarketing clinical studies *[see Warnings and Precautions (5.1, 5.8)]*.

6. ADVERSE REACTIONS

6.1. Overall Adverse Reaction Profile

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Use in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular Adverse Reactions, Including Stroke *[see Warnings and Precautions (5.2)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.3)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.4)]*
- Hyperglycemia and Diabetes Mellitus *[see Warnings and Precautions (5.5)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.6)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.7)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.8)]*
- Seizures *[see Warnings and Precautions (5.9)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.10)]*

- Body Temperature Regulation *[see Warnings and Precautions (5.11)]*
- Suicide *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*
- Use in Patients with Concomitant Illness *[see Warnings and Precautions (5.14)]*

The information below is derived from a clinical study database for LATUDA consisting of over 2096 patients with schizophrenia exposed to one or more doses with a total experience of 624 patient-years. Of these patients, 1004 participated in short-term placebo-controlled schizophrenia studies with doses of 20 mg, 40 mg, 80 mg or 120 mg once daily. A total of 533 LATUDA-treated patients had at least 24 weeks and 238 LATUDA-treated patients had at least 52 weeks of exposure.

Adverse events during exposure to study treatment were obtained by general inquiry and voluntarily reported adverse experiences, as well as results from physical examinations, vital signs, ECGs, weights and laboratory investigations. Adverse experiences were recorded by clinical investigators using their own terminology. In order to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. Treatment-emergent adverse events were defined as adverse experiences, which started or worsened on or after the date of the first dose through seven days after study medication discontinuation. There was no attempt to use investigator causality assessments; i.e., all events meeting the defined criteria, regardless of investigator causality are included. It is important to emphasize that, although the reactions occurred during treatment with LATUDA, they were not necessarily caused by it. The label should be read in its entirety to gain an understanding of the safety profile of LATUDA.

The figures in the tables and tabulations 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 that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses and investigators. The cited figures, however, do provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reaction incidence in the population studied.

6.2. Clinical Studies Experience

The following findings are based on the short-term placebo-controlled premarketing studies for schizophrenia in which LATUDA was administered at daily doses ranging from 20 to 120 mg (n = 1004).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, nausea, parkinsonism and agitation.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9.4% (94/1004) LATUDA-treated patients and 5.9% (27/455) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in patients with schizophrenia) are shown in Table 6.

Table 6: Adverse Reaction in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Short-term Schizophrenia Studies

Body System or Organ Class Dictionary-derived Term	Percentage of Patients Reporting Reaction Placebo (N = 455)	 All LATUDA (N = 1004)
Gastrointestinal Disorders		
Nausea	6	12
Vomiting	6	8
Dyspepsia	6	8
Salivary hypersecretion	<1	2
General Disorders and Administration Site Conditions		
Fatigue	3	4
Musculoskeletal and Connective Tissue Disorders		
Back Pain	3	4
Nervous System Disorders		
Somnolence*	10	22
Akathisia	3	15
Parkinsonism**	5	11
Dystonia***	1	5
Dizziness	3	5
Psychiatric Disorders		
Insomnia	7	8
Agitation	3	6
Anxiety	3	6
Restlessness	2	3

Note: Figures rounded to the nearest integer

* Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

*** Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

6.3. Dose-Related Adverse Reactions

Based on the pooled data from the placebo-controlled, short-term, fixed-dose studies, among the adverse reactions that occurred with a greater than 5% incidence in the patients treated with LATUDA, the apparent dose-related adverse reactions were akathisia and somnolence (Table 7).

Table 7: Dose-Related Adverse Events

Adverse Event Term	Percentage of Subjects Reporting Reaction				
	Placebo (N = 455) (%)	LATUDA 20 mg/day (N = 71) (%)	LATUDA 40 mg/day (N = 360) (%)	LATUDA 80 mg/day (N = 282) (%)	LATUDA 120 mg/day (N = 291) (%)
Akathisia	3	6	11	15	22
Somnolence*	10	15	19	23	26

Note: Figures rounded to the nearest integer
* Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

6.4. Extrapyramidal Symptoms

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported EPS-related events, excluding akathisia and restlessness, was 14.7% versus 5.1% for placebo-treated patients; and the incidence of akathisia for LATUDA-treated patients was 15.0% versus 3.3% for placebo-treated patients. Akathisia appeared to be dose-related and the greatest frequency of parkinsonism and dystonia occurred with the highest dose of LATUDA, 120 mg/day (Table 8).

Table 8: Percentage of EPS Compared to Placebo

Adverse Event Term	Placebo (N = 455) (%)	LATUDA 20 mg/day (N = 71) (%)	LATUDA 40 mg/day (N = 360) (%)	LATUDA 80 mg/day (N = 282) (%)	LATUDA 120 mg/day (N = 291) (%)
All EPS events	9	10	24	26	39
All EPS events, excluding Akathisia/Restlessness	5	6	13	11	22
Akathisia	3	6	11	15	22
Dystonia*	1	0	4	5	7
Parkinsonism**	5	6	10	7	17
Restlessness	2	1	4	1	3

Note: Figures rounded to the nearest integer
* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

In the short-term, placebo-controlled schizophrenia studies, data was objectively collected on the Simpson Angus Rating Scale for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (for akathisia) and the Abnormal Involuntary Movement Scale (for dyskinesias). The mean change from baseline for LATUDA-treated patients was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.2; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 16.0%; placebo, 7.6%) and the SAS (LATUDA, 5.3%; placebo, 2.5%).

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

In the short-term, placebo-controlled clinical trials, dystonia occurred in 4.7% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 4.2% LATUDA 40 mg, 4.6% LATUDA 80 mg and 6.5% LATUDA 120 mg) compared to 0.7% of subjects receiving placebo. Seven subjects (0.7%, 7/1004) discontinued clinical trials due to dystonic events – 4 were receiving LATUDA 80 mg/day and 3 were receiving LATUDA 120 mg/day.

6.5. Laboratory Test Abnormalities and ECG Changes in Clinical Studies

Laboratory Test Abnormalities

In a between-group comparison of the pooled data from short-term, placebo-controlled studies, there were no clinically important changes in total cholesterol measurements; triglycerides or glucose from Baseline to Endpoint [*see Warnings and Precautions (5.5)*]. There were also no clinically important differences between LATUDA and placebo in mean change from baseline to endpoint in routine hematology, urinalysis, or serum chemistry. LATUDA was associated with a dose-related increase in prolactin concentration [*see Warnings and Precautions (5.6)*]

Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in creatinine was 0.06 mg/dL for LATUDA-treated patients compared to 0.03 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.1% (30/977) of LATUDA-treated patients and 1.4% (6/439) on placebo. The threshold for high creatinine value varied from ≥ 1.1 to ≥ 1.3 mg/dL based on the centralized laboratory definition for each study [*see Dosage in Special Population (2.3); Use in Specific Populations (8)*].

Transaminases: The mean changes in AST and ALT for LATUDA- and placebo-treated patients were similar. The proportion of patients with transaminases (AST and ALT) elevations ≥ 3 times ULN was similar for all LATUDA-treated patients (0.8% and 0.8%, respectively) to placebo-treated patients (0.9% and 1.1%, respectively).

ECG Changes

Electrocardiogram (ECG) measurements were taken at various time points during the LATUDA clinical trial program. No post-baseline QT prolongations exceeding 500 msec were reported in patients treated with LATUDA. Within a subset of patients defined as having an increased cardiac risk, no potentially important changes in ECG parameters were observed. No cases of torsade de pointes or other severe cardiac arrhythmias were observed in the pre-marketing clinical program.

The effects of LATUDA on the QT/QTc interval were evaluated in a dedicated QT study involving 87 clinically stable patients with schizophrenia or schizoaffective disorder, who were treated with LATUDA doses of 120 mg daily, 600 mg daily, or ziprasidone 160 mg daily. Holter monitor-derived electrocardiographic assessments were obtained over an eight hour period at baseline and steady state. No patients treated with LATUDA experienced QTc increases > 60 msec from baseline, nor did any patient experience a QTc of > 500 msec.

6.6. Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of MedDRA terms that reflect adverse reactions reported by patients treated with LATUDA at multiple doses of ≥ 20 mg once daily during any phase of a study within the database of 2096 patients. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions listed in Table 6 are not included. Although the reactions reported occurred during treatment with LATUDA, they were not necessarily caused by it.

Reactions are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

Blood and Lymphatic System Disorders: ***Infrequent:*** *anemia;* ***Rare:*** *leukopenia, neutropenia*

Cardiac Disorders: ***Frequent:*** *tachycardia;* ***Infrequent:*** *AV block 1st degree, angina pectoris, bradycardia*

Ear and Labyrinth Disorders: ***Infrequent:*** *vertigo*

Eye disorders: ***Frequent:*** *blurred vision*

Gastrointestinal Disorders: ***Frequent:*** *abdominal pain, diarrhea;* ***Infrequent:*** *gastritis, dysphagia*

General Disorders and Administrative Site Conditions: ***Rare:*** *Sudden death*

Investigations: ***Frequent:*** *CPK increased*

Metabolic and Nutritional System Disorders: ***Frequent:*** *decreased appetite*

Musculoskeletal and Connective Tissue Disorders: ***Rare:*** *rhabdomyolysis*

Nervous System Disorders: ***Infrequent:*** *tardive dyskinesia, cerebrovascular accident, dysarthria, syncope;* ***Rare:*** *neuroleptic malignant syndrome, seizure*

Psychiatric Disorders: ***Infrequent:*** *abnormal dreams, panic attack, sleep disorder;* ***Rare:*** *suicidal behavior*

Renal and Urinary Disorders: ***Infrequent:*** *dysuria;* ***Rare:*** *renal failure*

Reproductive System and Breast Disorders: ***Infrequent:*** *amenorrhea, dysmenorrhea;* ***Rare:*** *breast enlargement, breast pain, galactorrhea, erectile dysfunction*

Skin and Subcutaneous Tissue Disorders: ***Frequent:*** *rash, pruritus;* ***Rare:*** *angioedema*

Vascular Disorders: ***Infrequent:*** *hypertension, orthostatic hypotension*

7. DRUG INTERACTIONS

Given the primary CNS effects of LATUDA, caution should be used when it is taken in combination with other centrally acting drugs and alcohol.

7.1. Potential for Other Drugs to Affect LATUDA

LATUDA is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes. This suggests that an interaction of LATUDA with drugs that are inhibitors or inducers of these enzymes is unlikely.

LATUDA is predominantly metabolized by CYP3A4; interaction of LATUDA with strong and moderate inhibitors or inducers of this enzyme has been observed (Table 9). LATUDA should not be used in combination with strong inhibitors or inducers of this enzyme *[see Contraindications (4)]*.

Table 9: Summary of Effect of Coadministered Drugs on Exposure to LATUDA in Healthy Subjects or Patients with Schizophrenia

Coadministered drug	Dose schedule		Effect on LATUDA pharmacokinetics		Recommendation
	Coadministered drug	LATUDA	C_{max}	AUC	
Ketoconazole (strong CYP3A4 inhibitor)	400 mg/day for 5 days	10 mg single dose	6.9-times LATUDA alone	9-times LATUDA alone	Should not be coadministered with LATUDA
Diltiazem (moderate CYP3A4 inhibitor)	240 mg/ day for 5 days	20 mg single dose	2.1- times LATUDA alone	2.2- times LATUDA alone	LATUDA dose should not exceed 40 mg/day if coadministered
Rifampin (strong CYP3A4 inducer)	600 mg/day for 8 days	40 mg single dose	1/7th of LATUDA alone	1/5th of LATUDA alone	Should not be coadministered with LATUDA
Lithium	600 mg BID for 8 days	120 mg/day for 8 days	0.9-times LATUDA alone	1.1- times LATUDA alone	No LATUDA dose adjustment required.

7.2. Potential for LATUDA to Affect Other Drugs

Digoxin (P-gp substrate): Coadministration of LATUDA (120 mg/day) at steady state with a single dose of digoxin (0.25 mg) increased C_{max} and $AUC_{(0-24)}$ for digoxin by approximately 9% and 13%, respectively relative to digoxin alone. Digoxin dose adjustment is not required when coadministered with LATUDA.

Midazolam (CYP3A4 substrate): Coadministration of LATUDA (120 mg/day) at steady state with a single dose of 5 mg midazolam increased midazolam Cmax and $AUC_{(0-24)}$ by approximately 21% and 44%, respectively relative to midazolam alone. Midazolam dose adjustment is not required when coadministered with LATUDA.

Oral Contraceptive (estrogen/progesterone): Coadministration of LATUDA (40 mg/day) at steady state with an oral contraceptive (OC) containing ethinyl estradiol and norelgestimate resulted in equivalent $AUC_{(0-24)}$ and C_{max} of ethinyl estradiol and norelgestromin relative to OC administration alone. Also, sex hormone binding globulin levels were not meaningfully affected by coadministration of LATUDA and OC. Dose adjustment of OC dose is not required when coadministered with LATUDA.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Teratogenic Effects

Pregnancy Category B

Lurasidone was not teratogenic in rats and rabbits. There are no adequate and well-controlled studies of LATUDA in pregnant women.

No teratogenic effects were seen in studies in which pregnant rats and rabbits were given lurasidone during the period of organogenesis at doses up to 25 and 50 mg/kg/day, respectively. These doses are 3 and 12 times, in rats and rabbits respectively, the maximum recommended human dose (MRHD) of 80 mg/day based on body surface area.

No adverse developmental effects were seen in a study in which pregnant rats were given lurasidone during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day; this dose is approximately equal to the MRHD based on body surface area.

Non-teratogenic Effects

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

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

8.2. Labor and Delivery

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

8.3. Nursing Mothers

LATUDA was excreted in milk of rats during lactation. It is not known whether LATUDA or its metabolites are excreted in human milk. Breast feeding in women receiving LATUDA should be considered only if the potential benefit justifies the potential risk to the child.

8.4. Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5. Geriatric Use

Clinical studies of LATUDA in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), lurasidone concentrations (20 mg/day) were similar to those in young subjects *[see Clinical Pharmacology (12.3)]*. No dose adjustment is necessary in elderly patients.

Elderly patients with dementia-related psychosis treated with LATUDA are at an increased risk of death compared to placebo. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

8.6. Renal Impairment

It is recommended that LATUDA dose should not exceed 40 mg/day in patients with moderate and severe renal impairment ($Cl_{cr} \geq 10$ mL/min to < 50 mL/min).

After administration of a single dose of 40 mg LATUDA to patients with mild, moderate and severe renal impairment, mean C_{max} increased by 40%, 92% and 54%, respectively and mean $AUC_{(0-\infty)}$ increased by 53%, 91% and 2- times, respectively compared to healthy matched subjects.

8.7. Hepatic Impairment

It is recommended that LATUDA dose should not exceed 40 mg/day in patients with moderate and severe hepatic impairment (Child-Pugh Class B and C). In a single-dose study of LATUDA 20 mg, lurasidone mean $AUC_{(0-last)}$ was 1.5-times higher in subjects with mild hepatic impairment (Child-Pugh Class A), 1.7-times higher in subjects with moderate hepatic impairment (Child-Pugh Class B) and 3-times higher in subjects with severe hepatic impairment (Child-Pugh Class C) compared to the values for healthy matched subjects. Mean C_{max} was 1.3, 1.2 and 1.3-times higher for mild, moderate and severe hepatically impaired patients respectively, compared to the values for healthy matched subjects.

8.8. Gender

Population pharmacokinetic evaluation indicated that the mean AUC of LATUDA was 18% higher in women than in men, and correspondingly, the apparent oral clearance of LATUDA was lower in women. Mean C_{max} of LATUDA was similar between women and men. No dosage adjustment of LATUDA is recommended based on gender.

8.9. Race

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of LATUDA, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of LATUDA. No dosage adjustment of LATUDA is recommended based on race.

8.10. Smoking Status

Based on in vitro studies utilizing human liver enzymes, LATUDA is not a substrate for CYP1A2; smoking is therefore not expected to have an effect on the pharmacokinetics of LATUDA.

9. DRUG ABUSE AND DEPENDENCE

9.1. Controlled substance

LATUDA is not a controlled substance.

9.2. Abuse

LATUDA has not been systematically studied in humans for its potential for abuse or physical dependence or its ability to induce tolerance. While clinical studies with LATUDA did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict the extent to which a CNS-active drug will be misused, diverted and/or abused once it is marketed. Patients should be evaluated carefully for a history of drug abuse, and such patients should be observed carefully for signs of LATUDA misuse or abuse (e.g., development of tolerance, drug-seeking behavior, increases in dose).

10. OVERDOSAGE

10.1. Human Experience

In premarketing clinical studies involving more than 2096 patients and/or healthy subjects, accidental or intentional overdosage of LATUDA was identified in one patient who ingested an estimated 560 mg of LATUDA. This patient recovered without sequelae. This patient resumed LATUDA treatment for an additional two months.

10.2. Management of Overdosage

Consult a Certified Poison Control Center for up-to-date guidance and advice. There is no specific antidote to LATUDA, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of LATUDA. Similarly the alpha-blocking properties of bretylium might be additive to those of LATUDA, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures. Epinephrine and dopamine should not be used, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of LATUDA-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

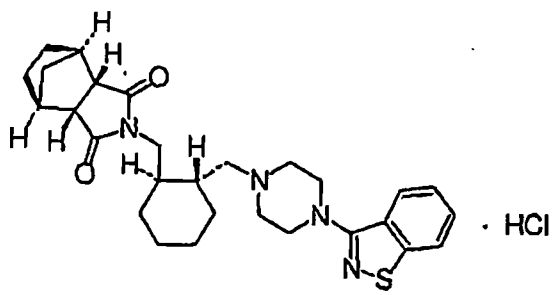
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

11. DESCRIPTION

LATUDA is a psychotropic agent belonging to the chemical class of benzoisothiazol derivatives.

Its chemical name is (3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl] cyclohexylmethyl}hexahydro-4,7-methano-2*H*-isoindole-1,3-dione hydrochloride. Its molecular formula is $C_{28}H_{36}N_4O_2S \cdot HCl$ and its molecular weight is 529.14.

The chemical structure is:



Lurasidone hydrochloride is a white to off-white powder. It is very slightly soluble in water, practically insoluble or insoluble in 0.1 N HCl, slightly soluble in ethanol, sparingly soluble in methanol, practically insoluble or insoluble in toluene and very slightly soluble in acetone.

LATUDA tablets are intended for oral administration only. Each tablet contains 40 mg, or 80 mg of lurasidone hydrochloride.

Inactive ingredients are mannitol, pregelatinized starch, croscarmellose sodium, hypromellose, magnesium stearate, Opadry® and carnauba wax. Additionally, the 80 mg tablet contains yellow ferric oxide and FD&C Blue No.2 Aluminum Lake.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

The mechanism of action of lurasidone, as with other drugs having efficacy in schizophrenia, is unknown. It has been suggested that the efficacy of lurasidone in schizophrenia is mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

12.2. Pharmacodynamics

In vitro receptor binding studies revealed that lurasidone is an antagonist with high affinity at dopamine D_2 receptors (Ki = 0.994 nM) and the 5-hydroxytryptamine (5-HT, serotonin) receptors $5\text{-}HT_{2A}$ (Ki = 0.47 nM; and $5\text{-}HT_7$ (Ki = 0.495 nM), is an antagonist with moderate affinity at human α_{2C} adrenergic receptors (Ki = 10.8 nM), is a partial agonist at serotonin $5\text{-}HT_{1A}$ (Ki = 6.38 nM) receptors, and is an antagonist at α_{2A} adrenergic receptors (Ki = 40.7 nM). Lurasidone exhibits little or no affinity for histamine H_1 and muscarinic M_1 receptors ($IC_{50} \geq 1{,}000$ nM and > 1,000 nM, respectively).

12.3. Pharmacokinetics

The activity of lurasidone is primarily due to the parent drug. The pharmacokinetics of lurasidone is dose-proportional within a total daily dose range of 20 mg to 160 mg. Steady-state concentrations of lurasidone are reached within 7 days of starting LATUDA.

Following administration of 40 mg of LATUDA, the mean (%CV) elimination half-life was 18 (7) hours.

Absorption and Distribution: Lurasidone is absorbed and reaches peak serum concentrations in approximately 1-3 hours. It is estimated that 9-19% of an administered dose is absorbed. Following administration of 40 mg of LATUDA, the mean (%CV) apparent volume of distribution was 6173 (17.2) L. Lurasidone is highly bound (~99%) to serum proteins.

In a food effect study, lurasidone mean C_{max} and AUC were about 3-times and 2-times, respectively, when administered with food compared to the levels observed under fasting conditions. Lurasidone exposure was not affected as meal size was increased from 350 to 1000 calories and was independent of meal fat content [see *Dosage and Administration (2.2)*].

In clinical studies, establishing the safety and efficacy of LATUDA, patients were instructed to take their daily dose with food [*see Dosage and Administration (2.2)*].

Metabolism and Elimination: Lurasidone is metabolized mainly via CYP3A4. The major biotransformation pathways are oxidative *N*-dealkylation, hydroxylation of norbornane ring, and *S*-oxidation. Lurasidone is metabolized into two active metabolites (ID-14283 and ID-14326) and two major non-active metabolites (ID-20219 and ID-20220).

Total excretion of radioactivity in urine and feces combined was approximately 89%, with about 80% recovered in feces and 9% recovered in urine, after a single dose of [^{14}C]-labeled lurasidone.

Following administration of 40 mg of LATUDA, the mean (%CV) apparent clearance was 3902 (18.0) mL/min.

13. NONCLINICAL TOXICOLOGY

Carcinogenesis: Lifetime carcinogenicity studies were conducted in ICR mice and Sprague-Dawley rats. Lurasidone was administered orally at doses of 30, 100, 300, or 650 (the high dose was reduced from 1200 in males) mg/kg/day to ICR mice and 3, 12, or 36 (high dose reduced from 50) mg/kg/day to Sprague-Dawley rats.

In the mouse study, there were increased incidences of malignant mammary gland tumors and pituitary gland adenomas in females at all doses; the lowest dose tested produced plasma levels (AUC) 2 times those in humans receiving the maximum recommended human dose (MRHD) of 80 mg/day. No increases in tumors were seen in male mice up to the highest dose tested, which produced plasma levels (AUC) 15-25 times those in humans receiving the MRHD.

In rats, an increased incidence of mammary gland carcinomas was seen in females at the two higher doses; the no-effect dose of 3 mg/kg produced plasma levels (AUC) 0.7 times those in humans receiving the MRHD. No increases in tumors were seen in male rats up to highest dose tested, which produced plasma levels (AUC) 10 times those in humans receiving the MRHD.

Proliferative and/or neoplastic changes in the mammary and pituitary glands of rodents have been observed following chronic administration of antipsychotic drugs and are considered to be prolactin mediated. The relevance of this increased incidence of prolactin-mediated pituitary or mammary gland tumors in rodents in terms of human risk is unknown *[see Warnings and Precautions (5.6)]*.

Mutagenesis: Lurasidone was not genotoxic in the Ames test, the *in vitro* chromosomal aberration test in Chinese Hamster Lung (CHL) cells, or the *in vivo* mouse bone marrow micronucleus test.

Impairment of Fertility: Lurasidone was administered orally to female rats at doses of 0.1, 1.5, 15, or 150 mg/kg/day for 15 consecutive days prior to mating, during the mating period, and through day 7 of gestation. Estrus cycle irregularities were seen at 1.5 mg/kg and above; the no-effect dose of 0.1 mg/kg is approximately 0.01 times the maximum recommended human dose (MRHD) of 80 mg/day based on body surface area. Fertility was reduced only at the highest dose and this was shown to be reversible after a 14 day drug-free period. The no-effect dose for reduced fertility was 15 mg/kg, which is 1.8 times the MRHD based on body surface area.

Fertility was not affected in male rats treated orally with lurasidone for 64 consecutive days prior to mating and during the mating period at doses up to 150 mg/kg/day (12 times the MRHD based on body surface area).

14. CLINICAL STUDIES

14.1. Schizophrenia

The efficacy of LATUDA for the treatment of schizophrenia was established in four short-term (6-week), placebo-controlled studies in adult patients (mean age of 38.8 years, range 18-72) who met DSM-IV criteria for schizophrenia. One study included an active-control arm (olanzapine) to assess assay sensitivity.

Several instruments were used for assessing psychiatric signs and symptoms in these studies:

1. Positive and Negative Syndrome Scale (PANSS), is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. PANSS total scores may range from 30 to 210.
2. Brief Psychiatric Rating Scale derived (BPRSd), derived from the PANSS, is a multi-item inventory primarily focusing on positive symptoms of schizophrenia, whereas the PANSS includes a wider range of positive, negative and other symptoms of schizophrenia. BPRSd scores may range from 18 to 126.
3. The Clinical Global Impression severity scale (CGI-S) is a validated clinician-rated scale that measures the subject's current illness state on a 1 to 7-point scale.

The endpoint associated with each instrument is change from baseline in the total score to the end of week 6. These changes are then compared to placebo changes for the drug and control groups.

The results of the studies follow:

1. In a 6-week, placebo-controlled trial (N=145) involving two fixed doses of LATUDA (40 or 120 mg/day), both doses of LATUDA at Endpoint were superior to placebo on the BPRSd total score, and the CGI-S.
2. In a 6-week, placebo-controlled trial (N=180) involving a fixed dose of LATUDA (80 mg/day), LATUDA at Endpoint was superior to placebo on the BPRSd total score, and the CGI-S.
3. In a 6-week, placebo and active-controlled trial (N=473) involving two fixed doses of LATUDA (40 or 120 mg/day) and an active control (olanzapine), both LATUDA doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.
4. In a 6-week, placebo-controlled trial (N=489) involving three fixed doses of LATUDA (40, 80 or 120 mg/day), only the 80 mg/day dose of LATUDA at Endpoint was superior to placebo on the PANSS total score, and the CGI-S.

Thus, the efficacy of LATUDA at doses of 40, 80 and 120 mg/day was established in two studies for each dose. However, the 120 mg dose did not appear to add additional benefit over the 40 mg dose (Table 10).

Table 10: Summary of Results for Primary Efficacy Endpoints

Study Number	Primary Endpoint	LS Mean (SE)[a] Difference from Placebo in Change from Baseline			
		LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day	Olanzapine 15 mg/day
1	BPRSd	-5.6* (2.1)	-	-6.7* (2.2)	-
2	BPRSd	-	-4.7* (1.8)	-	-
3	PANSS	-9.7* (2.9)	-	-7.5* (3.0)	-12.6* (2.8)
4	PANSS	-2.1 (2.5)	-6.4* (2.5)	-3.5 (2.5)	-

*adjusted p-value <0.05 (except for olanzapine)
[a] Least Squares Mean (Standard Error)

Examination of population subgroups based on age (there were few patients over 65), gender and race did not reveal any clear evidence of differential responsiveness.

16. HOW SUPPLIED/STORAGE AND HANDLING

LATUDA tablets are white to off-white, round (40 mg), or pale green, oval (80 mg) and identified with strength specific one-sided debossing , "L40" (40 mg), or "L80" (80 mg). Tablets are supplied in the following strengths and package configurations (Table 11):

Table 11: Package Configuration for LATUDA Tablets

Tablet Strength	Package Configuration	NDC Code
40 mg	Bottles of 30	63402-304-30
	Bottles of 90	63402-304-90
	Bottles of 500	63402-304-50
	Box of 28 4 blister cards, 7 tablets each	63402-304-04 Carton 63402-304-07 Blister
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-304-10 Carton 63402-304-01 Blister
80 mg	Bottles of 30	63402-308-30
	Bottles of 90	63402-308-90
	Bottles of 500	63402-308-50
	Box of 28 4 blister cards, 7 tablets each	63402-308-04 Carton 63402-308-07 Blister
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-308-10 Carton 63402-308-01 Blister

Storage

Store LATUDA tablets at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) *[See USP Controlled Room Temperature]*.

17. PATIENT COUNSELING INFORMATION

Physicians are advised to discuss with patients for whom they prescribe LATUDA all relevant safety information including, but not limited to, the following:

17.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Patients and caregivers should be advised that elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs are at increased risk of death compared with placebo. LATUDA is not approved for elderly patients with dementia-related psychosis [*see Boxed Warning; Warnings and Precautions (5.1)*].

17.2 Neuroleptic Malignant Syndrome

Patients and caregivers should be counseled that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) *[see Warnings and Precautions (5.3)]*.

17.3 Hyperglycemia and Diabetes Mellitus

Patients should be aware of the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those that develop these symptoms during treatment should have their blood glucose monitored at the beginning of and periodically during treatment [*see Warnings and Precautions (5.5)*].

17.4 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose *[see Warnings and Precautions (5.8)]*.

17.5 Leukopenia/Neutropenia

Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking LATUDA [*see Warnings and Precautions (5.7)*].

17.6 Interference with Cognitive and Motor Performance

Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that LATUDA therapy does not affect them adversely *[see Warnings and Precautions (5.10)]*.

17.7 Pregnancy and Nursing

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with LATUDA *[see Use in Specific Populations (8.1)]*.

17.8 Concomitant Medication and Alcohol

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. Patients should be advised to avoid alcohol while taking LATUDA *[see Drug Interactions (7)]*.

17.9 Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.11)]*.

SUNOVION

Manufactured for:
Sunovion Pharmaceuticals Inc.
Marlborough, MA 01752,

For Customer Service, call 1-888-394-7377.
For Medical Information, call 1-800-739-0565.
To report suspected adverse reactions, call 1-877-737-7226.

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CHAPTER FIVE - GENERAL CHARGE

DUTIES OF JURY AND JUDGE

I REMIND YOU THAT, DURING THIS TRIAL, YOU AND I HAVE CERTAIN DUTIES TO PERFORM. AS THE TRIAL JUDGE, IT IS MY RESPONSIBILITY TO PRESIDE OVER THE TRIAL OF THIS CASE, AND I ALSO HAVE THE DUTY TO RULE ON THE ADMISSIBILITY OF THE EVIDENCE OFFERED DURING THIS TRIAL. YOU ARE TO CONSIDER ONLY THE EVIDENCE BEFORE YOU THAT IS IN THE RECORD OF THIS CASE. IF THERE WAS ANY TESTIMONY ORDERED STRICKEN FROM THE RECORD DURING THIS TRIAL, AND THERE WERE MATTERS THAT I HAD STRICKEN FROM THE RECORD, YOU MUST DISREGARD ANT SUCH STRICKEN EVIDENCE IN ITS ENTIRETY. YOU ARE TO CONSIDER ONLY THE TESTIMONY WHICH HAS BEEN PRESENTED FROM THIS WITNESS STAND, ANY EXHIBITS WHICH HAVE BEEN MADE A PART OF THE RECORD IN THIS CASE, AND ANY STIPULATIONS OF COUNSEL.

I HAVE THE ADDITIONAL DUTY TO CHARGE YOU THE LAW APPLICABLE TO THIS CASE. IT IS YOUR DUTY AS JURORS TO ACCEPT AND APPLY THE LAW AS I NOW STATE IT TO YOU. IF YOU THINK YOU HAVE ANY IDEA AS TO WHAT THE LAW IS OR WHAT THE LAW OUGHT TO BE AND IT DOES NOT AGREE WITH WHAT I TELL YOU THE LAW IS, YOU MUST FORGET THAT IDEA BECAUSE YOU ARE SWORN TO ACCEPT THE LAW AND APPLY THE LAW EXACTLY AS I STATE IT TO YOU.

IN EVERY CASE TRIED IN THIS COURT BEFORE A JURY, THE JURY BECOMES THE SOLE AND EXCLUSIVE JUDGE OF THE FACTS.[1] A TRIAL JUDGE CANNOT COMMENT ON OR MAKE ANY STATEMENT ABOUT THE FACTS IN A CASE. SINCE YOU ARE THE

[1] Day v. Kilgore, 314 S.C. 365, 444 S.E.2d 515 (1994).

SOLE JUDGES OF THE FACTS, DO NOT THINK BY ANYTHING I HAVE SAID DURING THE TRIAL THAT I HAVE ANY OPINION ABOUT THE FACTS IN THIS CASE. THE LAW DOES NOT ALLOW ME TO HAVE AN OPINION ABOUT THE FACTS.

WHAT THE ATTORNEYS TELL YOU DURING THEIR OPENING AND CLOSING STATEMENTS IS NOT EVIDENCE IN THIS CASE, IT IS ONLY THEIR CONTENTIONS AS TO WHAT THE ISSUES ARE AND THEIR CLIENT'S VIEWS CONCERNING THAT EVIDENCE. THE EVIDENCE IN THIS CASE HAS BEEN PRESENTED TO YOU BY THE TESTIMONY OF SWORN WITNESSES FROM THIS WITNESS STAND OR IN SWORN DEPOSITIONS AND/OR BY EXHIBITS THAT MAY HAVE BEEN INTRODUCED INTO EVIDENCE AND FACTS ENTERED INTO THE RECORD BY WAY OF STIPULATION BETWEEN COUNSEL.

PREPONDERANCE OF THE EVIDENCE

THE PLAINTIFF (State of SC) HAS THE BURDEN OF PROOF OF THEIR ALLEGATIONS IN THIS CASE OR THE RESPONSIBILITY TO PRESENT THE LEGALLY REQUIRED PROOF IN THIS MATTER. THAT RESPONSIBILITY IS CALLED THE "BURDEN OF PROOF". THAT BURDEN OF PROOF IN THIS CASE IS BY A PREPONDERANCE OF THE EVIDENCE. A PREPONDERANCE OF THE EVIDENCE SIMPLY MEANS THE GREATER WEIGHT OF THE EVIDENCE. IT IS EVIDENCE WHICH, AS A WHOLE, SHOWS THAT THE FACT SOUGHT TO BE PROVED IS MORE LIKELY TRUE THAN NOT TRUE.[2]

THIS CAN BE ILLUSTRATED BY IMAGINING A SET OF SCALES. WHEN THE CASE BEGINS, THE SCALES ARE EVEN. AFTER ALL OF

[2] Metropolitan Stevedore Co. v. Rambo, 521 U.S. 121, 117 S. Ct. 1953, 138 L. Ed. 2d 327 (1997).

THE EVIDENCE HAS BEEN PRESENTED, IF THE SCALES REMAIN EVEN OR IF THEY TIP EVER SO SLIGHTLY IN FAVOR OF THE DEFENDANT, THEN THE PLAINTIFF HAS FAILED TO MEET THE BURDEN OF PROOF AND WOULD NOT BE ENTITLED TO RECOVER IN THIS CASE. IF, ON THE OTHER HAND, THE SCALES TIP EVER SO SLIGHTLY IN FAVOR OF THE PLAINTIFF, THE PLAINTIFF WILL HAVE MET THE BURDEN OF PROOF AND YOU SHOULD RETURN A VERDICT FOR THE PLAINTIFF.

THE PREPONDERANCE OF THE EVIDENCE IS NOT DETERMINED BY THE NUMBER OF WITNESSES. INSTEAD, IT MUST BE DETERMINED BY THE GREATER WEIGHT OF ALL OF THE EVIDENCE. THE WEIGHT THAT YOU GIVE TO ANY OF THE EVIDENCE IN THIS CASE IS DETERMINED BY THE WEIGHT THAT YOU GIVE TO ANY OF THE EVIDENCE THAT YOU HAVE HEARD IN THIS MATTER.

DIRECT AND CIRCUMSTANTIAL EVIDENCE

THERE ARE TWO TYPES OF EVIDENCE GENERALLY PRESENTED DURING A TRIAL - DIRECT EVIDENCE AND CIRCUMSTANTIAL EVIDENCE.

DIRECT EVIDENCE IS THE TESTIMONY OF A PERSON WHO CLAIMS TO HAVE ACTUAL KNOWLEDGE OF A FACT, SUCH AS AN EYEWITNESS. IT IS EVIDENCE WHICH IMMEDIATELY ESTABLISHES THE MAIN FACT TO BE PROVED.[3]

CIRCUMSTANTIAL EVIDENCE IS PROOF OF A CHAIN OF FACTS AND CIRCUMSTANCES INDICATING THE EXISTENCE OF A FACT. IT IS EVIDENCE WHICH IMMEDIATELY ESTABLISHES COLLATERAL FACTS FROM WHICH THE MAIN FACT MAY BE INFERRED. CIRCUMSTANTIAL EVIDENCE IS BASED ON

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[3] State v. Salisbury, 343 S.C. 520, 541 S.E.2d 247 (2001); Moriarty v. Garden Sanctuary Church of God, 341 S.C. 320, 534 S.E.2d 672 (2000).

INFERENCE AND NOT ON PERSONAL KNOWLEDGE OR OBSERVATION.[4] IT IS PROOF THAT DOES NOT ACTUALLY ESTABLISH THE FACT IN QUESTION, BUT THAT ASSERTS OR DESCRIBES SOMETHING ELSE FROM WHICH YOU MAY EITHER REASONABLY INFER THE TRUTH OF THE FACT OR AT LEAST REASONABLY INFER AN INCREASE IN THE PROBABILITY THAT THE FACT IS TRUE.[5] FOR CIRCUMSTANTIAL EVIDENCE TO BE SUFFICIENT TO WARRANT THE FINDING OF A FACT, THE CIRCUMSTANCES MUST LEAD TO THAT FACT WITH REASONABLE CERTAINTY. THE FACTS AND CIRCUMSTANCES SHOULD BE CONSIDERED IN LIGHT OF ORDINARY EXPERIENCE AND COMMON SENSE. THE EXISTENCE OF A FACT CANNOT BE BASED ON SPECULATION, SURMISE, OR CONJECTURE.[6]

THE LAW MAKES ABSOLUTELY NO DISTINCTION BETWEEN THE WEIGHT OR VALUE TO BE GIVEN TO EITHER DIRECT OR CIRCUMSTANTIAL EVIDENCE. NOR IS A GREATER DEGREE OF CERTAINTY REQUIRED OF CIRCUMSTANTIAL EVIDENCE THAN OF DIRECT EVIDENCE.

CREDIBILITY OF WITNESSES

NECESSARILY, YOU MUST DETERMINE THE CREDIBILITY OF WITNESSES WHO HAVE TESTIFIED IN THIS CASE. CREDIBILITY SIMPLY MEANS BELIEVABILITY. IT BECOMES YOUR DUTY AS JURORS TO EVALUATE THE EVIDENCE AND DETERMINE WHICH EVIDENCE CONVINCES YOU IT IS TRUE.[7]

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[4] State v. Salisbury, 343 S.C. 520, 541 S.E.2d 247 (2001).

[5] Gastineau v. Murphy, 323 S.C. 168, 473 S.E.2d 819 (Ct. App. 1996), rev'd on other grounds, 331 S.C. 565, 503 S.E.2d 712 (1998).

[6] Holland v. Georgia Hardwood Lumber Co., 214 S.C. 195, 51 S.E.2d 744 (1949).

[7] Small v. Pioneer Mach., Inc., 329 S.C. 448, 494 S.E.2d 835 (Ct. App. 1997).

IN DETERMINING THE BELIEVABILITY OF WITNESSES WHO HAVE TESTIFIED IN THIS CASE, YOU MAY BELIEVE ONE WITNESS OVER SEVERAL WITNESSES OR SEVERAL WITNESSES OVER ONE WITNESS. YOU MAY BELIEVE A PART OF THE TESTIMONY OF A WITNESS AND REJECT THE REMAINING PART OF THE TESTIMONY OF THAT SAME WITNESS. YOU MAY BELIEVE THE TESTIMONY OF A WITNESS IN ITS ENTIRETY OR REJECT THE TESTIMONY OF A WITNESS IN ITS ENTIRETY. YOU MAY CONSIDER WHETHER THE WITNESS HAS AN INTEREST IN THE RESULT OF THE TRIAL, WHETHER THE WITNESS IS PREJUDICED TOWARD EITHER THE PLAINTIFF OR THE DEFENDANT, THE OPPORTUNITY FOR THE WITNESS TO HAVE SEEN THE MATTERS AND THINGS ABOUT WHICH THE WITNESS MAY TESTIFY, AND THE WAY THE WITNESS ACTS ON THE WITNESS STAND.

EXPERT WITNESSES

THE RULES OF EVIDENCE ORDINARILY DO NOT PERMIT WITNESSES TO TESTIFY TO OPINIONS OR CONCLUSIONS. AN EXCEPTION TO THIS RULE EXISTS FOR WITNESSES WE CALL EXPERT WITNESSES. A WITNESS WHO, BY EDUCATION AND EXPERIENCE, HAS BECOME EXPERT IN SOME ART, SCIENCE, OR PROFESSION, MAY GIVE AN OPINION AS TO THE SUBJECT THE WITNESS CLAIMS TO BE AN EXPERT IN, AND MAY ALSO GIVE THE REASONS FOR THE OPINION.

YOU SHOULD CONSIDER ANY EXPERT OPINION GIVEN BY A WITNESS AND, LIKE ANY OTHER EVIDENCE, GIVE IT THE WEIGHT YOU THINK IT DESERVES. IF YOU DECIDE THAT AN EXPERT WITNESS' OPINION IS NOT BASED ON SUFFICIENT EDUCATION AND EXPERIENCE, OR IF YOU DECIDE THAT THE REASONS GIVEN IN SUPPORT OF THE OPINION ARE NOT SOUND, OR THAT THE OPINION IS OUTWEIGHED BY OTHER EVIDENCE, YOU MAY DISREGARD THE OPINION ENTIRELY.

AN EXPERT WITNESS' TESTIMONY IS TO BE GIVEN NO GREATER WEIGHT THAN THAT OF OTHER WITNESSES SIMPLY BECAUSE THE WITNESS IS AN EXPERT, YOU HAVE THE RIGHT TO WEIGH THAT TESTIMONY LIKE ANY OTHER WITNESS AND YOU DO NOT HAVE TO ACCEPT AN EXPERT'S OPINION, EVEN THOUGH IT IS CONTRADICTED.[8]

CORPORATION AS PERSON

IN THIS CASE THE TWO DEFENDANTS ARE CORPORATIONS. IN OUR COURTS, NO DISTINCTION IS MADE BETWEEN CORPORATIONS AND INDIVIDUALS. A CORPORATION IS A PERSON IN THE EYES OF THE LAW.[9] A CORPORATION IS ENTITLED TO THE SAME FAIR AND IMPARTIAL CONSIDERATION AND TO JUSTICE BY THE SAME LEGAL STANDARDS AS AN INDIVIDUAL.

THE SAME APPLIES TO THE PLAINTIFF, THE STATE OF SOUTH CAROLINA. IT ALSO IS A LEGAL ENTITY AND IS TREATED AS A PERSON IN THE EYES OF THE LAW. IT TOO IS ENTITLED TO THE SAME FAIR AND IMPARTIAL CONSIDERATION AND TO JUSTICE BY THE SAME LEGAL STANDARDS AS AN INDIVIDUAL.

ALTER EGO

IN THIS CASE A QUESTION HAS BEEN RAISED CONCERNING JUST WHICH, IF ANY, OF THE DEFENDANT CORPORATIONS CAN POSSIBLY BE HELD RESPONSIBLE IN THIS ACTION. TWO DEFENDANT CORPORATIONS HAVE BEEN NAMED. ORTHO-

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[8] Berkeley Elec. Coop., Inc. v. South Carolina Public Serv. Comm'n, 304 S.C. 15, 402 S.E.2d 674 (1991).

[9] Metropolitan Life Ins. Co. v. Ward, 470 U.S. 869, 105 S. Ct. 1676, 84 L. Ed. 2d 751 (1985).

MCNEIL JANSSEN PHARMACUTICALS, INC. AND THE PARENT CORPORATION JOHNSON &JOHNSON, I WILL GIVE YOU A SEPARATE VERDICT FORM FOR EACH DEFENDANT. AND THE CASE SHOULD BE DECIDED BY YOU AS TO EACH DEFENDANT SEPARATELY.

GENERALLY EACH CORPORATION LIKE EACH PERSON IS RESPONSIBLE FOR ITS OWN ACTIONS AND NOT RESPONSIBLE FOR THE ACTIONS OF OTHER PERSONS OR CORPORATIONS.

HOWEVER, UNDER THE LAW OF THIS STATE THERE ARE SITUATIONS WHERE A PARENT CORPORATION CAN BE HELD LIABLE FOR THE ACTIONS OF ONE OF ITS SUBSIDIARIES.

IN THIS CASE THE PARENT CORPORATION IS JOHNSON & JOHNSON, INC., THE OTHER CORPORATION IS A SUBSIDIARY OF THAT PARENT CORPORATION. IN THIS CASE THE PRIMARY ACTOR IS THE SUBSIDIARY ORTHO MCNEIL JANSSEN.

A PARENT CORPORATION CAN BE HELD LIABLE FOR THE ACTIONS OF ONE OF ITS SUBSIDIARIES IF THE SUBSIDIARIES IN QUESTION ARE CONSIDERED TO BE THE "ALTER EGOS" OF THE PARENT.

Under this theory, when a parent company controls the business decisions and actions of its subsidiary, the subsidiary becomes an instrument of or alter ego of the parent. > Peoples Fed. Sav. & Loan Ass'n v. Myrtle Beach Golf & Yacht Club, 310 S.C. 132, 148, 425 S.E.2d 764, 774 (Ct.App.1992). THE LEVEL OF CONTROL required for liability under an alter ego doctrine amounts to total domination of the subsidiary by the parent corporation to the extent the subsidiary manifested no separate corporate interests and functioned solely to achieve the purpose of the dominant corporation. > Id. (citing > Krivo Indus. Supply Co. v. Nat'l Distillers & Chem. Corp., 483 F.2d 1098, 1106 (5th Cir.1973)).

. 678 S.E.2d 819, 383 S.C. 259, Jones ex rel. Jones v. Enterprise Leasing Company-Southeast, (S.C.App. 2009)

---------- Excerpt from page 678 S.E.2d 823

... "[c]ommon officers and/or directors and public identification of one corporation as the other's subsidiary do not, without more, support the conclusion the subsidiary is its parent's alter ego or agent for the transaction of its business." Yarborough & Co. v. Schoolfield Furniture Indus., Inc., 275 S.C. 151,
153-54, 268 S.E.2d 42, 44 (1980)> To view preceding link please click here (citations omitted).

IF YOU DECIDE THAT THE PARENT CORPORATION HAS THE SUFFICIENT LEVEL OF CONTROL OVER THE SUBSIDIARY, THAT IS, TOTAL DOMINATION OF THE SUBSIDIARY, THEN THERE IS ANOTHER QUESTION THAT YOU SHOULD CONSIDER BEFORE DETERMINING THAT THE SUBSIDIARY IS THE "ALTER EGO" OF THE PARENT> IN ADDITION TO THE QUESTION OF THE LEVEL OF CONTROL. "one must [also] show that the retention of separate corporate personalities would promote fraud, wrong or injustice, TO OCCUR AND TO NOT SO FIND would contravene OR DEFEAT public policy." > Mid-South Mgt., 374 S.C. at 603, 649 S.E.2d at 143. "

678 S.E.2d 819, 383 S.C. 259, Jones ex rel. Jones v. Enterprise Leasing Company-Southeast, (S.C.App. 2009)
---------- Excerpt from pages 678 S.E.2d 823-678 S.E.2d 824

You must decide if the level of control by the parent corporation is sufficient to justify disregarding their SEPARATE corporate IDENTITIES.

YOU MUST DECIDE WHICH, IF ANY, OF THE DEFENDANTS IS LIABLE FOR ANY WRONG WHICH YOU MAY DETERMINE AND RETURN A VERDICT WHICH REFLECTS THOSE FINDINGS ONLY AGAINST THE CORPORATION OR CORPORATIONS WHICH YOU FIND TO BE RESPONSIBLE.

Plaintiffs' Claims

THE PLAINTIFF HAS CLAIMED THAT THE DEFENDANTS HAVE VIOLATED THE SCUTPA WHICH, PROVIDES FOR PENALTIES FOR THOSE WHO ARE FOUND TO HAVE VIOLATED ITS PROVISIONS. YOU HAVE NO ROLE IN DECIDING ANY POTENTIAL PENALTIES. YOUR ROLE IS TO DETRERMINE WHETHER OR NOT A VIOLATION OF THE LAW HAS OCCURRED. HOWEVER, BECAUSE OF THE NATURE OF THIS ACTION THE STATUTES THAT YOU ARE USING IN THIS CASE SHOULD BE STRICTLY INTERPRETED BY YOU ACCORDING TO THEIR TERMS AND ANY AMBIGUITIES IN THE INTERPRETATION OF THE STATUTES SHOULD BE RESOLVED AGAINST THE STATE.

THIS IS AN ACTION BROUGHT UNDER THE UNFAIR TRADE PRACTICES ACT.....

WHICH IS A PART OF THE CODE OF LAWS OF THE STATE OF SOUTH CAROLINA....IT IS THE LAW OF THIS STATE

THE SCUTPA IS CONTAINED IN THE CODE OF LAWS OF THE STATE OF SOUTH CAROLINA IN SECTIONS 39-5-10 THROUGH39-5-560. IN THIS CASE THE PLAINTIFF HAS ALLEGED THAT THE DEFENDANTS HAVE VIOLATED THE ACT. SPECIFICALLY, THE STATE ALLEGES THE VIOLATION OF TWO PARTICULAR CODE SECTIONS THAT ARE A PART OF THE SCUTPA. THE TWO CODE SECTIONS ALLEGED TO HAVE BEEN VIOLATED ARE SECTION 39-5-20 AND SECTION 39-5-110.

I CHARGE YOU THAT THIS IS AN ACTION UNDER THE SOUTH CAROLINA UNFAIR TRADE PRACTICES ACT AND IS NOT AN ACTION BROUGHT UNDER FEDERAL LAW OR REGULATIONS AND IS NOT AN EFFORT TO ENFORCE ANY FEDERAL LAWS

OR REGULATIONS, WHILE THE ACTIONS OF THE DEFENDANT ARE SOMETIMES GOVERNED BY FEDERAL LAWS OR REGULATIONS, THE VIOLATION OF A FEDERAL LAW OR REGULATION, IN AND OF ITSELF, DOES NOT CONSTITUTE A VIOLATION OF SCUTPA. THERE MUST BE A SHOWING THAT THE SCUTPA HAS BEEN VIOLATED BY THE ACTIONS OF THE DEFENDANT IN ORDER FOR THERE TO BE A FINDING FOR THE PLAINTIFF.

FIRST OF ALL, THESE ARE THE PERTINENT SOUTH CAROLINA CODE SECTIONS OF THE UNFAIR TRADE PRACTICES ACT THAT YOU SHOULD CONSIDER.

THE ACT ITSELF PROVIDES THE DEFINITION OF CERTAIN WORDS WHICH ARE USED IN THE ACT. WHEN CONSIDERING THE ACT YOU MUST APPLY THESE DEFINITIONS WHEN THESE WORDS APPEAR IN THE LAW.

SECTION 39-5-10. Short title; definitions.

This article may be cited as the "South Carolina Unfair Trade Practices Act."

As used in this article,

(a) "Person" shall include natural persons, corporations, trusts, partnerships, incorporated or unincorporated associations and any other legal entity.

(b) "Trade" and "commerce" shall include the advertising, offering for sale, sale or distribution of any services and any property, tangible or intangible, real, personal or mixed, and any other article, commodity or thing of value wherever situate, and shall include any trade or commerce directly or indirectly affecting the people of this State.

SO FOR PURPOSES OF THE CODE SECTIONS I AM ABOUT TO GO OVER WITH YOU THE DEFINITIONS I JUST GAVE TO YOU SHOULD BE USED BY YOU WHEN YOU HEAR THOSE TERMS.

THE PLAINTIFF HAS CITED TWO SPECIFIC SECTIONS OF SCUTPA AS HAVING BEEN VIOLATED BY THE DEFENDANT'S ACTIONS. THESE SECTIONS OF SCUTPA ARE:

SECTION 39-5-20. Unfair methods of competition and unfair or deceptive acts or practices unlawful

(a ..... unfair or deceptive acts or practices in the conduct of any trade or commerce are hereby declared unlawful.

SECTION 39-5-110. Civil penalties for willful violation or violations of injunction.

(a) If a court finds that any person is willfully using or has willfully used a method, act or practice declared unlawful by Section 39-5-20, the Attorney General, upon petition to the court, may recover.

(b) For purposes of this section, a willful violation occurs when a party committing the violation knew or should have known that his conduct was a violation of §39-5-20.

FOR AN ACT TO BE A VIOLATION OF SCUTPA THE ACT OR PRACTICE COMPLAINED OF MUST BE UNFAIR OR DECEPTIVE. WHETHER AN ACT, WHAT SOMEONE HAS DONE, OR PRACTICE IS UNFAIR OR DECEPTIVE WITHIN THE MEANING OF THE ACT

DEPENDS UPON THE FACTS AND CIRCUMSTANCES SURROUNDING THE ACT AND THE IMPACT OF THE ACT OR TRANSACTION ON THE MARKETPLACE.

THE PLAINTIFF CLAIMS THAT THE DEFENDANT COMMITTED UNFAIR TRADE PRACTICES.[10] A TRADE PRACTICE OR ACT IS AN UNFAIR TRADE PRACTICE OR ACT IF IT OFFENDS ESTABLISHED PUBLIC POLICY OR IT IS IMMORAL, UNETHICAL, OR OPPRESSIVE.[11] THIS DOES NOT INCLUDE ACTS, PRACTICES, OR REPRESENTATIONS THAT ARE NOTHING MORE THAN DEALER TALK, TRADE TALK OR WHAT IS CALLED PUFFING.[12]

Even a truthful statement may be deceptive under the Unfair Trade Practices Act (UTPA) if it has a capacity or tendency to deceive. (WHEN TAKEN IN THE CONTEXT OF THE CIRCUMSTANCES SURROUNDING THE MAKING OF THE STATEMENT) > Wright v. Craft (S.C.App. 2006) 372 S.C. 1, 640 S.E.2d 486, rehearing denied. Antitrust And Trade Regulation K 136

FURTHER, A FALSE OR MISLEADING ACT OR PRACTICE IS ONE THAT HAS THE CAPACITY OR TENDENCY TO DECEIVE. THERE IS NO NEED TO SHOW THAT A REPRESENTATION WAS INTENDED TO DECEIVE, BUT IT SHOULD BE SHOWN THAT THE ACT HAD THE CAPACITY, EFFECT OR TENDENCY TO DO SO.

IN ADDITION, THE PLAINTIFF MUST PROVE THAT THE UNFAIR TRADE PRACTICE OR ACT AFFECTED PERSONS OTHER THAN THE PARTIES TO THE TRANSACTION IN WHICH THE ACT

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[10] S.C. Code Ann. § 39-5-20.

[11] Gentry v. Younce, 337 S.C. 1, 522 S.E.2d 137 (1999).

[12] Fields v. Melrose Ltd. P'ship, 312 S.C. 102, 439 S.E.2d 283 (Ct. App. 1993).

COMPLAINED OF OCCURRED. EXPRESSED DIFFERENTLY, THE PLAINTIFF MUST PROVE THAT THE UNFAIR TRADE PRACTICE OR ACT HAS AN IMPACT ON THE PUBLIC'S INTEREST. THE PLAINTIFF MUST PROVE THE ADVERSE EFFECT OR IMPACT ON THE PUBLIC INTEREST BY SPECIFIC FACTS.

AN ACTION HAS AN IMPACT ON THE PUBLIC INTEREST IF IT IS SHOWN BY THE PREPONDERANCE OF THE EVIDENCE THAT THE UNFAIR TRADE PRACTICE OR ACT IS CAPABLE OF REPETITION.[13]

SHOWING THAT AN ACT IS CAPABLE OF REPETITION CAN BE SHOWN IN SEVERAL WAYS, BUT IT CAN BE SHOWN IN TWO SPECIFIC WAYS

(1) BY SHOWING THE SAME KIND OF ACTION HAS OCCURRED IN THE PAST, THUS MAKING IT LIKELY THEY WILL CONTINUE TO OCCUR ABSENT DETERRENCE; OR (2) THE COMPANY'S PROCEDURES CREATE A POTENTIAL FOR REPETITION. THESE ARE WAYS TO SHOW THE POTENTIAL FOR REPETITION, BUT NOT THE ONLY WAYS, THAT THE POTENTIAL FOR REPETITION MAY BE SHOWN. IT MAY BE SHOWN BY OTHER MEANS.

Since these two ways are not the only means for showing the potential for repetition or public impact, each case must be evaluated on its own merits to determine what a plaintiff must show to satisfy the potential for the repetition/public impact prong of the UTPA. > Daisy, 322 S.C. at 497, 473 S.E.2d at 51. Nevertheless, a plaintiff has proven an adverse effect on public interests if he proves, by the preponderance of the evidence, and by specific facts, the potential for repetition exists. > Id. at 493, 473 S.E.2d at 49;

640 S.E.2d 486, 372 S.C. 1, Wright v. Craft, (S.C.App. 2006)

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[13] Burbach v. Investors Mgmt. Corp., 326 S.C. 492, 484 S.E.2d 119 (Ct. App. 1997).

---------- Excerpt from page 640 S.E.2d 502

The remedies provided in SCUTPA create a new statutory cause of action and a Plaintiff is not required to prove the elements of the old common law fraud.

UNDER SCUPTA the Plaintiff is not required to prove that anyone actually relied to their detriment or injury on any of the acts or practices of the Defendants in order to have a cause of action under the Unfair Trade Practices Act.

[I]t is in the public interest generally to prevent the use of false and misleading statements in the conduct of business ... and actual deception need not be shown; a finding of a tendency to deceive and mislead will suffice.

And in > Royal Oil Corp. v. F. T. C., 262 F.2d 741 (4th Cir. 1959), the Fourth Circuit Court of Appeals held that the requisite capacity to deceive could be found without evidence that anyone was actually deceived.
294 S.E.2d 781, 278 S.C. 281, State ex rel. McLeod v. Brown, (S.C. 1982)
---------- Excerpt from page 294 S.E.2d 783

WILLFULNESS

SHOULD YOU THE JURY DETERMINE THAT THE ACTIONS OF THE DEFENDANT VIOLATED SECTION 39-5-20, THEN YOU MUST DETERMINE IF THE VIOLATION OF THE DEFENDANT WAS WILLFUL. UNDER SECTION 39-5-110.

I NEED FOR YOU TO ANSWER A QUESTION FOR ME. IN

ORDER FOR ME TO MAKE SOME LEGAL DETERMINATIONS

THAT I MAY HAVE TO MAKE, YOU WILL ALSO BE ASKED TO

TELL ME WHETHER THE PLAINTIFFS HAVE PROVEN THAT ANY OF THE DEFENDANTS ACTED WILLFULLY IN VIOLATING THE ACT [or knowingly violated the statute]. A WILLFUL VIOLATION OCCURS WHEN THE PARTY COMMITTING THE VIOLATION KNEW OR SHOULD HAVE KNOWN THAT THE CONDUCT CONSTITUTED AN UNFAIR OR DECEPTIVE TRADE PRACTICE. IF THE PLAINTIFF DOES RECOVER ON THIS CLAIM, YOU WILL NEED TO TELL ME WHETHER THE PLAINTIFFS HAVE PROVEN THAT THE DEFENDANT WILLFULLY OR KNOWINGLY VIOLATED THE UNFAIR TRADE PRACTICES ACT.

FOR PURPOSES OF SCUPTA.... conduct is willful if the defendant either actually knew or should have known its actions violated § 39-5-20. The standard being not one of actual knowledge, but of constructive knowledge, so if, in the ordinary exercise of due diligence, a person or corporation of ordinary prudence engaged in trade or commerce could have ascertained that his conduct would violate the Unfair Trade Practices Act, then if the act is done such conduct is "willful" within the meaning of the statute. > State ex rel. Medlock v. Nest Egg

Soc. Today, Inc. (S.C.App. 1986) 290 S.C. 124, 348 S.E.2d 381.

APPOINT A FOREMAN

LADIES AND GENTLEMEN, YOUR VERDICT MUST BE A UNANIMOUS ONE. MR./MADAM FOREPERSON, WHEN THE JURY AGREES ON THE VERDICT, YOU WILL WRITE THE VERDICT ON THE VERDICT FORMS THAT I WILL SUPPLY AND THEY WILL BE SIGNED AND DATED BY THE FOREMAN. THEN KNOCK ON THE JURY ROOM DOOR AND INFORM THE BAILIFF THAT YOU HAVE REACHED A VERDICT. AT THAT TIME, WE WILL RECEIVE YOU BACK INTO THE COURTROOM.

I ASK THAT YOU NOW RETURN TO YOUR JURY ROOM BUT DO NOT BEGIN DELIBERATIONS UNTIL YOU ARE TOLD BY THE CLERK OR THE BAILIFF TO DO SO. THERE ARE SOME MATTERS WHICH MUST BE DISCUSSED WITH THE ATTORNEYS BEFORE YOU BEGIN YOUR DELIBERATIONS.

HYATT

hyatt.com

Do we get a Copy of the Law?

RE

DIALING INSTRUCTIONS INSIDE

Court Exhibit 6

Court Exhibit 7

☆ In your general charge, the section highlighted by the jury -

"IN ADDITION, THE PLAINTIFF MUST PRO THAT THE UNFAIR TRADE PRACTICE OR ACT AFFECTED PERSONS OTHER THAN THE PARTIE TO THE TRANSACTION IN WHICH THE ACT COMPLAINED OF OCCURRED." -

- please define "AFFECTED" and "PERSO according to the law in relation to this case.

- what is the "burden of proof" and what "burden of proof" is required?

(☆PLEASE return our copy of your charge!)

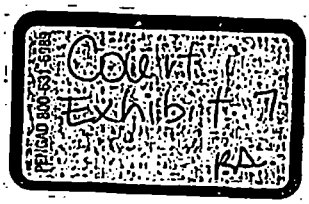

Exhibit P-5, Hard Drive Containing Sales Call Data, is a physical exhibit and was transferred to the Office of the Clerk of the Supreme Court of South Carolina in accordance with the Court's July 26, 2012 Order.

TOLLING AGREEMENT

THIS AGREEMENT is made as of this 16th day of February, 2007, by and between (i) Johnson & Johnson, Inc., Janssen Pharmaceutica, Inc., Janssen, LP and any of their subsidiaries, affiliates or related entities (hereinafter "Johnson & Johnson") and (ii) the State of South Carolina and its agencies, departments, representatives and related entities, (hereinafter "Parties" or "Party") in consideration of the mutual exchange of covenants and promises contained herein.

WHEREAS, South Carolina is investigating allegations regarding the antipsychotic drug Risperdal and believes that it may have some claims against Johnson & Johnson regarding these allegations.

WHEREAS, Johnson & Johnson and South Carolina are engaged in a productive dialogue, and mutually desire to continue to engage in negotiations to resolve any and all matters regarding such allegations.

NOW THEREFORE, in consideration of the mutual covenants contained herein and for other good and valuable consideration, the receipt and sufficiency of which is acknowledged by the Parties hereto and fully intending to be legally bound, IT IS HEREBY AGREED THAT:

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HOPE BLACKLEY

1. The Effective Date of this Tolling Agreement shall be January 24, 2007.

2. The statute of limitations, or any similar limitations period, and any other defense in law or equity relating to the passage of time are tolled from the Effective Date of this Tolling Agreement through and including the earlier of:

(a) three (3) months from the Effective Date of this Tolling Agreement; or

(b) the termination of this Tolling Agreement in writing as described below in paragraph 4.

3. None of the Parties hereto shall file any claim against any other Party hereto related to Risperdal prior to three (3) months from the Effective Date of this Tolling Agreement. However, if this Tolling Agreement is terminated pursuant to the procedures addressed in paragraph 4 below, a Party may file a claim against the other Party within the ten-day period of notice of termination and prior to the termination of this Tolling Agreement.

4. Any Party may terminate this Tolling Agreement. The termination shall be effective ten (10) days after receipt of a written notice of termination addressed to counsel for the other Party. Effective notice of termination shall be sent by certified mail, return receipt requested, fax, or email to the following persons at the addresses set out below:

For Johnson & Johnson:

Steven W. Hamm, Esquire
C. Jo Anne Wessinger Hill, Esquire
Richardson Plowden Carpenter & Robinson, P.A.
P.O. Drawer 7788
Columbia, SC 29202
(803) 771-4400
(803) 779-0016 facsimile
shamm@rpcrlaw.com
jwessingerhill@rpcrlaw.com

For the State of South Carolina:

C. Havird Jones, Jr.
South Carolina Attorney General's Office
P.O. Box 11549
Columbia, South Carolina 29211
(803) 734-3654 (phone)
(803) 734-3677 (fax)

M. HOPE BLACKLEY
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agsjones@ag.state.sc.us

5. Other than as set forth herein, the Parties reserve, and do not waive, any and all defenses and other rights they may have with respect to any claims asserted by the other, including, but not limited to, a defense based on lack of personal jurisdiction, and this Tolling Agreement shall not be asserted or construed to be a waiver of any claims, rights, or defenses of any Party as against the other Party.

6. Nothing in this Tolling Agreement shall constitute or be construed as an admission by any Party as to the applicability, running, expiration, or non-expiration of any statute of limitations or similar rule of law or equity prior to the Effective Date. This Tolling Agreement shall not be admissible in evidence for any purpose other than obtaining its enforcement.

7. Nothing in this Tolling Agreement shall have the effect of reviving any claims that are otherwise barred by any statute of limitations or similar rule of law or equity prior to the Effective Date. Moreover, this Tolling Agreement shall not operate to create any claims (except those necessary to enforce this Tolling Agreement) among the signatories to this Tolling Agreement.

8. This Tolling Agreement is not, and shall not be asserted or construed to be, an admission or indication that Johnson & Johnson bears any actual or potential liability on any claims.

9. This Tolling Agreement constitutes the entire and integrated Agreement of the Parties. No waiver, modification, extension, or addition to this Tolling Agreement shall be valid unless in writing and signed by each Party hereto.

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10. The construction and effect of this Tolling Agreement shall be governed by the laws of South Carolina without regard to conflict of laws principles.

11. This Tolling Agreement may be executed by facsimile and in two or more counterparts, each of which shall be deemed an original and all of which together shall constitute one and the same instrument.

12. A facsimile signature shall be deemed an original signature for the purpose of this Tolling Agreement.

13. The signatories to this Tolling Agreement represent and warrant that they have the authorization and power to bind the Parties on whose behalf they are executing this Tolling Agreement, and that this Tolling Agreement constitutes a legal, binding obligation of the Party, enforceable in accordance with its terms.

FOR JOHNSON & JOHNSON:

Dated: February 16, 2007

By: _____

Steven W. Hamm, Esquire
C. Jo Anne Wessinger Hill, Esquire
RICHARDSON PLOWDEN CARPENTER
& ROBINSON, P.A.
P.O. Drawer 7788
Columbia, SC 29202
(803) 771-4400
(803) 779-0016 facsimile
shamm@rpcrlaw.com
jwessingerhill@rpcrlaw.com

M. HOPE BLACKLEY
2011 MAR 21 PM 3:36

FOR THE STATE OF SOUTH CAROLINA:

Dated: February 20, 2007

By: _____

C. Havird Jones, Jr.
Senior Assistant Attorney General

South Carolina Attorney General's Office
PO Box 11549
Columbia, South Carolina 29211
(803) 734-3654 (phone)
(803) 734-3677 (fax)
agsjones@ag.state.sc.us

FILED
CLERK OF COURT
SPARTANBURG COUNTY
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M. HOPE BLACKLEY

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF SOUTH CAROLINA
SPARTANBURG DIVISION

STATE OF SOUTH CAROLINA ex rel. Henry McMaster, in his capacity as Attorney General of the State of South Carolina, Plaintiff, v. JANSSEN PHARMACEUTICA, INC., JANSSEN, LP and JOHNSON & JOHNSON, INC., Defendants.	No. _____ (Spartanburg C/A No. 2007-CP-42-1438)

NOTICE OF REMOVAL

TO: THE HONORABLE JUDGES OF THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF SOUTH CAROLINA

PLEASE TAKE NOTICE that defendants, Janssen Pharmaceutica Inc., Janssen, L.P., and Johnson & Johnson (collectively "defendants" or "Janssen"),[1] hereby remove this case from the Court of Common Pleas for the Seventh Judicial Circuit in the County of Spartanburg to the United States District Court for the District of South Carolina, Spartanburg Division, pursuant to 28 U.S.C. §§ 1331, 1441(a), (b), and (c), and 1446(a) and (b). The United States District Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. § 1331 and the principles set forth in *Grable & Sons Metal Products, Inc. v. Darue Engineering & Manufacturing*, 545 U.S. 308 (2005). As discussed below, this case raises important federal questions about the funding and reimbursement provisions of federal Medicaid law, the complex federal law regulating

[1] Defendants are improperly identified in the caption.

pre-market testing, warning, labeling, and marketing of prescription drugs, and the interactions of the two federal statutory and regulatory schemes.

All prerequisites to removal have been satisfied. Accordingly, defendants hereby remove this case to federal court and state as follows:

I. BACKGROUND

1. Plaintiff, the State of South Carolina ("the State" or "plaintiff"), by and through its Attorney General, commenced this action on April 23, 2007 by filing a Complaint in the Court of Common Pleas for the Seventh Judicial Circuit in the County of Spartanburg (No. 2007-CP-42-1438). A copy of the Complaint is attached to this notice as Exhibit A. Defendants accepted service of the Complaint on April 25, 2007.

2. This action involves allegations about the U.S. Food and Drug Administration ("FDA")-approved medicine Risperdal® and the State's obligation under federal Medicaid law, 42 U.S.C. § 1396, *et seq.*, to reimburse for prescriptions of Risperdal. Risperdal is an "atypical antipsychotic" prescription drug. Cases involving substantially similar claims against other manufacturers of atypical antipsychotics are pending before the Honorable Jack B. Weinstein in the United States District Court for the Eastern District of New York, *In re Zyprexa Products Liability Litigation*, MDL No. 1596 (Eli Lilly & Co.), and before the Honorable Anne C. Conway in the United States District Court for the Middle District of Florida, *In re Seroquel Products Liability Litigation*, MDL No. 1769 (AstraZeneca Pharmaceuticals, L.P.).[2]

[2] Another case involving nearly identical claims against Janssen, Lilly, and AstraZeneca was removed from the Philadelphia Court of Common Pleas to the United States District Court for the Eastern District of Pennsylvania. *Commonwealth of Pennsylvania v. Eli Lilly & Company, Inc., et al.*, No. 2:07-cv-01083. A remand motion has been filed.

3. In its Complaint, plaintiff alleges that defendants caused Risperdal to be prescribed by doctors to Medicaid recipients for indications that were not "medically accepted" and for uses that were not "medically necessary"– terms used in the Medicaid statute and given their meaning by federal law – and seeks to collect damages for reimbursements for those prescriptions on the ground, *inter alia*, that federal law did not mandate those reimbursements. The resolution of those claims turns on a determination of the nature and extent of plaintiff's obligations, under the federal Medicaid law and implementing regulations, to reimburse for prescriptions for Risperdal. The resolution of those and other claims also requires a determination of whether defendants' sales and marketing practices, which allegedly prompted the prescriptions, violated the Federal Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. § 301, *et seq.* and its implementing regulations.

4. According to plaintiff's Complaint, defendants' alleged conduct (1) resulted in the submission of false and fraudulent claims under the State's Medicaid program (Compl. ¶¶ 86-99); (2) resulted in physical injury to patients participating in the State's Medicaid program, for which plaintiff covered the costs of treatment (Compl. ¶¶ 100-110); (3) violated South Carolina's Unfair Trade Practices Act (Compl. ¶¶ 111-123); (4) constituted negligence (Compl. ¶¶ 124-134); (5) breached express and implied warranties (Compl. ¶¶ 135-141); (6) constituted common-law fraud and misrepresentation (Compl. ¶¶ 142-155); and (7) resulted in unjust enrichment (Compl. ¶¶ 156-162). Plaintiff seeks compensatory, punitive, and statutory damages.

II. FEDERAL QUESTION JURISDICTION

5. This Court has jurisdiction pursuant to 28 U.S.C. § 1331 and the principles set forth in *Grable & Sons Metal Products, Inc. v. Darue Engineering & Manufacturing*, 545 U.S. 308 (2005).

6. Under *Grable*, a complaint that asserts only state law causes of action is removable if it raises a federal question, "actually disputed and substantial, which a federal forum may entertain without disturbing any congressionally approved balance of federal and state judicial responsibilities." *Id.* at 315. The Supreme Court made clear in *Grable* that federal question jurisdiction does not require a plaintiff to assert a violation of a federal statute that provides a private right of action. *See id.* at 316-19 (limiting the holding of *Merrell Dow Pharmaceuticals v. Thompson*, 478 U.S. 804 (1986), to the extent that it implied that a federal cause of action was required to remove a pharmaceutical products liability case).

7. Plaintiff's claims raise disputes about and require construction and application of two federal laws: (1) federal Medicaid law, which determines the drugs a State Medicaid program must cover and the limited circumstances in which a State may decline to pay for such drugs, *see* 42 U.S.C. §§ 1396r-8(d)(1)(B), (d)(4); and (2) the FDCA, 21 U.S.C. § 301, *et seq.*, and its implementing regulations, which govern approval of prescription drugs and regulate manufacturers' public and promotional statements and all aspects of warning and labeling.

8. In *In re Zyprexa Products Liability Litigation*, 375 F. Supp. 2d 170 (E.D.N.Y. 2005), the United States District Court for the Eastern District of New York found that there was federal question jurisdiction over indistinguishable state-law claims involving

another manufacturer's marketing of an antipsychotic prescription drug and the State of Louisiana's reimbursements for that drug pursuant to Medicaid. Judge Weinstein held that the involvement in the case of "substantial federal funding provisions" under Medicaid "and the allegations about the violation of federal law through improper off-label use" together "present[ed] a core of substantial issues" that were federally-oriented and therefore established federal jurisdiction. *Id.* at 172-73. In *West Virginia v. Eli Lilly & Co.*, 476 F. Supp. 2d 230, 237 (E.D.N.Y. 2007), Judge Weinstein held that claims for damages arising from payments for drugs made as part of a state's participation in the federal Medicaid program require "[r]esolution of the question of the state's obligation [under federal law] to reimburse its insureds . . ., using funds largely provided by the federal government" and thus present a substantial federal issue properly before a federal court.[3]

9. Plaintiff's claims here, like those in *Grable*, *In re Zyprexa*, and *West Virginia*, require resolution of substantial federal questions. This Court, therefore, has federal question jurisdiction over them.

A. Alleged Violations of Federal Medicaid Law

10. The federal Medicaid law authorizes federal grants to states to provide medical assistance to low income residents. 42 U.S.C. § 1396, *et seq.* When the state chooses to participate in the federal program, the state's Medicaid program must comply with federal Medicaid law and regulations. *See Wilder v. Virginia Hosp. Ass'n*, 496 U.S. 498, 502 (1990).

[3] Courts that have reached different conclusions have provided no analysis of the federal questions presented to them. *See Alaska v. Eli Lilly & Co.*, No. 03-88, 2006 U.S. Dist. LEXIS 52783, at *4 (D. Alaska July 28, 2006); *Charles Foti ex rel. Louisiana v. Janssen Pharms. Inc., et al.*, Order of June 21, 2005 (W.D. La. No. 04-cv-2575, doc. No. 51).

11. With certain narrow exceptions, the federal Medicaid law requires participating states to reimburse for FDA-approved prescription drugs of any manufacturer that has entered into and complies with a rebate agreement with the Secretary of Health and Human Services. *See* 42 U.S.C. § 1396r-8(d)(4)(B).

12. Federal Medicaid law allows a participating state to deny reimbursement if the prescribed use is not a "medically accepted indication," a term that is defined by federal law. 42 U.S.C. § 1396r-8(k)(6)) (citing 21 U.S.C. § 301); *see* Compl. ¶ 19 ("The Federal Medicaid Act provides for reimbursement for 'medically accepted indications' only."). Federal Medicaid law also allows a participating state to deny reimbursement if a drug subject to a rebate agreement has been excluded from the state's formulary. A drug may be excluded from the formulary "with respect to the treatment of a specific disease or condition for an identified population (if any) *only if*, based on the drug's labeling (or, in the case of a drug the prescribed use of which is not approved under the Federal Food, Drug, and Cosmetic Act [21 U.S.C.A. 301 et seq.] but is a medically accepted indication, based on information from the appropriate compendia described in subsection (k)(6) of this section), the excluded drug does not have a significant clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome of such treatment for such population over other drugs included in the formulary and there is a written explanation (available to the public) of the basis for exclusion." 42 U.S.C. § 1396r-8(d)(4)(C) (emphasis supplied).

13. Plaintiff's claims require proof that federal law permitted plaintiff to spend less to reimburse for prescriptions for Risperdal and proof that, but for defendants' alleged misrepresentations, plaintiff would in fact have spent less.

14. The Complaint presents substantial federal questions because plaintiff's right to relief depends upon the interpretation and application of federal statutory provisions governing what state Medicaid programs may include or reject for reimbursement, including what indications are "medically accepted indications" and what uses are "medically necessary" uses.[4] Count I challenges the "compensation . . . to which [defendants] are legally entitled" through Medicaid reimbursements and alleges that defendants caused prescriptions for "non-medically accepted indications and non-medically necessary uses of Risperdal" to be submitted for payment. (Compl. ¶ 90.) Count II alleges that defendants caused prescriptions to be submitted for uses that were "medically unnecessary." (Compl. ¶ 99.) Counts I and II both seek "reimbursement of all funds" expended in purchasing Risperdal for "non-medically accepted indications" and for "non-medically necessary" or "medically unnecessary" uses. (Compl. ¶¶ 91, 98, 99.) Defendants dispute the allegations, and specifically dispute the interpretation proposed by the Complaint of the terms "medically accepted indication" and "medically necessary."

B. Alleged Violations of the FDCA and Its Implementing Regulations

15. Plaintiff premises its claims and theories of liability on alleged violations of the FDCA by defendants. Central to the Complaint are allegations that defendants marketed Risperdal for uses that were not "medically accepted" or "medically necessary" as those terms are used in 42 U.S.C. § 1396r-8(k)(6) and § 1396r-8(g)(1)(A)(ii), thereby causing harm to plaintiff. Such a promotion for non-FDA approved uses would be "a

[4] (*See, e.g.*, Compl. ¶¶ 19-21.) Like "medically accepted indication," "medically necessary" is a term whose meaning is determined by federal law. *See* 42 U.S.C. § 1396r-8(g)(1)(A)(ii).

promotion that violates the [FDA's] strictures on off-label marketing." *United States ex rel. Franklin v. Parke-Davis, Div. of Warner-Lambert Co.*, Civ. A. No. 96-11651, 2003 WL 22048255, at *2 (D. Mass. Aug. 22, 2003). Defendants dispute that they violated the FDCA by marketing Risperdal for indications that are not medically accepted or uses that are not medically necessary.

16. The FDA's responsibility to regulate prescription drugs sold in the United States, such as Risperdal, and to enforce laws with respect to such drugs, is plenary and exclusive. *See* 21 U.S.C. § 301, *et seq.* This responsibility includes regulation of the precise content and format of prescription drug labeling, instructions, warnings, precautions, and marketing materials. *See id.* The FDA has announced that its approval of product labeling preempts most state law claims related to the adequacy of prescription drug warnings because such claims frustrate "the full objectives of the Federal law." *See* Requirements on Content and Format of Labeling for Human Prescription Drug and Biologic Products, 71 Fed. Reg. 3922, 3934, 3935 (Jan. 24, 2006).

17. The FDCA requires the FDA to ensure that "drugs are safe and effective" for their intended uses, 21 U.S.C. § 393(b)(2)(B), in part by "promptly and officially reviewing clinical research and taking appropriate action on the marketing of regulated products," 21 U.S.C. § 393(b)(1). The FDCA authorizes the Secretary of the Department of Health and Human Services (the FDA is an agency within that Department) to implement and enforce the statute by promulgating regulations, 21 U.S.C. § 371(a), which are codified in the *Code of Federal Regulations*, 21 C.F.R. § 200, *et seq.*

18. To accomplish its purpose, the FDA maintains a Center for Drug Evaluation and Research (the "CDER"), which evaluates and monitors the effectiveness and safety

of prescription drugs. *See* http://www.fda.gov/cder/about/faq/default.htm. The CDER regulates pharmaceutical companies' development, testing and research, and manufacture of drugs. The CDER examines data generated by these companies to conduct a risk/benefit analysis and make an approval decision. The CDER also ensures truthful advertising for prescription drugs, in part by approving Package Inserts that properly outline benefit and risk information. Once prescription drugs are marketed, the CDER continues to monitor them for unexpected health risks that may require public notification, a change in labeling, or removal of the product from the market.

19. Promotional communications to physicians about Risperdal are contained within and restricted by warning, labeling, and promotional materials, such as the Package Insert, that are approved and monitored by the FDA to ensure the provision of accurate information about the drug's risks and benefits. Under federal regulations, claims in promotional materials or advertising must be consistent with approved labeling. 21 C.F.R. § 202.1(e)(4)(2005).

20. The Complaint presents substantial federal questions regarding whether defendants marketed Risperdal for uses other than "medically accepted indications" and whether they violated the FDCA by allegedly marketing Risperdal for non-approved uses. Additionally, the Complaint raises the substantial federal question whether the FDA would have allowed defendants to re-write the FDA-approved label for Risperdal to include the warnings that plaintiff deems "adequate" or "sufficient" regarding alleged risks. (*E.g.*, Compl. ¶¶ 37, 104.)

C. Federal Interest in Providing a Federal Forum

21. The federal government has a strong interest in having a federal court decide several important issues in this case, including whether federal Medicaid law required the State to reimburse for Risperdal for certain uses, whether defendants' alleged marketing of Risperdal for "non-medically necessary" or "non-medically accepted" uses violated federal law related to the labeling and marketing of the drug, whether the FDA-approved labels for Risperdal were false and misleading, and whether a state may impose liability on Janssen for not providing more information about alleged risks.

22. Plaintiff's claims rise or fall on the construction of federal Medicaid law, the FDCA, and federal regulations. The federal interest in uniform interpretation of the "intricate federal regulatory scheme including detailed" and substantial "federal funding provisions" is clear. *West Virginia*, 2007 WL 685587 at *4. The availability of a federal forum to protect the important federal interests at issue in this case is consistent with *Grable*. *See Grable*, 545 U.S. at 315.

III. PROPRIETY OF REMOVAL

23. For all of the foregoing reasons, this Court has jurisdiction over this matter.

24. All defendants consent to and have joined in this Notice of Removal.

25. Venue is proper in this Court pursuant to 28 U.S.C. § 121(10) because this is the "district and division embracing the place where such action is pending." *See* 28 U.S.C. § 1441(a).

26. This Notice is being filed within 30 days after service of the Complaint, the initial pleading setting forth the plaintiff's claim for relief, and is timely filed pursuant to 28 U.S.C. § 1446(b).

27. All process, pleadings and orders in the state-court action are attached to this Notice as Exhibit A, as required by 28 U.S.C. § 1446(a).

28. Defendants will promptly file a true and correct copy of this Notice with the Clerk of the Court of Common Pleas for the Seventh Judicial Circuit, in accordance with 28 U.S.C. § 1446(d), and serve plaintiff's counsel with a true and correct copy of this Notice of Removal, in accordance with 28 U.S.C. § 1446(d).

WHEREFORE, defendants notice the removal of this case to the United States District Court for the District of South Carolina, Spartanburg Division, pursuant to 28 U.S.C. §§ 1331 and 1441, *et seq.*

Respectfully submitted,

Dated: May 22, 2007.

s/ Steven W. Hamm
Steven W. Hamm [Federal I.D. No. 1692]
C. Jo Anne Wessinger Hill [Federal I.D. No. 7198]
RICHARDSON, PLOWDEN,
CARPENTER & ROBINSON, P.A.
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Columbia, SC 29201
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Attorneys for Defendants Janssen Pharmaceutica Inc., Janssen, L.P., and Johnson & Johnson

STATE OF SOUTH CAROLINA	)	**IN THE COURT OF COMMON PLEAS**
COUNTY OF SPARTANBURG	)	**FOR THE SEVENTH JUDICAL CIRCUIT**
STATE OF SOUTH CAROLINA ex rel. Henry McMaster, in his capacity as Attorney General of the State of South Carolina,	)	**CIVIL ACTION COVERSHEET**
Plaintiff(s)	)	
vs.	)	____ - CP - ____ - ____
JANSSEN PHARMACEUTICA, INC., JANSSEN, LP and JOHNSON & JOHNSON, INC.,	)	**2007-CP-42-1438**
Defendant(s)	)	

(Please Print) John S. Simmons	**SC Bar #:**	
Submitted By: Simmons Law Firm, LLC	**Telephone #:**	803-779-4600
Address: 1711 Pickens Street, PO Box 5	**Fax #:**	803-254-8874
Columbia, SC 29202	**Other:**	
	E-mail:	

NOTE: The cover sheet and information contained herein neither replaces nor supplements the filing and service of pleadings or other papers as required by law. This form is required for the use of the Clerk of Court for the purpose of docketing. It must be filled out completely, signed, and dated. A copy of this cover sheet must be served on the defendant(s) along with the Summons and Complaint.

FILED
CLERK OF COURT
SPARTANBURG COUNTY
2007 APR 23 AM 11:30
MARC HITCHENS

DOCKETING INFORMATION (*Check all that apply*)

If Action is Judgment/Settlement do not complete

- ☒ **JURY TRIAL** demanded in complaint. ☐ **NON-JURY TRIAL** demanded in complaint.
- ☐ This case is subject to **ARBITRATION** pursuant to the Circuit Court Alternative Dispute Resolution Rules.
- ☐ This case is subject to **MEDIATION** pursuant to the Circuit Court Alternative Dispute Resolution Rules.
- ☐ This case is exempt from ADR (certificate attached).

NATURE OF ACTION (*Check One Box Below*)

Contracts
- ☐ Constructions (100)
- ☐ Debt Collection (110)
- ☐ Employment (120)
- ☐ General (130)
- ☐ Breach of Contract (140)
- ☐ Other (199)

Torts - Professional Malpractice
- ☐ Dental Malpractice (200)
- ☐ Legal Malpractice (210)
- ☐ Medical Malpractice (220)
- ☐ Other (299)

Torts – Personal Injury
- ☐ Assault/Slander/Libel (300)
- ☐ Conversion (310)
- ☐ Motor Vehicle Accident (320)
- ☐ Premises Liability (330)
- ☐ Products Liability (340)
- ☐ Personal Injury (350)
- ☐ Other (399)

Real Property
- ☐ Claim & Delivery (400)
- ☐ Condemnation (410)
- ☐ Foreclosure (420)
- ☐ Mechanic's Lien (430)
- ☐ Partition (440)
- ☐ Possession (450)
- ☐ Building Code Violation (460)
- ☐ Other (499)

Inmate Petitions
- ☐ PCR (500)
- ☐ Sexual Predator (510)
- ☐ Mandamus (520)
- ☐ Habeas Corpus (530)
- ☐ Other (599)

Judgments/Settlements
- ☐ Death Settlement (700)
- ☐ Foreign Judgment (710)
- ☐ Magistrate's Judgment (720)
- ☐ Minor Settlement (730)
- ☐ Transcript Judgment (740)
- ☐ Lis Pendens (750)
- ☐ Other (799)

Administrative Law/Relief
- ☐ Reinstate Driver's License (800)
- ☐ Judicial Review (810)
- ☐ Relief (820)
- ☐ Permanent Injunction (830)
- ☐ Forfeiture (840)
- ☐ Other (899)

Appeals
- ☐ Arbitration (900)
- ☐ Magistrate-Civil (910)
- ☐ Magistrate-Criminal (920)
- ☐ Municipal (930)
- ☐ Probate Court (940)
- ☐ SCDOT (950)
- ☐ Worker's Comp (960)
- ☐ Zoning Board (970)
- ☐ Administrative Law Judge (980)
- ☐ Public Service Commission (990)
- ☐ Employment Security Comm (991)
- ☐ Other (999)

Special/Complex /Other
- ☐ Environmental (600)
- ☐ Automobile Arb. (610)
- ☐ Medical (620)
- ☒ Pharmaceuticals (630)
- ☐ Unfair Trade Practices (640)
- ☐ Other (699)

Submitting Party Signature: _____ **Date:** April 20, 2007

Note: Frivolous civil proceedings may be subject to sanctions pursuant to SCRCP, Rule 11, and the South Carolina Frivolous Civil Proceedings Sanctions Act, S.C. Code Ann. §15-36-10 et. seq.

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,	2007-CP-42-1438
PLAINTIFF,	Case No.: _____
v.	
JANSSEN PHARMACEUTICA, INC., JANSSEN, LP and JOHNSON & JOHNSON, INC.	
DEFENDANTS.	

FILED
CLERK OF COURT
SPARTANBURG COUNTY
2007 APR 23 AM 11:39
MARC KITCHENS

SUMMONS

YOU ARE HEREBY SUMMONED and required to answer the Complaint in this action, a copy of which is herewith served upon you, and to serve a copy of your Answer to said Complaint on the subscriber at their offices, 1711 Pickens Street, Post Office Box Five, Columbia, South Carolina, 29202, within thirty (30) days after the service hereof, exclusive of the date of service; and if you fail to answer the Complaint within time aforesaid, judgment by default will be rendered against you for the relief demanded in the Complaint.

SIMMONS LAW FIRM, L.L.C.

April 20, 2007

By: _____

John S. Simmons
State Bar No. 10260
1711 Pickens Street
Columbia, South Carolina 29202
(803) 779-4600 Telephone
(803) 254-8874 Fax
jsimmons@simmonslawfirm.com

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,

v.

JANSSEN PHARMACEUTICA, INC., JANSSEN, LP and JOHNSON & JOHNSON, INC.

DEFENDANTS.

2007-CP-42-1438

Case No.: _____

FILED
CLERK OF COURT
SPARTANBURG COUNTY
2007 APR 23 AM 11:30
MARC KITCHENS

CIVIL ACTION COMPLAINT

The State of South Carolina, Plaintiff herein, by and through its Attorney General ("the State"), according to law and equity, and as *parens patriae*, brings this action on behalf of the State Medicaid program, the South Carolina Department of Mental Health ("SCDMH") and the South Carolina State Employees Health Plan ("SHP") as injured purchasers and/or reimbursers of prescription drugs. Under the South Carolina Constitution and other positive law of the State, including South Carolina's common law and including, among other laws, S.C. CODE ANN. §§43-7-20, *et seq.*, 39-5-10, *et seq.*, and 1-7-10, *et seq.*, the State is responsible for, and has a duty to protect, the health, safety and welfare of its citizens. The State is further entitled to bring these actions pursuant to 42 U.S.C. §1396, *et seq.*, also known as the Social Security Act, Chapter 7, subchapter XIX, entitled Grants to States for Medical Assistance Programs. The State seeks to obtain compensatory, punitive and other damages, restitution, civil penalties, injunctive and other equitable relief against Defendants Janssen Pharmaceutica, Inc., Janssen, LP and

Johnson & Johnson, Inc. ("Defendants"), as more fully set forth below and, in support thereof, avers as follows:

PARTIES

1. The plaintiff is the State of South Carolina, with this suit being brought by its Attorney General, Henry McMaster, in the State's capacity as sovereign, in its proprietary capacity, and in a *parens patriae* capacity on behalf of the Department of Health & Human Services, SCDMH and the SHP.

2. The Attorney General is statutorily authorized to initiate and maintain this action, and does so, pursuant to S.C. CODE ANN. §1-7-40, the South Carolina Unfair Trade Practices Act, S.C. CODE ANN. §39-5-50 and S.C. CODE ANN. §43-7-60(E), 90. This action is also maintained pursuant to the Attorney General's common law *parens patriae* powers.

3. Defendant Janssen Pharmaceutica, Inc. ("JPI") is a Pennsylvania corporation. JPI can be served by serving its president, Marvin Woodall at 500 Iolab Dr., Claremont, Pennsylvania 91711. Janssen Pharmaceutica, Inc. is the general partner of Janssen, LP ("JLP"). JLP is a New Jersey Limited Partnership which can be served at its principal place of business at 1125 Trenton-Harbourton Road, Titusville, New Jersey 08560. Johnson & Johnson, Inc. is a New Jersey Corporation which can be served at its principal place of business at One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933. Johnson & Johnson, Inc. is the parent company of both JPI and JLP and is responsible as respondent superior for the actions of its subsidiaries (all defendants referred to collectively herein as "Defendants").

4. The acts alleged to have been done by Defendants herein were authorized, ordered done and/or ratified by Defendants' officers, directors, agents, employees or

representatives while engaged in the management, direction, control or transaction of Defendants' business affairs.

JURISDICTION & VENUE

5. The jurisdiction of this Court is founded upon S.C. CONST. ANN. ART. V. §11 which gives the Circuit Court general jurisdiction over civil actions.

6. This Court has personal jurisdiction over Defendants because Defendants do business in South Carolina and/or have the requisite minimum contacts with South Carolina necessary to constitutionally permit the Court to exercise jurisdiction with such jurisdiction also being within the contemplation of the South Carolina "long arm" statute (S.C. CODE ANN. §36-2-803).

7. Defendants did, individually or in conjunction with others, research, develop manufacture, create, design, test, label, sterilize, package, distribute, supply, market, sell, promote, advertise, warn and otherwise distribute Risperidone ("Risperdal") in South Carolina and specifically in Spartanburg County.

8. Venue in this Court is proper pursuant to the Rules of the South Carolina Supreme Court and the South Carolina Code.

INTRODUCTION

9. This is an action to recover funds expended by the State in providing medical treatment to Medicaid, SCDMH and SHP participants suffering from Risperdal-related illnesses and to recover funds expended in purchasing Risperdal for uses not covered by the State's Medicaid, SCDMH and SHP programs. Many of the details and critical facts related to Defendants' scheme are exclusively known by Defendants.

10. The State seeks reimbursement of funds expended by South Carolina pursuant to the Medicaid program created by Title XIX of the United States Social Security Act, the SCDMH and its State Employees Health Plan ("SHP"). The State is required by 42 U.S.C. §1396a(a)(25)(A),(B) to take all reasonable measures to ascertain the legal liability of third parties to pay for care and services available under the Medicaid Act, and to seek reimbursement to the public fund to the extent of such legal liability.

11. The State seeks to recover damages to its SHP. The SHP is a State-sponsored program that administers prescription drug benefits for the State's SHP participants. The South Carolina Budget and Control Board oversees the SHP, which currently covers approximately 350,000 individuals. The SHP reimburses pharmacies, doctors and hospitals for prescriptions written for and dispensed to SHP participants.

12. The State seeks to recover damages to the SCDMH. The SCDMH is a State-sponsored program that purchases Risperdal for the State's mental hospitals, clinics and centers, joint State and community sponsored mental health clinics and centers and facilities for the treatment and care of alcohol and drug addicts. The SCDMH is a direct purchaser of Risperdal for patients under its care.

13. The State has discovered that Defendants have engaged in a protracted and willful course of corporate misconduct and misrepresentation in violating numerous State laws, and in actionable breach of the duties owed to the State and its citizens. Defendants have concealed their wrongdoing from the State.

14. The State brings this action exclusively under the common law and statutes of the State of South Carolina. No federal claims are being asserted and to the extent that any claim or

factual assertion set forth herein may be construed to have stated any claim under federal law, such claim is expressly and undeniably disavowed and disclaimed by the State.

15. The claims asserted herein are brought solely by the State, and result from the damages incurred by the State itself and are wholly independent of any claims that individual users of Risperdal may have against Defendants.

16. Defendants manufacture Risperdal and promote the drug to physicians in South Carolina through their representatives. For years, the State has incurred significant expenses associated with the provision of necessary health care and other assistance necessary under its Medicaid, SCDMH and SHP programs to citizens who suffer, or who have suffered, from Risperdal-related injuries, diseases or sickness.

APPLICABLE STATUTORY FRAMEWORK

17. The State participates in the Medicaid program to promote the general welfare of its citizens and meet the specific objective that adequate and high quality health care is available to those South Carolina citizens who cannot afford it.

18. The Medicaid program includes individualized provisions, by statute and regulation, concerning reimbursement for prescription drugs, drug utilization review, eligibility of various drugs for full federal participation ("FFP"), price controls on prescription drugs, and drug manufacturer rebate agreements. Medicaid is also a direct payer of medically necessary inpatient and outpatient treatment for its participants.

19. The Federal Medicaid Act provides for reimbursement for "medically accepted indications" only. 42 U.S.C. §1396r-8(k)(6). The term medically accepted is defined as "any use for a covered outpatient drug which is approved under the Federal Food, Drug, and Cosmetic Act, or the use of which is supported by one or more citations included or approved for inclusion

in" American Hospital Formulary Service Drug Information, United States Pharmacopeia-Drug Information and the DRUGDEX Information System. 42 U.S.C. §1396r-8(g)(1)(B)(i)(I)-(III), (k)(6).

20. Under the Medicaid system, whether the use of a drug is medically accepted and medically necessary is material to the State's decision to reimburse for the prescription. The State does not intend to reimburse providers for drugs whose uses are not medically accepted, medically unnecessary or are likely to result in adverse medical outcomes.

21. Defendants are deemed to be on notice of Medicaid regulations regarding the scope of prescription drug reimbursement. Defendants have a duty to prevent non-medically accepted and non-medically necessary prescriptions for Risperdal from being submitted to Medicaid for reimbursement. Upon information and belief, Defendants breached this duty by knowingly causing prescriptions for non-medically accepted indications and non-medically necessary uses of Risperdal to be submitted to Medicaid for reimbursement.

22. S.C. CODE ANN. §43-7-60 provides as follows:

> (B) It is unlawful for a provider of medical assistance, goods, or services to knowingly and willfully make or cause to be made a false claim, statement, or representation of a material fact: (1) in an application or request, including an electronic or computer generated claim, for a benefit, payment, or reimbursement from a state...agency which administers or assists in the administration of the state's medical assistance or Medicaid program; or (2) on a report, certificate, or similar document, including an electronic or computer generated claim, submitted to a state...agency which administers or assists in the administration of the state's Medicaid program in order for a provider or facility to qualify or remain qualified under the state's Medicaid program to provide assistance, goods, or services, or receive reimbursement, payment, or benefit for this assistance, goods or services.
>
> (C) It is unlawful for a provider of medical assistance, goods, or services knowingly and willfully to conceal or fail to disclose any material fact, event, or transaction which affects the:

a. Provider's initial or continued entitlement to payment, reimbursement, or benefits under the state's Medicaid plan; or

b. Amount of payment, reimbursement, or benefit to which the provider may be entitled for services, goods, or assistance rendered.

For purposes of this subsection, each fact, event, or transaction concealed or not disclosed constitutes a separate offense.

(E) In addition to all other remedies provided by law, the Attorney General may bring an action to recover damages equal to three times the amount of an overstatement or overpayment and the court may impose a civil penalty of two thousand dollars for each false claim, representation, or overstatement made to a state...agency which administers funds under the state's Medicaid program.

23. As persons receiving payment, reimbursement and/or benefit for services, goods or assistance rendered under the State's public assistance program, Defendants are providers within the meaning of S.C. CODE ANN. §43-7-60(A)(1). According to the South Carolina legislature, the purpose of Medicaid Fraud Act is to preserve the integrity of the Medicaid Program by providing a statutory deterrent to any person causing the submission of inappropriate claims to the Program.

24. The State of South Carolina, as is true of many states, lacks a practical means of ensuring that each prescription for every drug constitutes a medically necessary use of that drug. The State thus relies on persons receiving payment and benefits to turn square corners in their dealings with the Medicaid, SCDMH and SHP Programs. Nevertheless, this lack of practical ability represents a loophole in the scheme of the Medicaid, SCDMH and SHP Programs.

25. Defendants have recognized and aggressively exploited this loophole in two ways. First Defendants have engaged in a direct, illegal, nationwide program of promotion of the use of Risperdal for non-medically accepted indications and non-medically necessary uses. Defendants have conducted this program of promotion knowing that prescriptions for Risperdal are generally reimbursed by the State Medicaid, SCDMH and SHP programs even though

prescriptions for non-medically accepted indications and non-medically necessary uses of Risperdal fall outside the coverage of state programs.

26. Second, since the inception of their promotion of Risperdal, Defendants have falsely represented to the State, and to the public in general, that Risperdal is safer and more effective than less expensive, first generation antipsychotics.

27. Finally, Defendants' failure to provide an adequate warning of the risks of using Risperdal has compromised the general health and welfare of South Carolina citizens. The State, in its common law duty to act as *parens patriae*, thus has standing to recover its necessary costs of treatment of South Carolina citizens resulting from Risperdal-related injuries for which Defendants are liable.

RISPERDAL'S MEDICALLY ACCEPTED INDICATIONS

28. Risperdal is a prescription antipsychotic drug belonging to the atypical antipsychotic class. Defendants obtained approval from the U.S. Food and Drug Administration (hereinafter the "FDA") to market Risperdal oral tablets for the management of manifestations of psychotic disorders in adults on December 29, 1993. On June 10, 1996, the FDA approved Risperdal oral solution for the management of manifestations of psychotic disorders in adults. On March 3, 2002, both indications above were changed by the FDA to "treatment of schizophrenia" in adults. On April 2, 2003, the FDA approved Risperdal M-Tab for the treatment of adults with schizophrenia. On October 29, 2003, the FDA approved Risperdal Consta for the treatment of schizophrenia in adults. On December 4, 2003, the FDA approved Risperdal oral tablets, Risperdal oral solution and Risperdal M-Tab as monotherapy for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder, and as

combination therapy, with lithium or valproate, for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

29. The United States Pharmacopeia-Drug Information and the DRUGDEX Information System support the use of Risperdal for the indications approved by the FDA. The American Hospital Formulary Service Drug Information ("AHFS") supports the use of Risperdal for the indications approved by the FDA and, in 2003, initiated support for the use of Risperdal to treat behavioral problems in children 5-17 years old with autistic disorder. The AHFS noted that it did not support the use of Risperdal to treat the core symptoms of autism, but only manifestations of moderate to severe behavioral problems associated with autistic disorder. Prior to 2003, the compendia supported only the uses of Risperdal approved by the FDA. The uses supported by these three Compendia and the FDA-approved labeling are collectively defined as "Medically Accepted Indications" in the Federal Medicaid Act, 42 U.S.C.A. §1396r-8.

30. Neither the Compendia cited above nor the FDA-approved labeling support any use of Risperdal by children or adults with depression, anxiety, ADD, ADHD, sleep disorders, anger management, mood enhancement or mood stabilization.

31. Schizophrenia is one of the most complex and challenging of psychiatric disorders. It represents a heterogeneous syndrome of disorganized and bizarre thoughts, delusions, hallucinations, inappropriate affect and impaired psycho-social functioning. Fortunately, schizophrenia is somewhat rare, occurring in only about 1% of the population.

32. There are many clinical presentations of schizophrenia. Despite common misconceptions of schizophrenia as a "split-personality," in fact schizophrenia is a chronic disorder of thought and affect. The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, (DSM-IV) assigns a diagnosis of schizophrenia when a patient suffers two or more of the

following characteristic symptoms: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior and negative symptoms.1

33. Although the etiology of schizophrenia is unknown, research has demonstrated various abnormalities in schizophrenic brain structure and function. The cause of schizophrenia is likely multi-factorial, that is, multiple pathophysiologic abnormalities may play a role in producing the similar but varying clinical phenotypes we refer to as schizophrenia.

34. Since the discovery of the effects of antipsychotics, such as chlorpromazine in the 1950s, and the observation that traditional anti-psychotic drugs are post-synaptic dopamine-receptor antagonists, the hypothesis has emerged that dopamine hyperactivity underscores the neurochemical basis for the primary symptoms of schizophrenia.

35. Over the years, treatment of schizophrenia has relied on antipsychotic drugs that target dopamine D2 receptors. The many antipsychotic drugs introduced during the following decades were increasingly potent, as medicinal chemists improved the drugs' affinity for the D2 receptor.

36. The traditional or "typical" antipsychotics include chlorpromazine (Thorazine), fluphenzine (Proxilin), haloperidol (Haldol), loxapine (Loxitane), molindone (Moban), mesoridazine (Serentil), perphenazine (Trilafon), thioridazine (Mellaril), thiothixene (Navane), and trifluoperazine (Stelazine). Until the early 1990's, the typical antipsychotics were the common drug therapy for schizophrenia.

37. Although there were many traditional antipsychotics, the efficacy of these drugs was similar because they all had similar mechanisms of action. A troubling side effect of typical

[1] Only one of these criteria are required if delusions are bizarre or if hallucinations consist of a voice keeping a running commentary on the person's behavior or two or more voices conversing with each other. To achieve a diagnosis of schizophrenia, schizo-affective or mood disorder must be excluded, and the disorder must not be due to medical disorder or substance use.

antipsychotics was that the blockage of dopaminergic neurotransmission in the basal ganglia caused extrapyramidal syndromes (EPS) such as parkinsonian effects. A long-lasting movement disorder, tardive dyskinesia, also occurred with prolonged treatment. And as to efficacy, the early promise that these drugs might dramatically improve patients' long-term psychosocial and cognitive disabilities was only partially fulfilled.

38. By the 1980s, clozapine was being investigated for the treatment of schizophrenia on the theory that it might be more effective and cause less movement disorder than other antipsychotics. Clozapine was termed an atypical antipsychotic because it had an "atypical index" when measuring its effect on brain activity in different parts of the brain. It was hypothesized that the different effects by clozapine on the areas of the brain that control movement would cause less movement disorder than other antipsychotics. However, the potential of clozapine to cause toxic side effects, including agranulocytosis, limited its prescription to about 10 percent of persons with schizophrenia.

RISPERDAL'S SAFETY PROFILE

39. During the 1990's pharmaceutical companies, acting on the "atypical" hypothesis, introduced newer drugs attempting to capture the enhanced therapeutic effect of clozapine without its toxicity and without the increased EPS caused by traditional antipsychotics. Before 1993, the only atypical antipsychotic in the United States market was clozapine, and due to its toxicity it had very little market share. Ten years later, atypical antipsychotics such as Risperdal would account for about 90% of all antipsychotic drugs prescribed for all psychiatric purposes, regardless of whether they were approved for those indications.

40. The atypical antipsychotics include clozapine (Clozaril), olanzapine (Zyprexa), quetiapine (Seroquel), Risperdal, aripiprazole (Abilify), and ziprasidone (Geodon), and are considered the second-generation antipsychotics (SGA).

41. In part, this lawsuit describes how Defendants achieved, through a series of unlawful acts and practices, the largest United States market share for atypical antipsychotics, both for FDA-approved purposes and for unapproved purposes.

42. In late 1993, Risperdal became the second atypical antipsychotic to receive FDA approval. In early 1994, Janssen, a subsidiary of Johnson & Johnson, began marketing and selling Risperdal. During the next several years, Janssen heavily marketed and promoted Risperdal for its approved indication, management of the manifestation of psychotic disorders, and for multiple non-approved purposes of the drug, for example, attention deficit-hyperactivity disorder (ADHD), depression, anxiety, mood disorder, bipolar disorder, and aggression associated with late-onset dementia. By late 1996, Janssen had significant market share for United States antipsychotic drug use, and demonstrated the sales potential of marketing atypical antipsychotic usage for non-approved indications.

43. Medical literature dating as far back as the 1950s, and Defendants' own pre-clinical studies of Risperdal, demonstrated that Risperdal, like older antipsychotic medications, had the potential to cause diabetes, diabetes-related injuries (e.g. weight gain and hyperglycemia), cardiovascular and cerebrovascular complications, and other severe adverse effects. By the time Risperdal was first marketed, the neurochemical bases for the efficacy and side-effects were generally known to Defendants, i.e., effects on dopamine, serotonin, and histamine systems in the brain. Therefore, prior to marketing Risperdal, Defendants should have been concerned about Risperdal causing neurological problems, weight gain, diabetes,

pancreatitis, hyperglycemia, cardiovascular complications, and metabolic syndrome. And yet Risperdal's original label, and all label changes until 2004, did not adequately warn of these adverse effects.

44. Despite having been on notice, for years, of the potential for deadly diabetes-related side effects, Defendants opted for the bare minima of clinical trials, of limited duration, such that no side effects were likely to be revealed.

45. Further, Risperdal's pre-marketing clinical trials did not support an assertion that it was less likely to cause extra pyramidal symptoms ("EPS") than traditional antipsychotics. Upon information and belief, Defendant's trials were designed to produce similar rates of EPS in patients sorted into placebo groups and those taking Risperdal. In order to produce their desired result, Defendants selected patients for the placebo groups that were already in the course of treatment with high doses of typical antipsychotics.

46. The manifestation of EPS in a patient taking antipsychotic drugs is largely dose-dependent. In other words, the larger the dose, the more likely EPS become. Further, patients that develop EPS generally continue to experience EPS for months, even after discontinuing antipsychotic drug treatment. Because of this, patients in Defendants' placebo groups continued to experience EPS at the rate at which they had experienced EPS while on antipsychotic drug treatment before participating in the trials. Meanwhile, patients in the Risperdal group predictably developed EPS at the rate to be expected in a population taking antipsychotic medication, a rate which essentially matched the placebo group.

47. Based on the similar levels of EPS in the placebo and Risperdal group, Defendants claimed, in their marketing, that patients taking Risperdal were as likely to develop

EPS as patients taking nothing and thus less likely to develop EPS than patients taking traditional antipsychotics.

48. Nevertheless, because the mechanism of action for Risperdal is fundamentally the same as other antipsychotics the FDA required warnings for Risperdal that included neuroleptic malignant syndrome (NMS) and tardive dyskinesia (TD).

49. Defendants had actual knowledge that Risperdal causes weight gain, which significantly increases a patient's risk of contracting diabetes. Despite such knowledge, Defendants failed to include a Warning of the potential for weight gain and the possible development of diabetes as a result of the use of Risperdal in its U.S. labeling for years. In fact, Defendants concealed the true safety profile of Risperdal from patients from 1993 until 2004. Even then, Defendants did not warn citizens of the State of the risk of diabetes associated with Risperdal.

50. In 1999, the FDA caught Janssen promoting Risperdal for the non-medically accepted treatment of the elderly. In a letter from the FDA to Todd McIntyre, Director of Janssen's Regulatory Affairs department, the agency strongly disagreed with certain promotional materials that it had received as part of its monitoring and surveillance program. According to the FDA, Janssen engaged in a false and misleading campaign to promote Risperdal to geriatric patients. Among the items found by the FDA to be **false and misleading** were:

- Janssen's claims in its promotions that Risperdal was safe and effective for elderly patients, despite little or no data to support such claims;
- Janssen's claims that Risperdal has a low incidence of movement disorders;
- Janssen's claims that Risperdal has a low incidence of sedation;

- Janssen's claims that Risperdal has a low incidence of anticholinergic effects (variety of movement disorder);
- Janssen's claims that Risperdal treatment is associated with a low incidence of adverse events coupled with presentations of adverse events associated with Risperdal's discontinuation because such presentations imply that the only adverse events associated with Risperdal result from a patient being taken off the drug;
- Janssen's claims that Risperdal is safer or more effective than other antipsychotics;
- Janssen's claims that Risperdal "enhances daily living" or that it offers "quality control of symptoms for daily living";
- Janssen's claims that Risperdal can "control health-related quality of life";
- Janssen's failure to warn that the use of Risperdal by healthy elderly patients created a greater potential for hepatic and renal dysfunction and cardiovascular sensitivity;
- Janssen's marketing Risperdal outside its education by representing that Risperdal is a safe and effective treatment for hostility in the elderly; and
- Janssen's claims that Risperdal is a safe and effective treatment for "psychotic symptoms associated with a broad range of disorders," including schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder and elderly psychosis.

51. The FDA further found that Janssen's promotion of Risperdal lacked fair balance because:

- The risk information in its promotional literature "appears in pale and tiny font at the bottom or back of a journal ad or other presentation, or after the closing of a letter",

thus lacking the "prominence and readability that is reasonably comparable to the presentation of efficacy information"; and

- It minimized important information related to tardive dyskinesia and extrapyramidal symptoms.

52. Upon information and belief, despite studies and data that confirm the lack of efficacy and significant health and safety risks associated with the promotion of Risperdal for the elderly, Defendants continue this practice.

53. Prior to Risperdal's FDA approval, Defendants had a well-developed strategy to expand the use of Risperdal beyond patients with schizophrenia. Upon information and belief, Defendants sought ghost written research and paid "key opinion leaders" to support Defendants' marketing aims. These "key opinion leaders" were nothing more than third-party consultants and researchers who were put on Defendants' payroll to support and lend credibility to Defendants' scientific and marketing goals.

54. Among these goals were plans to create a series of studies designed to illustrate Risperdal's superior profile to both (a) placebo and (b) a representative conventional antipsychotic while providing funding to engage key opinion leaders in publication worthy trials.

55. Throughout these years, Janssen never provided a prominent warning about the increased risk of diabetes and hyperglycemia and of the need to provide baseline diabetes screening and glucose monitoring. A warning did not appear until it was forced by the FDA in mid-September of 2003.

56. On September 11, 2003, the FDA informed all manufacturers of atypical antipsychotic drugs, including Defendants, that due to an increasing prevalence of diabetes-

related illnesses associated with this class of drugs, that all labeling must bear the following language in the Warnings section:

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

57. Despite the FDA's mandate that Defendants immediately warn of the dangers described above, Defendants waited two more months, until November of 2003, to send prescribing physicians a "Dear Doctor Letter" advising of the new warnings.

58. On April 19, 2004, that November letter was rebuked by the FDA for being brazenly "false" and "misleading."

59. According to the FDA, Janssen's November letter mislead doctors by failing to disclose information relating to hyperglycemia and diabetes mellitus to the labeling, minimizing the risks of potentially fatal hyperglycemia-related adverse events, failing to recommend regular

glucose control monitoring to identify diabetes mellitus and misleadingly claiming that Risperdal is safer than other atypical antipsychotics.

60. The FDA demanded that Janssen immediately cease the dissemination of promotional materials for Risperdal containing claims similar to the foregoing and provide a plan of action to correct the effects of its false and misleading letter.

61. Finally, the FDA admonished Janssen that the violations detailed above did not constitute an exhaustive list, and that it was continuing to "evaluate other aspects" of Janssen's promotional campaign for Risperdal. The FDA reserved the right to determine that "additional measures" would be necessary to "fully correct the false or misleading messages resulting from your [Janssen's] violative conduct."

62. Months later, in July of 2004, Janssen finally sent a dear healthcare provider letter, that was acceptable to the FDA, containing the new warnings.

63. Risperdal is the most widely used atypical antipsychotic in the world. Risperdal has gone from annual sales of zero on 1/1/94 to over $3,500,000,000 in 2005. Crucial to this blockbuster success was Defendants' aggressive marketing of Risperdal, which consisted chiefly of overstating the drug's efficacy, while concealing its life-threatening side effects. As a direct result of Defendants' marketing efforts, the State has paid millions of dollars for non-medically accepted indications of Risperdal.

64. There is no valid scientific evidence to support Defendants' contention that Risperdal is safe and effective for treatment of any non-medically accepted indication, including any use in children. There is no valid scientific evidence concerning the therapeutic equivalence of Risperdal for any non-medically accepted indication, including any use in children.

65. Further, even in cases where treatment with an antipsychotic was appropriate, Risperdal prescriptions should not have been submitted to the State, as Risperdal is no safer or more effective than less expensive first generation antipsychotics.

ALLEGATIONS

66. Defendants did business in the State of South Carolina; made contracts to be performed in whole or in part in South Carolina and/or manufactured, tested, sold, offered for sale, supplied or placed in the stream of commerce, or in the course of business materially participated with others in so doing, Risperdal, which Defendants knew to be defective, unreasonably dangerous and hazardous, and which Defendants knew would be substantially certain to cause injury to the State and to persons within the State thereby negligently and intentionally causing injury to persons within South Carolina and to the State, and as described herein, committed and continue to commit tortious and other unlawful acts in the State of South Carolina.

67. From the 1993 product launch of Risperdal to the present, Defendants engaged in widespread fraudulent statements and conduct, and pervasive false and misleading marketing, advertising and promotion of Risperdal. Defendants deceived physicians, consumers, the State, and others regarding the comparative efficacy of Risperdal to other traditional and atypical antipsychotics. Defendants failed to warn – and affirmatively misled – physicians, consumers, the State, and others in the medical community regarding Risperdal's association with diabetes, diabetes-related conditions and other adverse effects. And even though Risperdal is a antipsychotic drug and thereby limited to its FDA-approved indications, Defendants actively marketed and promoted Risperdal for unapproved uses in several populations where the efficacy and safety of the drug had yet to be established – marketing Risperdal for the treatment of

various conditions or symptoms in children, marketing Risperdal for treatment in the elderly for dementia, and marketing Risperdal for treatment of patients who experience depressive or other physiological conditions.

68. After achieving FDA approval of Risperdal, Defendants plotted and schemed to increase the sales of Risperdal while avoiding the substantial expense and delay of petitioning the FDA for approval of expanded or additional uses of Risperdal. The scheme consisted of elaborate and clandestine promotion of non-medically accepted indications and non-medically necessary uses of Risperdal.

69. Upon information and belief, this scheme was carried out by: employing the illegal direct solicitation of physicians to prescribe Risperdal for non-medically accepted indications and non-medically necessary uses; the making of false statements to physicians and pharmacists concerning the efficacy and safety of Risperdal for non-medically accepted indications and non-medically necessary uses; the use of active concealment to avoid the utilization policies of Medicaid, SCDMH and SHP, which are intended to refuse payment for uses of drugs which are not medically accepted and medically unnecessary; and the active training of Defendants' employees in methods of avoiding detection of their activities by the FDA.

70. The State spends millions of dollars each year to provide or pay for health care and other necessary facilities and services on behalf of indigents and other eligible citizens whose said health care costs are directly caused by Risperdal-induced diabetes, stroke, pancreatitis, seizures and other diseases.

71. Defendants collectively sold or aided and abetted in the sale of Risperdal which was and is defective and unreasonably dangerous.

72. Upon information and belief, at all pertinent times, Defendants knew, or should have known, that Risperdal was and is unreasonably hazardous to human health.

73. Defendants, through their funding and control of certain studies concerning the effects of Risperdal on human health, their control over trade publications, promoting, marketing, and/or through other agreements, understandings and joint undertakings and enterprises, conspired with, cooperated with and/or assisted in the wrongful suppression, active concealment and/or misrepresentation of the true relationship between Risperdal and various diseases, all to the detriment of the public health, safety and welfare and thereby causing harm to the State.

74. Risperdal is inherently, abnormally, and unreasonably dangerous. The health risks and costs of Risperdal to the citizens of the State and to the State greatly outweigh any claimed utility of Risperdal. Defendants knew or should have known of the dangers inherent in the use of Risperdal, and that the public and the State would be harmed by the intended and foreseeable use of Risperdal.

75. As a direct and proximate result of the defective marketing practices of Defendants, Risperdal was and is defective and unreasonably dangerous.

76. Risperdal reached the users and consumers thereof in substantially the same condition which it was in when originally manufactured, distributed and sold by Defendants. At the time Risperdal was sold or placed on the market, it was in a defective condition and unreasonably dangerous to users and consumers.

77. The defective condition of Risperdal directly and proximately caused South Carolina residents to suffer various Risperdal-induced diseases, injuries and sicknesses, and directly and proximately caused the State to expend millions of dollars in order to provide

necessary health care to these citizens through its Medicaid, SCDMH and SHP programs, thereby directly damaging the State.

78. At all pertinent times, it was foreseeable by Defendants that certain of the South Carolina Medicaid, SCDMH and SHP participants who used Risperdal would become ill and suffer injury, disease and sickness as a result of using Risperdal as Defendants intended, and it was further foreseeable by Defendants that the State would be required to expend millions of dollars each year in order to provide necessary medical treatment and facilities to those citizens.

79. Defendants individually, and through their representatives, fraudulently mislead the public, physicians treating Medicaid, SCDMH and SHP participants and the State, with regard to the health risks of Risperdal, all for the purpose of increasing Defendants' profits from the sale of Risperdal.

80. Specifically, and in addition to the allegations above, Defendants knew of the hazards associated with Risperdal. Defendants nevertheless affirmatively and actively concealed information which clearly demonstrated the dangers of Risperdal and affirmatively misled the public and physicians treating Medicaid, SCDMH and SHP participants with regard to the material and clear risks of Risperdal. Defendants did so with the intent that physicians treating Medicaid, SCDMH and SHP participants would continue to prescribe Risperdal. However, Defendants knew that prescribing physicians would not be in a position to discover the true risks of Risperdal and would rely upon the misleading information that Defendants promulgated. Defendants further knew that physicians treating Medicaid, SCDMH and SHP participants would write Risperdal prescriptions that would be paid for by the State's Medicaid, SCDMH and SHP program.

81. At all pertinent times, Defendants purposefully and intentionally engaged in these activities, and continue to do so, knowing that when the State's Medicaid, SCDMH and SHP participants use Risperdal as it was and is intended to be used, that the State's Medicaid, SCDMH and SHP participants would be substantially certain to suffer disease, injury and sickness, including diabetes, stroke, pancreatitis, seizures and other illnesses, and that the State would be directly injured thereby, all as described above.

82. Also at all pertinent times, Defendants purposefully and intentionally engaged in these activities, and continue to do so, knowing that the State, in the absence of any such efforts by Defendants, would be obligated to, and would, provide health care and other necessary facilities and services for certain of the State's Medicaid, SCDMH and SHP participants harmed by the intended use of Risperdal, and that the State itself would thereby be directly harmed.

83. Upon information and belief, the statements, representations and promotional schemes publicized by Defendants were deceptive, false, incomplete, misleading and untrue. Defendants knew, or should have known, that their statements, representations and advertisements were deceptive, false, incomplete, misleading and untrue at the time of making such statements. Defendants had an economic interest in making such statements. Neither the State nor the physicians in South Carolina who prescribed Risperdal had knowledge of the falsity or untruth of Defendants' statements, representations and advertisements when Medicaid, SCDMH and SHP claims for Risperdal were submitted; moreover, the State had a right to rely on Defendants to act honestly when dealing with the State. Each of the Defendants' statements, representations and advertisements were material to the State's purchase of Risperdal in that the State would not have reimbursed for or purchased Risperdal if it had known that Defendants'

statements, representations and advertisements related to Risperdal were deceptive, false, incomplete, misleading and untrue.

84. The State has a right to rely upon the representations of Defendants and was directly and proximately injured by such reliance, all as described above.

85. A significant percentage of South Carolina Medicaid, SCDMH and SHP participants, believed to number in the hundreds, if not thousands, suffered serious diseases and/or potentially life-threatening medical conditions after taking Risperdal and such risks of use were known, or should have been known, to Defendants who failed to warn South Carolina physicians treating Medicaid, SCDMH and SHP participants of those risks.

COUNT I

SUBMISSION OF FALSE & FRAUDULENT CLAIMS UNDER MEDICAID PROGRAM

86. The State incorporates by reference the foregoing allegations as if set forth at length herein.

87. A significant percentage of patients who use or have used Risperdal are persons whose prescriptions are paid for in whole or in part by Medicaid.

88. Defendants' aggressive, illegal scheme of off-label promotion has induced a misallocation of State Medicaid funds through a pattern of fraudulent conduct by causing the State to pay out sums for prescriptions for which reimbursement was not intended. Defendants' conduct constitutes Medicaid fraud within the meaning of S.C. CODE ANN. §43-7-60.

89. Defendants have, as alleged, actively concealed their promotion of Risperdal for non-medically accepted indications and non-medically necessary uses from the State's regulatory authorities. Said active concealment is motivated by the desire to, and has had the effect of, preserving the flow of State funds to reimburse Risperdal prescriptions for non-medically accepted indications and non-medically necessary uses. Said active concealment constitutes a pattern of fraudulent conduct through which State payments are derived, and constitutes Medicaid fraud within the meaning of S.C. CODE ANN. §43-7-60.

90. Defendants have knowingly caused false claims for payment to the State's Medicaid program by intentionally promoting non-medically accepted indications and non-medically necessary uses of Risperdal to prescribing physicians for the purpose of receiving greater compensation than that to which they are legally entitled, with the costs ultimately being borne, in whole or in part, by the State through its Medicaid reimbursement to pharmacies.

These prescriptions constitute false claims because Medicaid reimbursement is not intended for non-medically accepted indications and non-medically necessary uses of Risperdal.

91. Violation of the Medicaid statute entitles the State to reimbursement of all funds for which payment was fraudulently induced, including but not limited to, all funds paid by the State for reimbursement of non-medically accepted indications and non-medically necessary uses of Risperdal.

92. Further, Defendants caused the foregoing false claims to be submitted with knowledge that they were not medically accepted indications and non-medically necessary uses. Such conduct entitles the State to recover an amount equal to three times the amount wrongfully reimbursed and two thousand dollars per false claim.

WHEREFORE, the State respectfully requests that this Honorable Court enter judgment in its favor and against Defendants and that the State be awarded reimbursement for all expenditures made for non-medically accepted and non-medically necessary prescriptions of Risperdal, three times the amount Defendants knowingly caused to be submitted for wrongful reimbursement of Risperdal, two thousand dollars per false claim and such other relief as justice and equity may require.

COUNT II

SUBMISSION OF FALSE & FRAUDULENT CLAIMS UNDER MEDICAID PROGRAM

93. The State incorporates by reference the foregoing allegations as if set forth at length herein.

94. A significant percentage of patients who use or have used Risperdal are persons whose prescriptions are paid for in whole or in part by Medicaid.

95. Defendants have fraudulently represented that Risperdal is safer and more effective than less expensive, first generation antipsychotics. Defendants' conduct constitutes Medicaid fraud within the meaning of S.C. CODE ANN. §43-7-60.

96. Since the inception of their marketing of Risperdal, Defendants knowingly misrepresented that Risperdal is more effective in the treatment of the negative symptoms of schizophrenia and less likely to produce certain adverse events involving involuntary movement disorders, which are commonly associated with first generation antipsychotics. Defendants knew these representations were false at the time they were made and that Risperdal is no more effective than appropriate doses of first generic antipsychotic drugs and no less likely to produce these adverse events. Defendants touted Risperdal's added efficacy dimension and the reduction of these adverse events as justification for its higher cost. As a result of these representations, and in an effort to spare their patients from experiencing these adverse effects, South Carolina doctors treating Medicaid participants opted for Risperdal instead of less expensive first generation antipsychotics.

97. Defendants have knowingly caused false claims to be submitted to the Medicaid Program by fraudulently representing that Risperdal is safer and more effective than less expensive, first generation antipsychotics. The increased incremental cost of Risperdal, relative to available first generation antipsychotics, was borne by the State and resulted in excessive payment to Defendants. All prescriptions for Risperdal submitted to the State's Medicaid Program constitute false claims under the Medicaid Fraud Act.

98. Violation of the Medicaid statute entitles the State to reimbursement of all funds for which payment was fraudulently induced, including but not limited to the incremental cost of purchasing Risperdal instead of less expensive first generation antipsychotics.

99. Further, Defendants caused the foregoing false claims to be submitted with knowledge that they were medically unnecessary. Such conduct entitles the State to recover an amount equal to three times the amount wrongfully reimbursed and two thousand dollars per false claim.

WHEREFORE, the State respectfully requests that this Honorable Court enter judgment in its favor and against Defendants and that the State be awarded reimbursement for the amount of the incremental cost of reimbursement for Risperdal instead of available first generation antipsychotics, three times the amount Defendants knowingly caused to be submitted for wrongful reimbursement of Risperdal, two thousand dollars per false claim and such other relief as justice and equity may require.

COUNT III

RECOVERY OF THE COST OF TREATMENT FOR INJURIES CAUSED BY RISPERDAL

100. The State incorporates by reference the foregoing allegations as if set forth at length herein.

101. The method by which Risperdal was marketed in South Carolina rendered it defective and unreasonably dangerous.

102. The design and/or manufacture of Risperdal rendered it a dangerously defective drug in that its use causes dangerous, and potentially life-threatening, medical conditions when taken as recommended by Defendants and such risks were not generally known by South Carolina physicians, the State and/or South Carolina Medicaid, SCDMH and SHP participants.

103. Risperdal was a dangerously defective drug in that Defendants failed to conduct adequate pre-marketing testing, notwithstanding the known side effects associated with Risperdal, atypicals as a class and anti-psychotic medications generally.

104. Risperdal was dangerously defective because it lacked a sufficient warning of the risks associated with its use and also because:

(a) the lack of an adequate warning caused South Carolina physicians treating Medicaid, SCDMH and SHP participants to prescribe Risperdal in inappropriate circumstances and on inappropriate classes of patients;

(b) Defendants had a duty to warn South Carolina physicians treating Medicaid, SCDMH and SHP participants of the risks and potentially life-threatening side effects associated with Risperdal use and failed to do so; and

(c) the warning and/or labeling provided by Defendants for Risperdal failed to include the risks and or potentially life-threatening side effects associated with Risperdal use that were known to, or readily ascertainable by, Defendants and such risks were concealed from South Carolina physicians treating Medicaid, SCDMH and SHP participants.

105. Risperdal is abnormally and unreasonably dangerous as marketed in that the health risks and costs associated with Risperdal greatly outweigh any claimed utility of Risperdal to the State and its Medicaid, SCDMH and SHP participants.

106. Risperdal reached the users and consumers thereof in substantially the same condition that it was when originally manufactured, distributed and sold by Defendants. At the time Risperdal was sold or placed on the market, it was in a defective condition and unreasonably dangerous to South Carolina Medicaid, SCDMH and SHP participants.

107. South Carolina Medicaid, SCDMH and SHP participants, and their physicians, used Risperdal in the manner in which it was intended to be used, without any substantive alteration or change in the product.

108. As a result of Risperdal's defective nature, certain South Carolinians whose care is provided by Medicaid, SCDMH and SHP were injured.

109. The State was forced to expend significant sums of money, through its Medicaid, SCDMH and SHP programs, to treat Medicaid, SCDMH and SHP participants who sustained Risperdal-related injuries.

110. The State is entitled to recover the costs of such treatment as *parens patriae*.

WHEREFORE, the State respectfully requests that this Honorable Court enter judgment in its favor and against Defendants and award the State compensatory damages and any other relief as justice may require.

COUNT IV

VIOLATION OF THE SOUTH CAROLINA UNFAIR TRADE PRACTICES ACT

111. The State incorporates by reference the foregoing allegations as if set forth at length herein.

112. By labeling, distributing, marketing, promoting and selling Risperdal through South Carolina physicians and pharmacies to the State, and South Carolina consumers, Defendants are engaging in trade or commerce directly, or indirectly, affecting the people of the State.

113. Defendants have repeatedly and willfully engaged in the following conduct which constitutes a deceptive trade practice and a violation of the SCUTPA:

(a) Misrepresenting that Risperdal is safe and effective for indications for which safety and efficacy had not been demonstrated which caused South Carolina physicians treating Medicaid, SCDMH and SHP participants to prescribe Risperdal in inappropriate, non-medically necessary circumstances;

(b) Making 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;

(c) Misrepresenting and concealing material facts and/or failing to inform and educate South Carolina physicians as to the risks and dangers associated with Risperdal use when such facts were well known to, or readily ascertainable by, Defendants;

(d) Misrepresenting and concealing material facts which were known to Defendants, and unknown to South Carolina physicians, when Defendants knew that South Carolina physicians rely on such facts when deciding whether to prescribe Risperdal to their patients;

(e) Misrepresenting that Risperdal is safer and more effective than less expensive first generation antipsychotics;

(f) Misrepresenting Risperdal as being of a particular standard, quality or grade when it is not; and

(g) Intentionally creating a likelihood of confusion or misunderstanding in the minds of South Carolina physicians as to whether Risperdal was safe, medically necessary and/or FDA-indicated, for Medicaid, SCDMH and SHP participants.

114. Defendants made, and continue to make, orally and in writing, false, misleading or deceptive representations in advertisements, promotions and statements, and otherwise disseminated, and continue to disseminate, false, misleading or deceptive information to the public, including South Carolina citizens, physicians and the State regarding non-medically necessary and non-medically accepted uses of Risperdal and the health risks and benefits associated with using Risperdal.

115. Defendants acted knowingly and willfully in committing the violations of the SCUTPA described herein.

116. Each Risperdal prescription written without an adequate warning, for a non-medically necessary or non-medically accepted use or where a first generation antipsychotic was available constitutes a separate and distinct violation of the SCUTPA.

117. As a consequence of Defendants' illegal and deceptive sales and marketing practices, the State made monetary expenditures on behalf of South Carolina Medicaid, SCDMH

and SHP participants who were prescribed Risperdal for conditions which were not FDA-approved or medically accepted, and/or where a first generation antipsychotic was as safe and effective and less expensive.

118. As a further consequence of Defendants' illegal and deceptive sales and marketing practices, many South Carolina Medicaid, SCDMH and SHP participants, including children, were prescribed Risperdal by their physicians and sustained serious and potentially life-threatening side effects.

119. The State was forced to expend significant sums of money for the treatment of those South Carolina Medicaid, SCDMH and SHP participants who sustained serious and potentially life-threatening side injuries as a result of using Risperdal.

120. The Attorney General has determined that the imposition of an injunction against Defendants prohibiting the conduct set forth herein is in the public interest.

121. The State seeks the entry of a permanent injunction prohibiting Defendants' unlawful and deceptive conduct and the imposition of all appropriate remedies available under the SCUTPA.

122. The State seeks restitution for all expenditures resulting from non-medically necessary or non-medically accepted uses of Risperdal caused by Defendants' unlawful and deceptive sales and marketing practices and the difference in cost between the State's expenses for Risperdal and what the State would have spent on first generation antipsychotics, absent Defendants violations of the SCUTPA.

123. The State seeks compensatory damages for all State expenditures resulting from the treatment of those South Carolina Medicaid, SCDMH and SHP participants who sustained injuries, side effects and/or adverse medical events after using Risperdal.

WHEREFORE, the State respectfully requests that this Honorable Court enter judgment in its favor and against Defendants and also seeks;

(a) a permanent injunction preventing Defendants from deceptively marketing and/or promoting Risperdal as appropriate for non-medically necessary or non-medically accepted uses;

(b) restitution of all State expenditures for prescriptions caused by Defendants' deceptive marketing and/or promotion of Risperdal;

(c) compensatory damages for all expenditures made by the State on behalf of South Carolina Medicaid, SCDMH and SHP participants who sustained injuries associated with Risperdal use;

(d) imposition of $5,000 SCUTPA civil penalty for each method, act or practice deemed to violate this Act;

(e) three times the actual damages sustained by the State; and

(f) such further justice and other relief as justice and equity may require.

COUNT V

NEGLIGENCE

124. The State incorporates by reference the foregoing allegations as if set forth at length herein.

125. Defendants owed the State a duty to use reasonable care in the design, manufacture and marketing of its product, Risperdal.

126. Defendants negligently, carelessly, recklessly, willfully and/or intentionally engaged in the following conduct:

(a) Marketing and/or promoting Risperdal for non-medically necessary or non-medically accepted uses;

(b) Failing to adhere to all applicable laws and regulations pertaining to the marketing, promotion and/or labeling of pharmaceutical products, such as Risperdal;

(c) Marketing and/or promoting Risperdal as appropriate for children;

(d) Failing to adequately train their sales force so that when South Carolina physicians treating Medicaid, SCDMH and SHP participants raised safety concerns regarding Risperdal important safety information was withheld;

(e) Supplying a product that they knew, or should have known, contained inadequate warnings of side effects and risks that were known to, or based on facts available to Defendants;

(f) Supplying a product lacking sufficient warnings and/or instructions when they knew, or should have known, the side effects associated with Risperdal were not generally known by South Carolina physicians treating Medicaid, SCDMH and SHP participants;

(g) Representing that Risperdal was safer than less expensive, first generation antipsychotics;

(h) Continuing to promote, market and/or sell Risperdal after they knew, or should have known, of the serious side effects and risks associated with Risperdal use;

(i) Allowing Risperdal to be used indiscriminately for uses far beyond its indications, which are limited to schizophrenia and, recently, mania associated with bipolar disorder; and

(j) Not disclosing data pertaining to such use.

127. Defendants' negligent, careless, reckless, willful and/or intentional conduct was the proximate cause of injuries and damages sustained by the State.

128. At all relevant times, Defendants knew, or should have known, that Risperdal was, and is, hazardous to human health.

129. Risperdal is abnormally and unreasonably dangerous as marketed in that the health risks and costs associated with Risperdal greatly outweigh any claimed utility of Risperdal to Medicaid, SCDMH and SHP participants.

130. As a direct result of the unreasonable marketing practices of Defendants, Risperdal was, and is, defective and unreasonably dangerous.

131. Risperdal reached the users and consumers thereof in substantially the same condition as when originally manufactured, distributed and sold by Defendants. At the time Risperdal was sold or placed on the market, it was in a defective condition and unreasonably dangerous to Medicaid, SCDMH and SHP participants.

132. South Carolina Medicaid, SCDMH and SHP participants used Risperdal in the manner in which it was intended to be used, without any substantive alteration or change in the product.

133. Due to the negligent, careless, reckless, willful and/or intentional conduct of Defendants, as set forth above, the State misallocated millions of dollars of Medicaid, SCDMH and SHP funds in purchasing Risperdal prescriptions and was also forced to expend significant sums of money for the care and treatment of South Carolina Medicaid, SCDMH and SHP participants injured by Risperdal, all of which was foreseeable to Defendants.

134. The reprehensible nature of Defendants' conduct entitles the State to an award of punitive damages.

WHEREFORE, the State respectfully requests that this Honorable Court enter judgment in its favor and against Defendants and award the State compensatory and punitive damages and any other relief as justice may require.

COUNT VI

BREACH OF WARRANTY

135. The State incorporates by reference the foregoing allegations as if set forth at length herein.

136. Through their sales and marketing practices to South Carolina physicians treating Medicaid, SCDMH and SHP participants, Defendants warranted that Risperdal was fit and

appropriate for patients suffering from conditions less serious than schizophrenia and bipolar disorder, the only conditions for which Risperdal was arguably proven safe and effective.

137. Through their sales and marketing practices to South Carolina physicians treating Medicaid, SCDMH and SHP participants, Defendants warranted that Risperdal was fit and appropriate for pediatric use.

138. Through their sales and marketing practices to South Carolina physicians treating Medicaid, SCDMH and SHP participants, Defendants warranted that Risperdal had no significant risks or side effects that were not identified on its labeling. Defendants further warranted that Risperdal was safer than less expensive, first generation antipsychotics.

139. South Carolina physicians treating Medicaid, SCDMH and SHP participants relied on the warranties made by Defendants regarding the appropriate uses and safety profile for Risperdal.

140. Defendants breached the express and implied warranties they made to the State, through South Carolina physicians treating Medicaid, SCDMH and SHP participants, since the product was not appropriate for use in children, or for adults with conditions less serious than schizophrenia and bipolar disorder. Also, Risperdal was far less safe than warranted by Defendants.

141. The State misallocated millions of dollars in Medicaid, SCDMH and SHP expenditures for non-medically accepted uses of Risperdal and in purchasing Risperdal when a less expensive, first generation antipsychotic was available. The State also spent significant sums of money, through its Medicaid, SCDMH and SHP programs, for medical treatment for those South Carolina citizens who developed serious side effects and/or adverse reactions after

using Risperdal. The State's expenses were caused by Defendants' express and implied warranties.

WHEREFORE, the State respectfully requests that this Honorable Court enter judgment in its favor and against Defendants and award the State compensatory damages and any other relief as justice may require.

COUNT VII

FRAUD & MISREPRESENTATION

142. The State incorporates by reference the foregoing allegations as if set forth at length herein.

143. As part of their promotion of Risperdal, Defendants, through their sales representatives and other advertising and promotion, willfully, knowingly and deceptively communicated to South Carolina physicians treating Medicaid, SCDMH and SHP participants that Risperdal was safe and effective for South Carolina children and elderly, that it was safe and effective for South Carolina Medicaid, SCDMH and SHP participants suffering from conditions less serious than schizophrenia and bipolar disorder and that it was safer and more effective than less expensive first generation antipsychotics, all of which were knowingly false.

144. Defendants had a duty to disclose the conditions for which Risperdal was approved by the FDA, and thus arguably proven safe and effective, and not to go beyond those indications in their sales and marketing to South Carolina physicians, the intermediary between Defendants and the State.

145. Defendants intended to induce South Carolina physicians treating Medicaid, SCDMH and SHP participants to prescribe Risperdal for South Carolina Medicaid, SCDMH and

SHP participants for whom Risperdal was not medically accepted, appropriate or medically necessary.

146. South Carolina physicians treating Medicaid, SCDMH and SHP participants as well as the State, were justified in relying on Defendants to educate the physicians as to the appropriate uses, indications and risks of Risperdal.

147. The State, through its Medicaid, SCDMH and SHP programs, was forced to expend significant amounts of money for non-medically accepted, non-medically necessary Risperdal prescriptions which were directly caused by the fraudulent and misleading statements of Defendants.

148. Defendants willfully, knowingly and deceptively withheld material facts regarding the risks and side effects associated with Risperdal use from South Carolina physicians treating Medicaid, SCDMH and SHP participants.

149. Defendants had a duty to disclose known risks and side effects associated with Risperdal use, particularly, but not solely, when specifically asked about those risks by South Carolina physicians.

150. Defendants intentionally withheld information regarding the safety risks and side effects associated with Risperdal use with the intention of inducing South Carolina physicians to prescribe Risperdal for South Carolina Medicaid, SCDMH and SHP participants in greater quantities than they otherwise would have, or was otherwise appropriate.

151. South Carolina physicians treating Medicaid, SCDMH and SHP participants, as well as the State, were justified in their reliance on Defendants to educate them as to the risks and dangerous and potentially life-threatening side effects associated with Risperdal use.

152. Defendants knew that the State and South Carolina Medicaid, SCDMH and SHP participants, particularly children, would not be in a position to discover and understand the true risks of using Risperdal, and the public relied upon the misleading information that Defendants promulgated to South Carolina physicians to the detriment of the State.

153. Defendants knew that the representations that were relied on by South Carolina physicians treating Medicaid, SCDMH and SHP participants were false or were made recklessly without any knowledge of the truth.

154. Each of Defendants' misleading and deceptive statements, representations and advertisements related to non-medically accepted and other inappropriate uses of Risperdal were material to the State's purchase of Risperdal in that the State would not have been required to reimburse pharmacies for non-non-medically accepted, non-medically necessary uses of Risperdal if Defendants had marketed Risperdal legally.

155. The State, through its Medicaid, SCDMH and SHP programs, was forced to expend significant amounts of money to treat South Carolina citizens who contracted serious and potentially life-threatening medical conditions resulting from Defendants' deceptively withholding adequate safety information regarding Risperdal use and/or misrepresenting Risperdal's safety profile.

WHEREFORE, the State respectfully requests that this Honorable Court enter judgment in its favor and against Defendants and award the State compensatory and punitive damages and any other relief as justice may require.

COUNT VIII

UNJUST ENRICHMENT

156. The State incorporates by reference the foregoing allegations as if set forth at length herein.

157. Defendants knowingly, willfully and intentionally marketed and promoted Risperdal for conditions and illnesses for which it was not medically accepted or necessary.

158. Defendants knowingly, willfully and intentionally withheld information from South Carolina physicians treating Medicaid, SCDMH and SHP participants regarding the risks associated with Risperdal use.

159. As a result of the deceptive marketing practices of Defendants, South Carolina physicians treating Medicaid, SCDMH and SHP participants prescribed Risperdal in far greater numbers than would have been generated absent Defendants' deceptive and illegal conduct. The inflated levels of Risperdal reimbursement for Medicaid, SCDMH and SHP participants resulted in a financial windfall for Defendants.

160. The State paid, reimbursed and/or otherwise conferred a benefit upon Defendants to the extent of the inflated numbers of Risperdal prescriptions that directly resulted from Defendants' fraudulent marketing practices relative to South Carolina Medicaid, SCDMH and SHP participants who were not suffering from illnesses for which Risperdal is the medically accepted or necessary treatment.

161. Further, Defendants have been unjustly enriched as a result of their false representations that Risperdal is safer and more effective than less expensive, first generation antipsychotics. The State would not have purchased Risperdal instead of first generation antipsychotics in the absence of Defendants' fraudulent representations.

162. Defendants have been unjustly enriched to the extent of the increased revenue received by Defendants from Risperdal prescriptions that were ultimately reimbursed by the State and resulted from Defendants' deceptive and illegal marketing program.

WHEREFORE, the State respectfully requests that this Honorable Court enter judgment in its favor and against Defendants and that Defendants be required to make restitution to the State for all expenditures made for non-medically accepted or non-medically necessary prescriptions of Risperdal as well as the incremental cost of reimbursing for Risperdal instead of less expensive first generation antipsychotics and such other relief as justice and equity may require.

REQUEST FOR JURY TRIAL

The State respectfully requests that all issues presented by its above Complaint be tried before a jury, with the exception of those issues that, by law, must be tried before the court.

Dated this 19th day of April, 2007,

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STATE OF SOUTH CAROLINA)	IN THE COURT OF COMMON PLEAS
COUNTY OF SPARTANBURG)	FOR THE SEVENTH JUDICAL CIRCUIT
STATE OF SOUTH CAROLINA ex rel. Henry McMaster, in his Capacity as Attorney General of the State of South Carolina,	CA No.: 2007-CP-42-1438
PLAINTIFF,	Acceptance of Service
v.	
JANSSEN PHARMACEUTICA, INC., JANSSEN, LP and JOHNSON & JOHNSON, INC.	
DEFENDANTS.	

Due and legal service of the within Amended Summons and Complaint is accepted and copy retained this 25th day of April, 2007.

STEVE HAMM, ESQUIRE

WITNESS:

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MARC KITCHENS

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,	Civil Action No.: 2007-CP-42-1438
PLAINTIFF,	
v.	**PLAINTIFF THE STATE OF SOUTH CAROLINA'S MOTION TO EXCLUDE THE TESTIMONY OF CERTAIN RISPERDAL PRESCRIBERS AT TRIAL**
ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA, INC., and/or JANSSEN, L.P., AND JOHNSON & JOHNSON, INC.	
DEFENDANTS.	

2010 JUL -2 PM 3:45
M. HOPE BLACKLEY

Plaintiff, the State of South Carolina, *ex rel.* Henry McMaster, in his capacity as Attorney General of the State of South Carolina (hereinafter, "the State"), by and through the undersigned counsel, hereby submits its Motion to Exclude the Testimony of Certain Risperdal Prescribers at Trial, seeking the Court's order excluding the testimony of Risperdal prescribers deposed by Defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. f/k/a Janssen Pharmaceutica, Inc., and/or Janssen, L.P., and Johnson & Johnson, Inc., (collectively, "Janssen" or "Defendant") from the trial of this matter as the testimony is irrelevant and unfairly prejudicial.

I.
SUMMARY OF THE ARGUMENT

As predicted, the testimony Janssen lobbied to obtain from the depositions of a selection of Risperdal prescribers during the discovery phase of this litigation amounts to nothing more than an irrelevant, anecdotal accounting of certain physicians' prescribing habits with respect to Risperdal and other antipsychotics and has no bearing on the State's SCUTPA claims or any

viable defense thereto. In addition to being irrelevant, the testimony is unfairly prejudicial and its admission would cause confusion of the issues and unquestionably mislead the trier of fact.

As this Court is aware, the State no longer seeks reimbursement of funds paid for Risperdal prescriptions on the basis that any particular Risperdal prescription was medically unnecessary. Rather, the State seeks to recover civil penalties under SCUTPA alone for Janssen's willful, deceptive and unfair course of conduct in its labeling of Risperdal declared unlawful by S.C. Code Ann. § 39-5-20. As part of its civil penalties claim, the State is not required to prove causation or reliance, and accordingly Janssen cannot defend against such claim by way of the learned intermediary doctrine. The doctrine simply does not apply to, let alone serve to bar, the State's SCUPTA claims for the recovery of civil penalties for Janssen's knowing and willful deceptive labeling of Risperdal.

Therefore, the testimony of individual Risperdal prescribers is irrelevant to any defense of the State's SCUTPA claim. Further, such testimony would only serve to prejudice the State by confusing the issues before the trier of fact. The Court should therefore exclude from trial the testimony of these prescribers.

II.
STATEMENT OF THE CASE

On April 23, 2007, the State initiated this action against Janssen, manufacturer of the atypical antipsychotic drug Risperdal, to recover, *inter alia*, civil penalties pursuant to S.C. Code Ann. § 39-5-110(a) for Janssen's willful, deceptive and unfair course of conduct in its product labeling. On March 19, 2010, the State filed its Second Amended Civil Action Complaint, (hereinafter, "Amended Complaint"), petitioning the Court to assess against Janssen such penalties in an amount up to five thousand dollars for each "method, act or practice declared unlawful by § 39-5-20" and the willful use thereof. S.C. Code Ann. § 39-5-110(a). The State's

Amended Complaint alleges, in brief, that Janssen: (1) "willfully engaged in a protracted, deceptive and unfair course of conduct in violation of SCUTPA" through its "labeling of Risperdal, which willfully, deceptively, and unfairly minimized, misrepresented, and/or concealed the drug's dangerous side effects"; (2) "had actual knowledge that Risperdal causes weight gain" and "other severe adverse effects" upon product launch, but "failed to include a warning of the potential for weight gain and the possible development of diabetes as a result of the use of Risperdal in its U.S. labeling for many years," and "failed to warn adequately of these adverse effects," in all subsequent label changes; (3) was "chastised by the FDA for being brazenly 'false' and 'misleading'" in its Dear Doctor Letters by "[f]ailing to disclose the addition of information relating to hyperglycemia and diabetes mellitus to the labeling; [m]inimizing the risks of potentially fatal hyperglycemia-related adverse events; [f]ailing to recommend regular glucose control monitoring to identify diabetes mellitus as soon as possible; and [m]isleadingly claiming that Risperdal is safer than other atypical antipsychotics"; and, (4) "made, and continue[s] to make, orally and in writing, false, misleading or deceptive representations," and "continue[s] to disseminate false, misleading, or deceptive information to the public . . . regarding the health risks and benefits associated with using Risperdal." (Pl.'s Second Am. Compl. ¶¶ 8, 13, 24, 26, 45, 46, 57, 58.)

III.
ARGUMENT

A. Standard.

Under South Carolina law, only relevant evidence that tends to prove or disprove the existence of a material fact is admissible. *Jamison v. Ford Motor Co.*, 644 S.E.2d 755, 766 (S.C. Ct. App. 2007) (citing S.C. R. Evid. 401). "Evidence which is not relevant is not admissible."

Doe v. Doe, 634 S.E.2d 51, 59 (S.C. Ct. App. 2006) (quoting S.C. R. Evid. 402). In addition, "[t]he dictates of Rule 401 are subject to the balancing requirement of Rule 403, SCRE, which requires a court to exclude relevant evidence upon a showing that its admission would be more prejudicial that probative." *Watson ex rel. Watson v. Chapman*, 540 S.E.2d 484, 487 (S.C. Ct. App. 2000). Thus, under Rule 403, "[a]lthough relevant, evidence may be excluded if its probative value is substantially outweighed by the danger of unfair prejudice, confusion of the issues, or misleading the jury, or by considerations of undue delay, waste of time, or needless presentation of cumulative evidence." S.C. R. Evid. 403; *see also Jamison*, 644 S.E.2d at 755, 766 (probative value of videos "was substantially outweighed by danger of unfair prejudice, confusion of the issues, and misleading" the trier of fact); *Gause v. Livingston*, 159 S.E.2d 604, 607 (S.C. 1968) (where testimony, admitted over objection, "was not relevant to any issue existing between the respondent and the appellant," and a reasonable probability existed "that . . . sympathy . . . was aroused in favor of the respondent by the admission of such extraneous evidence, all to the prejudice of the appellant . . . the only remedy [was] a reversal of the judgment so that a trial [could] be had with this irrelevant evidence excluded.").

The testimony Janssen seeks to admit does not have any tendency to make the existence of any fact that is of consequence to the determination of this action more probable or less probable. *See* S.C. R. Evid. 401. It is not only irrelevant to these proceedings, but its purported probative value is vastly outweighed by the danger of unfair prejudice, confusion of issues, misleading the fact finder, and causing undue delay and waste of time. *See* S.C. R. Evid. 403. For these reasons, the evidence should be excluded. *See* S.C. R. Evid. 402, 403.

B. The Testimony of Risperdal Prescribers That Janssen Seeks to Admit at Trial is Irrelevant to the State's SCUTPA Claim and Any Defense Thereto.

In its Second Amended Complaint, the State distilled the matters in controversy to the following: Did Janssen violate SCUTPA through Risperdal's product labeling, including its Dear Doctor Letter disseminated subsequent to the class labeling change in 2004; and, if so, how many violations occurred, were they willful and what penalty should be imposed per violative act? The State expressly relinquished its theories of recovery related to medical necessity and health care costs attributed to Risperdal-related injuries.

In the absence of an actual damages claim, under South Carolina law the State is not required to prove that anyone relied on deceptive acts or that such acts caused anyone damages. *See* S.C. Code Ann. §§ 39-5-110(a) and 39-5-20(a); *see also State ex rel. McLeod v. C & L Corp.*, 313 S.E.2d 334, 338 (S.C. Ct. App. 1984) ("State courts have . . . refused to link proof of unfair or deceptive trade practices to proof of common law fraud, and "proof of common law fraud is not required to establish a violation of the Act."). Rather, SCUTPA declares intrinsically unlawful any "[u]nfair methods of competition and unfair or deceptive acts or practices in the conduct of any trade or commerce," and the willful use of such method, act or practice subject to civil penalties. *See* S.C. Code Ann. §§ 39-5-20(a) and 39-5-110(a). As such, deception consummates liability in a penalties-only claim under the Act.

Recognizing this liberal construction of SCUTPA and the Act's capacity for "broad enforcement," this Court, in rejecting related statutory construction arguments in *Lilly*, relied on the decision of the district court in *City of Charleston v. Hotels.com, LP*, 520 F. Supp. 2d 757, 775 (D.S.C. 2007), which found that the defendants' practice of collecting from consumers a higher accommodation tax than the defendants intended to remit was unfair and deceptive and actionable under SCUTPA despite the consumers' "close connection" with the defendants and

"the fact that the [consumer] victims could have protected themselves." *State of South Carolina v. Eli Lilly & Co., Inc.*, Case No. 2007-CP-1855, at *27-28 (S.C. Ct. Com. Pl. Sept. 22, 2009) (citing *City of Charleston v. Hotels.com, LP*, 520 F. Supp. 2d 757, 775 (D.S.C. 2007

Without a requirement that the State proffer reliance and causation evidence and because any such evidence that would be used by Janssen to disprove reliance or causation is irrelevant to its liability under the SCUTPA claim, the admittance of the anecdotal testimony of Risperdal prescribers at trial would add nothing probative to the determination of this case by the trier of fact, would lead to confusion of the issues and would likely mislead the trier of fact in reaching case-determinative conclusions.

By its protracted deposition discovery of Risperdal prescribers, Janssen has nevertheless sought to cultivate evidence to refute claims that stem from theories of recovery the State no longer asserts. Janssen's consistent inability to identify any legitimate basis for the use of the testimony at trial is a tacit acknowledgment of the utter futility and lack of probative value of such testimony. But, Janssen still intends to seek admission of such testimony to undermine the (now abandoned) theory that any individual physician prescribed Risperdal for a medically unnecessary purpose, and particularly that such a prescription was induced by Janssen's conduct. Additionally, Janssen seeks to admit wholly anecdotal testimony from South Carolina prescribers that they "like" Risperdal, they consider it a "good drug," and they prescribe it to their patients. Thus, Janssen seeks to invoke a learned intermediary defense to the State's claims similar to that which was rejected by this Court in *Lilly*. *See State of South Carolina*, Case No. 2007-CP-1855, at *32-34 (denying Lilly's motion for summary judgment on State's failure to prove causation where "Lilly argue[d] that the learned intermediary doctrine breaks the causal chain of proof"). As in *Lilly*, the State's claim is not one involving the manufacturer's failure to provide an

adequate warning to a particular prescribing physician who relied on the information provided or would have changed his or her prescribing decision if he or she had known the information omitted, and thus the claim cannot be defended on those grounds. And, distinct from even *Lilly*, the State asserts no claims for common law fraud, nor does it seek to recover actual damages under any fraud-based statute and, therefore, evidence of prescribing decisions is entirely irrelevant.

Further, the fact that each prescription was tainted with misrepresentations and omissions has nothing to do with the physicians' conduct, as it was *Janssen's omissions* regarding the safety and efficacy of Risperdal to the individuals who filled Risperdal prescriptions that constituted the actionable "method, act or practice" under SCUPTA—*not the writing of the prescription or any other conduct by the prescriber.* Janssen's attempt to establish a direct representation or reliance gloss on SCUPTA by admittance of this testimony is untenable and should be rejected by the Court.

Because the causal chain is uninterrupted and unaffected by the learned intermediary doctrine, including any anecdotal testimony by Janssen's selected prescriber witnesses, Janssen should be precluded from introducing such testimony at trial.

C. The Testimony is Unfairly Prejudicial and Its Admittance Will Result in Confusion and Mislead the Trier of Fact.

The testimony Janssen seeks to introduce at trial is unfairly prejudicial. Because it lacks relevance, its admittance will lead to confusion of the issues and mislead the trier of fact. *See* S.C. R. Evid. 402, 403. More specifically, and for the reasons outlined above, this testimony will likely lead to confusion of the issues and mislead the trier of fact in determining the burden the State must meet in showing a violation of SCUTPA. For the additional reason that the testimony is largely cumulative and unreliable, as the State and the Court expected, its admittance would be

unfairly prejudicial to the State. *See Wright v. Craft*, 640 S.E.2d 486, 504 (S.C. Ct. App. 2006) (in SCUTPA case, trial court did not abuse its discretion in refusing to admit cumulative evidence to avoid prejudice and waste of time). (*See* Tr. of Hr'g, May 4, 2009, at 45:23-25, 46:2-4; 46:11 (Court: "it would seem to me that . . . 150 depositions of similarly situated practitioners, about one particular drug might be cumulative").)

"Generally, there is no abuse of discretion where the excluded testimony is merely cumulative of other evidence proffered to the [trier of fact]." Commerce *Ctr. of Greenville, Inc. v. W. Powers McElveen & Assocs., Inc.*, 556 S.E.2d 718, 726 (S.C. Ct. App. 2001) (citing *Ott v. Pittman*, 463 S.E.2d 101, 105 (S.C. Ct. App. 1995) (affirming trial court's decision to exclude witness's testimony which the Court of Appeals characterized as "cumulative to that of other witnesses")). Particularly where "such evidence [is] arguably irrelevant under Rule 403," the exclusion of cumulative testimony is warranted. *Henderson v. Allied Signal, Inc.*, 644 S.E.2d 724, 727 (S.C. 2007). And even if such testimony were erroneously excluded, "there is no reversible error where the testimony would have been cumulative." *South Carolina Dept. of Highways & Public Transp. v. Galbreath*, 431 S.E.2d 625, 628 (S.C. Ct. App. 1993); see *Patterson v. I.H. Servs., Inc.*, 368 S.E.2d 215, 220 (S.C. Ct. App. 1998) (even if the trial court erred in excluding testimony, "its exclusion was harmless and affords no basis for reversal," because the testimony was cumulative to other testimony)).

Janssen has elicited from each of its selected Risperdal prescribers testimony regarding, *inter alia*, Risperdal's safety and efficacy profile, including its comparative safety and efficacy with other atypicals and typical antipsychotics as perceived by these particular prescribers; the prescribers' opinions regarding off-label use of prescription drugs, including Risperdal, and their propensity to write prescriptions for off-label use; whether Janssen engaged in off-label

marketing of Risperdal to these particular prescribers; and, whether these particular prescribers were influenced by Janssen's sales force in their prescribing decisions. In addition to being irrelevant for the reasons described herein, the testimony elicited is repetitive and otherwise cumulative and its admittance would unfairly prejudice the State. Importantly, the prejudice is ***not cured*** by ***limiting the number*** of physicians who may testify, because the irrelevance to the State's claim or Janssen's defenses, as discussed above, and the potential to confuse the issues before the trier of fact still remains.

Lastly, because the testimony was derived from Janssen's own selection of prescribers, the testimony is not only irrelevant but highly unreliable. Janssen was not required to disclose its mechanism for selection of prescriber witnesses, nor was it required to make a scientifically-reliable random selection among South Carolina physicians. Janssen has made no showing that its "sampling" of prescriber testimony can be presented at trial in any reliable manner, as it must. Janssen's use of Medicaid data to identify physicians who may have been seemingly more favorable witnesses, such as those who prescribe Risperdal more frequently or those who prescribe Risperdal, or have prescribed, to adults and strictly for on-label uses, would not produce a random or statistically significant sample, but instead cherry-picked, unreliable testimony. For that additional reason, the admittance of such testimony would unfairly prejudice the State, and it should, therefore, be excluded.

IV.
RELIEF

For the foregoing reasons, the State's Motion to Exclude the Testimony of Certain Risperdal Prescribers at Trial should be granted, and Defendant should be precluded from offering the above-referenced testimony in its entirety.

Respectfully submitted,

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July 2, 2010

Attorneys for the State of South Carolina

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STATE OF SOUTH CAROLINA COUNTY OF SPARTANBURG	)	IN THE COURT OF COMMON PLEAS FOR THE SEVENTH JUDICIAL CIRCUIT
STATE OF SOUTH CAROLINA ex rel. Henry McMaster, in his capacity as Attorney General of the State of South Carolina, Plaintiff, v. JANSSEN PHARMACEUTICA, INC., JANSSEN, L.P. and JOHNSON & JOHNSON, INC., Defendants.	)	Civil Action No. 2007-CP-42-1438 **DEFENDANTS' NOTICE OF MOTION AND MOTION *IN LIMINE* TO PRECLUDE THE INTRODUCTION INTO EVIDENCE OF THE APRIL 19, 2004 DDMAC LETTER AND ANY EVIDENCE OF OR REFERENCE TO THE LETTER AT TRIAL**

TO: JOHN B. WHITE, JOHN S. SIMMONS, AND FLETCHER V. TRAMMELL, ATTORNEYS FOR PLAINTIFF

Defendants, Ortho-McNeil-Janssen Pharmaceuticals, Inc. and Johnson & Johnson (erroneously named as Johnson & Johnson, Inc.), by and through their undersigned counsel, hereby move the Court for entry of an Order precluding Plaintiff, the State of South Carolina, from introducing into evidence the April 19, 2004 DDMAC letter involving Risperdal®, or any evidence of or references to the letter at trial. Such evidence is inadmissible hearsay and, in any event, unfairly prejudicial.

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WHEREFORE, for the reasons stated herein and in the accompanying Memorandum of Law, the Court should grant Defendants' Motion in its entirety.

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January 7, 2011

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STATE OF SOUTH CAROLINA COUNTY OF SPARTANBURG	IN THE COURT OF COMMON PLEAS FOR THE SEVENTH JUDICIAL CIRCUIT
STATE OF SOUTH CAROLINA ex rel. Henry McMaster, in his capacity as Attorney General of the State of South Carolina, Plaintiff, v. JANSSEN PHARMACEUTICA, INC., JANSSEN, L.P. and JOHNSON & JOHNSON, INC., Defendants.	Civil Action No. 2007-CP-42-1438 **MEMORANDUM OF LAW IN SUPPORT OF DEFENDANTS' MOTION *IN LIMINE* TO PRECLUDE THE INTRODUCTION INTO EVIDENCE OF THE APRIL 19, 2004 DDMAC LETTER AND ANY EVIDENCE OF OR REFERENCE TO THE LETTER AT TRIAL**

Defendants Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Janssen") and Johnson & Johnson (erroneously named as Johnson & Johnson, Inc.), by and through their undersigned counsel, hereby respectfully submit this Memorandum of Law in Support of Defendants' Motion *in Limine* to Preclude the Introduction Into Evidence Of The April 19, 2004 DDMAC Letter And Any Evidence Of Or Reference To The Letter At Trial.

I. INTRODUCTION

After several amendments and the abandonment of multiple claims, Plaintiff, the State of South Carolina ("Plaintiff") now pursues a single claim – that Defendants are in violation of the South Carolina Unfair Trade Practices Act ("SCUTPA"). As part of its sole remaining claim, Plaintiff seeks a civil penalty of five thousand dollars for every copy of a November 10, 2003 mailing involving Risperdal® that was disseminated to South Carolina physicians. *See* Nov. 10, 2003 mailing to healthcare professionals (Ex.

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A). Plaintiff alleges that the November 10, 2003 mailing violated SCUTPA because, it contends, the mailing was likely to deceive South Carolina physicians.

On April 19, 2004, the Division of Drug Marketing, Advertising, and Communication ("DDMAC"), a division of the U.S. Food and Drug Administration ("FDA") responsible for reviewing prescription drug advertising and promotional labeling, sent a warning letter to Janssen concerning the November 10, 2003 mailing. *See* April 19, 2004 letter from Thomas W. Abrams to Dr. Ajit Shetty (the "April 19, 2004 DDMAC letter") (Ex. B). The April 19, 2004 DDMAC letter stated that the November 10, 2003 mailing was "false or misleading in violation of Sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act ..." *Id.* at 1. This Court should exclude the April 19, 2004 DDMAC letter from evidence - and should preclude any evidence of or reference to the letter – because the letter is inadmissible hearsay for which there is no recognized exception under South Carolina law.

II. ARGUMENT AND AUTHORITIES

A. Hearsay and Other Evidentiary Issues.

The admission or exclusion of evidence is within the sound discretion of the trial court, and absent an abuse of discretion, the trial court's ruling will not be reversed. *See, e.g., Jamison v. Ford Motor Co.*, 373 S.C. 248, 268, 644 S.E.2d 755, 765 (S.C. Ct. App. 2007). As a general matter, hearsay is inadmissible at trial unless a particular exception applies. *See* Rule 802, SCRE. Hearsay is any "statement, other than one made by the declarant while testifying at the trial or hearing, offered in evidence to prove the truth of the matter asserted." Rule 801(c), SCRE.

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South Carolina courts exclude as inadmissible hearsay letters and reports that are offered for the truth of the matters asserted. *See, e.g., Fesmire v. Digh*, 385 S.C. 296, 309-10, 683 S.E.2d 803, 810 (Ct. App. 2009) (reversing trial court and finding prejudicial error where trial court admitted letters offered for the truth of the matter asserted; letters were inadmissible hearsay); *Menne v. Keowee Key Prop. Owners' Ass'n*, 629 S.E.2d 690 (Ct. App. 2006) (affirming trial court's decision to exclude letters as inadmissible hearsay). Such letters and reports raise fundamental concerns about the reliability of the evidence where the submitting party does not present the author as a witness at trial, thus preventing the opposing party from questioning the author at trial about his knowledge or motivations. *See, e.g., Stevenson v. Emerson Elec. Corp.*, 286 S.C. 331, 335, 333 S.E.2d 355, 357-58 (Ct. App. 1985) ("[w]ritten reports of investigations made by persons not offered as witnesses are inadmissible as hearsay"). For example, in *Culbreath v. Investors Syndicate*, 203 S.C. 213, 26 S.E.2d 809 (1943), the Supreme Court of South Carolina affirmed the trial court's order denying admission of certain letters as evidence. The court explained:

> [These letters] would have subjected [the defendant] to a possible verdict against him on the strength of the information contained in the letters without any opportunity on his part to examine the writers of the letters, and to have these letters explained in the light of the financial facts which existed in 1938, when the transaction now in question occurred. These letters are hearsay testimony and come within none of the exceptions to the hearsay rule.

203 S.C. 213, 26 S.E.2d at 813.

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There are exceptions to the hearsay rule, including a relatively narrow public records and reports exception. *See* Rule 803(8), SCRE. That exception permits admission of "[r]ecords, reports, statements, or data compilations, in any form, of public

offices or agencies, setting forth . . . matters observed pursuant to duty imposed by law as to which matters there was a duty to report . . . *provided, however*, that investigative notes involving opinions, judgments, or conclusions are not admissible." Rule 803(8), SCRE (emphasis in original). By its terms, records or reports that contain "opinions, judgments, or conclusions," are ineligible for the exception and, therefore, remain inadmissible hearsay. *Id.* Based on this limitation, the Supreme Court of South Carolina affirmed a trial court's decision to exclude a bankruptcy report which "contain[ed] a great deal of investigative opinions, legal analysis, and potential conclusions." *State v. Morris*, 376 S.C. 189, 207, 656 S.E.2d 359, 368-69 (2008) (footnotes omitted).

Even if a document were to fall within an exception to the hearsay rule, a trial court may exclude it if its probative value is "substantially outweighed by the danger of unfair prejudice, confusion of the issues, or misleading the jury." Rule 403, SCRE; *see also Jamison v. Ford Motor Co.*, 373 S.C. 248, 269, 644 S.E.2d 755, 766 (S.C. Ct. App. 2007) (affirming trial court's decision to exclude evidence where prejudice outweighed any probative value). Unfair prejudice "means an undue tendency to suggest decision on an improper basis[.]" *State v. Alexander*, 303 S.C. 377, 382, 401 S.E.2d 146, 149 (1991) (quoting Fed. R. Evid. 403 cmt.).

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B. <u>The April 19, 2004 DDMAC Letter Is Inadmissible Hearsay; For That Reason And To Avoid Unfair Prejudice, The Court Should Not Admit The Letter Into Evidence Or Allow Any Reference To It</u>.

The Court should exclude the April 19, 2004 DDMAC letter, and prohibit any evidence of or reference to it at trial. First, the April 19, 2004 DDMAC letter itself is classic hearsay. It is an out-of-court statement by an FDA employee that Plaintiff will

offer to prove the truth of the matter asserted – that Janssen's November 10, 2003 mailing was "false or misleading." *See* Rule 801(c), SCRE; *see also* Second Am. Compl. ¶¶ 46-48 (alleging "Janssen's November [10, 2003] letter was chastised by the FDA for being brazenly 'false' and 'misleading'" and asserting SCUTPA claim based on letter). The State is not offering the author of the April 19, 2004 DDMAC letter as a witness at trial. Thus, if the April 19, 2004 DDMAC letter were to be admitted as evidence, Defendants could not question the author about his statements or motivations for making them. Defendants also could not question the author about the facts available to him in early 2004 that might have influenced his statements. Without an opportunity to cross-examine the author, the April 19, 2004 DDMAC letter necessarily raises the fundamental issues of reliability that are the very reason courts exclude hearsay evidence. *See Culbreath*, 203 S.C. 213, 26 S.E.2d at 813; *Stevenson*, 286 S.C. at 335, 333 S.E.2d at 357-58.

Second, there are no applicable hearsay exceptions which would allow admission of the April 19, 2004 DDMAC letter. The only possible hearsay exception – the public records and reports exception – does not apply because the letter contains the author's "opinions, judgments, and conclusions." *See* Rule 803(8); *Morris*, 376 S.C. at 207, 656 S.E.2d at 368-69 (affirming trial court's decision to exclude bankruptcy officer's report which "contain[ed] a great deal of investigative opinions, legal analysis, and potential conclusions"). For example, the author draws the legal conclusion that the November 10, 2003 mailing is "false or misleading in violation of Sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act[.]" Ex. B at 1. He expresses the opinions that the November 10, 2003 mailing "fails to communicate" certain safety

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information and that it "minimizes risks of Risperdal." *Id.* at 3. The author also contends that the eight epidemiological studies cited in the November 10, 2003 mailing "do not represent the weight of the pertinent scientific evidence." *Id.* Such opinions and conclusions fall outside the public records and reports exception to the hearsay rule. *See* Rule 803(8), SCRE; *see also Morris*, 376 S.C. at 207, 656 S.E.2d at 368-69. The April 19, 2004 DDMAC letter, therefore, is inadmissible hearsay to which no exception applies.

Third, the April 19, 2004 DDMAC letter, and any evidence of or reference to the April 19, 2004 DDMAC letter, should be excluded because exposure of the jury to the letter would unfairly prejudice Defendants. *See* Rule 403, SCRE. The April 19, 2004 DDMAC letter contains an FDA employee's application and analysis of highly technical federal regulations, implementing a sophisticated and complicated regulatory scheme. As an initial, and very important, matter, the FDA regulations governing prescription drug promotion attach a particular meaning to the phrases "false", "misleading", and "lacking in fair balance." *See, e.g.*, 21 U.S.C. §§ 321(n), 352(a); 21 C.F.R. §§ 201.1 et seq., 202.1 et seq. Under those regulations, some statements may be characterized as "false or misleading" even if they are, in fact, true. What is "false or misleading" for purposes of FDA regulation, then, is not necessarily "deceptive" for purposes of SCUTPA. *See* S.C. Code Ann. § 39-5-20(a) (addressing "deceptive acts or practices"). Without extensive expert testimony regarding the applicable regulations, a jury might improperly confuse DDMAC's "false or misleading" language with SCUTPA's "deceptive acts" language. *See Alexander*, 303 S.C. at 382, 401 S.E.2d at 149 (unfair prejudice "means an undue tendency to suggest decision on an improper basis").

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Equally important, a DDMAC warning letter – such as the April 19, 2004 DDMAC letter – is not a final agency action. *See* Chapter 4 FDA *Regulatory Procedures Manual: Advisory Actions* at 2 (2010) (Ex. C). Rather, the April 19, 2004 DDMAC letter is an "informal and advisory" letter that merely "communicates the agency's position on a matter." *Id.* It "does not commit FDA to tak[e] enforcement action" and does not prove actual wrongdoing. *Id.* A jury, however, might erroneously construe the language in the April 19, 2004 DDMAC letter as something other than an "informal and advisory" communication from the FDA. The April 19, 2004 DDMAC letter therefore poses a significant risk of conveying the *appearance* of wrongdoing and confusing a jury about the applicable standards of liability. Such a result would severely prejudice Defendants. *See Alexander*, 303 S.C. at 382, 401 S.E.2d at 149 (defining unfair prejudice as "an undue tendency to suggest decision on an improper basis"). As such, the April 19, 2004 DDMAC letter should not be admitted into evidence, and the Court should bar any evidence of or reference to the letter at trial.

III. CONCLUSION

For all the foregoing reasons, Defendants respectfully request that the Court exclude the April 19, 2004 DDMAC letter, and enter an order precluding any reference to the letter at trial.

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ATTORNEYS FOR DEFENDANTS

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EXHIBIT A

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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 research[1-6] suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

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

Sincerely,

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

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1125 TRENTON-HARBOURTON ROAD
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TITUSVILLE, NEW JERSEY 08560-0200
(609) 730-2000
US.JANSSEN.COM

References:

1. Buse JB, Cavazzoni 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):1158-1171.

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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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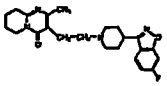
RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION

RISPERDAL® M-TAB™
(RISPERIDONE)
ORALLY DISINTEGRATING TABLETS

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL® M-TAB™ Orally Disintegrating Tablets are available in 0.5 mg, 1.0 mg, and 2.0 mg strengths and are light coral in color.

RISPERDAL® M-TAB™ Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (KI of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H$_1$ histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (KI of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (KI of 620 to 800 nM) for the dopamine D$_1$ and haloperidol-sensitive sigma sites, and no affinity (when tested at concentrations >10^{-4} M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Pharmacokinetic studies showed that RISPERDAL® M-TAB™ Orally Disintegrating Tablets are bioequivalent to RISPERDAL® Tablets.

Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 µg/mL), warfarin (10 µg/mL), and carbamazepine (10 µg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through *N*-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug (i.e., the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions (see Drug Interactions under PRECAUTIONS). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of ^{14}C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of the active moiety, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Special Populations

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly

In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (see DOSAGE AND ADMINISTRATION).

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

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® to doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (> 20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

INDICATIONS AND USAGE

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6 to 8 weeks) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia and Diabetes Mellitus

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

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

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

PRECAUTIONS

General

Orthostatic Hypotension

RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2-3 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% (8/2607) of RISPERDAL®-treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia

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

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

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

Priapism

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

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic Effect

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

Body Temperature Regulation

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

Suicide

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

Use in Patients With Concomitant Illness

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

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

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

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

Orthostatic Hypotension

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

Interference With Cognitive and Motor Performance

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

Pregnancy

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

Nursing

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

Concomitant Medication

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

Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL®.

Phenylketonurics

Phenylalanine is a component of aspartame. Each 2 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.56 mg phenylalanine; each 1 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

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

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

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

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

Carbamazepine and Other Enzyme Inducers

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

Fluoxetine

Fluoxetine (20 mg QD) has been shown to increase the plasma concentration of risperidone 2.5-2.8 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 RISPERDAL®. 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 (n=13).

Valproate

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone.

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, MP, 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, 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 (or 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m² (mg/kg)	
			Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6 (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 (MRHD) on a mg/m² basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the MRHD on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C

The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m² basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m² basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m² basis. In three reproductive studies in rats (two Segment II and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

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

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regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m² basis.

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

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

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

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

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

ADVERSE REACTIONS

Associated With Discontinuation of Treatment

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in Phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.5% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL®-related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients, but 3.6% in active-control patients in the Phase 2-3 trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials

In two 6 to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events occurred at an incidence of at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

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 non-drug factors to the side effect incidence rate in the population studied.

Table 1 Incidence of Treatment-Emergent Adverse Events in 6 to 8-Week Controlled Clinical Trials[1]

Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric			
Insomnia	28%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Central & peripheral nervous system			
Extrapyramidal symptoms[2]	17%	34%	15%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory system			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a whole - general			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%

Table 1 (continued) Incidence of Treatment-Emergent Adverse Events in 6 to 8-Week Controlled Clinical Trials[1]

Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see DOSE DEPENDENCY OF ADVERSE EVENTS).

Dose Dependency of Adverse Events

Extrapyramidal Symptoms

Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

Vital Sign Changes

RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Changes

The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6 to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (8%).

Laboratory Changes

A between-group comparison for 6 to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Changes

Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute).

Other Events Observed During the Premarketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® (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-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included, except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders

Frequent: increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders

Frequent: increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma; migraine, hyperreflexia, choreoathetosis.

Gastrointestinal Disorders

Frequent: anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena; dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders

Frequent: fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders

Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

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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 ichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders
Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders
Infrequent: abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders
Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders
Frequent: polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-Skeletal System Disorders
Infrequent: myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female
Frequent: menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders
Infrequent: increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithesis, 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 clinical reports.

Postintroduction Reports
Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, hyperglycemia, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class
RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychologic Dependence
RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience
Premarketing experience included eight reports of acute RISPERDAL® (risperidone) overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® overdose, include torsade de pointes, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage
In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Because of the rapid disintegration of risperidone orally disintegrating tablets, pill fragments may not appear in gastric contents obtained with lavage.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose
RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL®; however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 8 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Pediatric Use
Safety and effectiveness of RISPERDAL® 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 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.

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 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 an appropriate dose.

Reinitiation of Treatment in Patients Previously Discontinued
Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

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

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

RISPERDAL® M-TAB™ (risperidone) Orally Disintegrating Tablets are etched on one side with R0.5, R1, and R2, respectively, and are packaged in blister packs of 4 (2 X 2) tablets.

0.5 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-395-28, bingo card of 30 tablets NDC 50458-395-30.

1 mg light coral, square, biconvex tablets: 7 blister packages per box, NDC 50458-315-28, bingo card of 30 tablets NDC 50458-315-30.

2 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-325-28.

Storage and Handling
RISPERDAL® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.
Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.
Keep out of reach of children.

RISPERDAL® M-TAB™ Orally Disintegrating Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F).
Keep out of reach of children.

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US Patent 4,804,663
Revised October 2003
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RISPERDAL® tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico or
Janssen-Cilag, SpA, Latina, Italy

RISPERDAL® oral solution is manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium

RISPERDAL® M-TAB™ Orally Disintegrating Tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico

RISPERDAL® tablets, RISPERDAL® M-TAB™ Orally Disintegrating Tablets, and oral solution are distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

JANSSEN PHARMACEUTICA PRODUCTS, L.P.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Exhibit
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TRANSMITTED BY FACSIMILE

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

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

WARNING LETTER

Dear Dr. Shetty:

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

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Background

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

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

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

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

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

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

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Omission of Material Information

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

Minimization of Risks/Misleading Comparative Claim

The DHCP letter states:

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

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

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

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

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

Failure to Submit Post-Marketing Reports

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

Conclusions and Requested Actions

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

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

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

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

Sincerely,

{See appended electronic signature page}

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

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

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Chapter 4
ADVISORY ACTIONS

This chapter defines and establishes uniform guidance and procedures for Warning Letters and Untitled Letters.

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4-1 WARNING LETTERS

4-1-1 Warning Letter Procedures

When it is consistent with the public protection responsibilities of the agency and depending 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

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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; and,

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 is adulterated under Section 402(a)(3) or 402(a)(4) of the Act;
2. There is a violation of CGMP;
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 establishments should be held to the same standards as nongovernment 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 nongovernment 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 government establishment'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.

Whenever significant violations are observed at a government establishment, or if attempts to achieve compliance have been ineffective, the district (or center) should arrange a meeting with OE, OCC, and the relevant center to determine a strategy to achieve timely and effective compliance. The meeting should include ORO/DFSR if the government establishment is a state or local 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.

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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 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. Warning Letters may also be generated through work done at agency headquarters (ORA or centers), processed under appropriate procedures and issued under the authority of a division or office director. (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.)

1. ***General Considerations:***
   In determining whether to issue a Warning Letter, district directors and center or other officials with authority to issue should consider whether:

   a. 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 agency consideration of an enforcement action;

   b. The violation(s) are determined to be of regulatory significance, and the issuance of a Warning Letter is appropriate and consistent with agency policy, as described in Compliance Policy Guides or elsewhere; and,

   c. There is a reasonable expectation that the responsible firm and persons will take prompt corrective action.

2. ***Ongoing or Promised Corrective Actions***
   Corrective action may be undertaken or promised during an establishment inspection or addressed in correspondence to the agency after an inspection. Ongoing or promised corrective actions generally do not preclude the issuance of a Warning Letter. In addition to being the agency's primary means to achieve prompt, voluntary compliance, Warning Letters remain a primary means to establish prior notice (see Chapter 10) and serve to ensure that the seriousness and scope of the observed violations are understood by top management and that the appropriate resources are allocated to fully correct the violations and to prevent recurrence.

   When a firm is in the process of correcting the violations or has made a written promise to take prompt corrective action, a district or center should consider the following factors when determining whether or not to issue a Warning Letter:

   a. The firm's compliance history, e.g., a history of serious violations, or failure to prevent the recurrence of violations;

   b. The nature of the violation, e.g., a violation that the firm was aware of (was evident or discovered) but failed to correct;

   c. The risk associated with the product and the impact of the violations on such risk;

   d. The overall adequacy of the firm's corrective action and whether the corrective action addresses the specific violations, related violations, related products or facilities, and

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contains provisions for monitoring and review to ensure effectiveness and prevent recurrence;

e. Whether documentation of the corrective action was provided to enable the agency to undertake an informed evaluation;

f. Whether the timeframe for the corrective action is appropriate and whether actual progress has been made in accordance with the timeframe; and,

g. Whether the corrective action taken ensures sustained compliance with the law or regulations. In the case of Warning Letters being considered for products offered for sale through internet web sites, corrective action to remove claims or inactivate the website is easily reversible, and should be carefully considered, along with the other factors above, in determining whether or not to issue a Warning Letter. Warning Letters for, or involving, internet web sites should be issued in as close proximity as possible to the time when the claims were last observed, and reference to the date on which the claims were observed should be included in the letter.

If a decision is made not to issue a Warning Letter, see "Response Letter" below. Relying on a firm's promised corrective actions does not preclude consideration of regulatory action should we later observe that the same or similar violations have not been corrected.

3. ***Completed Corrective Actions***
As a general rule, a Warning Letter should not be issued if the agency concludes that a firm's corrective actions are adequate and that the violations that would have supported the letter have been corrected. If you believe that an exception is necessary due to the facts or circumstances of the case (e.g., the firm's compliance history, the nature of the violation, or the risk associated with the product) discuss this background in the Warning Letter referral package and be sure to adapt the language in the proposed letter to fit the circumstances (e.g., recite the history and the consequences if there is a recurrence).

If a decision is made not to issue a Warning Letter, see "Response Letter" below. Relying on a firm's completed corrective actions does not preclude consideration of regulatory action should we later observe that the same or similar violations have not been corrected.

4. ***Response Letter***
If a decision is made to not issue a Warning Letter because adequate corrective action has been taken, or because corrective action is being taken or has been promised, it is recommended that an alternative form of communication (e.g., a response letter to the firm's letter promising corrective action) be issued to the responsible individuals at the firm to supplement the record of the violation(s) and reflect the agency's decision to rely on the firm's actions and/or promises. The response letter should indicate that the agency is relying on the firm's corrections or commitment regarding corrective actions. Further, the letter may include a statement that should we later observe that these or similar violations have not been corrected; regulatory action (e.g., seizure, injunction and, if appropriate, civil penalties) may be taken without further notice.

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5. ***Verification of Corrective Actions***
   Verification of the overall completeness and effectiveness of the corrective action should be undertaken during the next inspection, the timing of which may be expedited or routine as determined by the issuing office.

4-1-4 Center Concurrence And Letters Issued By Centers

Center concurrence is required prior to issuing Warning Letters in the areas listed below, 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.

1. ***All Centers***

   a. All labeling violations - except where specific guidance has been provided, e.g., Compliance Programs, Compliance Policy Guides, and Drug Health Fraud Bulletins;

   b. Computer application and software violations;

   c. Bioresearch Monitoring Program violations; and

   d. Product advertising violations.

   Note: Only centers issue Warning Letters for violations associated with product advertising, OTC drug monographs, and the Bioresearch Monitoring Program.

2. ***Center For Drug Evaluation And Research (CDER)***

   a. New drug charges - including unapproved changes in processes or formulations and recommendations to withhold approvals of applications or supplements;

   b. Adverse drug experience reporting violations;

   c. Novel and unusual tamper-evident packaging violations;

   d. Prescription Drug Marketing Act violations;

   e. Investigational drug use violations;

   f. CGMP charges involving active pharmaceutical ingredients and other drug component manufacturing deficiencies;

   g. CGMP charges involving all dosage forms, including medical gases;

   h. CGMP charges involving inspections of facilities for therapeutic biologic products regulated by CDER; and

   i. Pharmacy compounding issues.

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The Compliance Management System (CMS) is now being used for electronic submission of Warning Letter recommendations from district offices. All recommendations by the district offices must use CMS for submitting the proposed Warning Letter, the FDA 483 supporting alleged violations, the EIR, and any written response by the firm. For any questions, or if you need to submit a document as a hardcopy, the CDER contact is: Branch Chief, Domestic Case Management and Guidance Branch, HFD-326, voice 301-796-3281, fax 301-847-8741.

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.

3. ***Center For Biologics Evaluation And Research (CBER)***

   a. Donor re-entry violations (e.g., HBsAg, anti-HIV-1);

   b. Violations relating to drug CGMP*;

   c. Violative inspections of federal government agencies;

   d. Violative inspections of Team Biologics (Core Team) facilities for biologic products regulated by CBER;

   e. Viral marker test run deficiencies** (See below);

   f. Violations in areas where specific guidance has not been provided*** (See below);

   g. Violations relating to HIV and HCV lookback; and

   h. Violative inspections of manufacturers of human cell, tissue, and cellular and tissue-based products (HCT/Ps).

*CGMP regulations in Part 211 and blood establishments: CBER concurrence is required for Warning Letters involving deviations from Part 211 that are not associated with provisions in Part 606, such as 21 CFR 211.68(b) or 211.113.

**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: 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.

4. ***Center For Devices And Radiological Health (CDRH)***

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a. All 21 U.S.C. 352(j) danger to health violations;

b. Medical device reporting violations which cite failure to report malfunctions as defined in 21 CFR 803.3(n). Center medical and technical expertise is necessary for these evaluations;

c. Restricted device violations;

d. Radiation Control for Health and Safety Act violations - except for sunlamp products and x-ray assemblers;

e. Violation of requirements for post market surveillance studies;

f. Any violation of device tracking regulations other than failure of the firm to implement any form of a tracking system;

g. All suspected violations of the user reporting regulations;

h. Failure to submit a premarket notification (510(k)) or Premarket Approval (PMA) Application;

i. 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;

j. All violations arising from pre-approval PMA inspections including supplements to a previously approved PMA application; and,

k. Mammography Quality Standards Act (MQSA) violations in the following situations, unless superseded by a relevant Compliance Program or other directive:

   i. 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

   ii. 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.

5. ***Center For Veterinary Medicine (CVM)***

   a. Product approval violations;

   b. Tissue residue violations involving meat and poultry where no tolerance has been established, extra-label use is documented, and/or those which involve the use of compounded drugs or other drug adulteration;

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c. Tissue residue violations involving aquacultured seafood, and other animal-derived products;

d. Feed contaminant violations where no tolerance has been established;

e. Adverse drug reaction reporting violations;

f. Low acid canned pet food violations requiring technical review; and,

g. 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).

Districts should ***only*** submit recommendations, coupled with their supporting evidence, using the Compliance Management System (CMS), an electronic case submission system. This system is available from the IT Applications page on FDA's intranet site.

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.

6. ***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:

a. Pesticide and chemical contamination violations not covered by direct reference authority;

b. Dietary supplements, medical foods, and infant formulas;

c. Low acid and acidified canned foods (LACF) violations;

d. Food and color additive violations;

e. Seafood HACCP violations not covered by direct reference authority in the Compliance Program;

f. All situations involving violations of section 402 (a) (4) of the Act, including deviations from CGMP regulations for foods, low acid and acidified canned foods, bottled water and any other CGMP regulation concerning CFSAN issues, e.g., dietary supplements;.

g. Mycotoxins;

h. Animal drugs in foods (aquaculture chemotherapeutic agents);

i. Food standards; and

j. Cosmetics.

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Districts should ***only*** submit recommendations, coupled with their supporting evidence, to CFSAN via the Compliance Management System (CMS), an electronic case submission system. This system is available from the IT Applications page on FDA's intranet site.

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.

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. 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

For issues in a Warning Letter that require review by more than one center, a designation of "lead center" should be made at the earliest possible opportunity. This is necessary to ensure a timely and appropriately coordinated review process. The lead center is responsible for communication with the other involved center(s), the district, and OCC. The lead center is responsible for shepherding the Warning Letter through the review process, including the review and incorporation of comments as appropriate from the other involved entities.

For issues in a Warning Letter that require review by more than one center, the district should, prior to submission of the recommendation, communicate with each center and identify which center will serve as the lead. The recommendation should identify the lead center and the other involved center(s). The recommendation should be sent electronically via CMS to the lead center, and the lead center will create a consult task to the other reviewing center(s). The centers should conduct concurrent (not sequential) reviews.

If the district did not identify the need for multiple reviews prior to submission of the recommendation, the center receiving the recommendation should communicate with the district and the other involved center(s) to appropriately designate the lead center. The district should then promptly send a copy of the recommendation to the other involved center(s).

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, HFC-230, and HFC-240. If the Warning Letter is approved, the center will forward its

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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.

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 Warning Letter contains violations that by their nature are not correctable, then no close-out letter will issue.

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. Usually, the standard for verifying that corrections have been implemented will be a follow-up inspection. Follow-up inspections should be conducted promptly after the agreed upon date of completion of the promised corrections.

1. ***Acknowledgment Of Response To A Warning Letter***

   The district or center that issued the Warning Letter should acknowledge, in writing, receipt of Warning Letter responses. The district or center should save a PDF copy of the issued correspondence under the Final Outcome tab in CMS, identified as doc type = "courtesy acknowledgment correspondence".

2. ***Warning Letter Close-out Letter***

   A Warning Letter close-out letter ("close-out letter") will not be issued based on representations that some action will or has been taken. The corrective actions must actually have been made and verified by FDA.

   The district or center that issued the Warning Letter should issue a close-out letter for Warning Letters issued on or after September 1, 2009, if the violations in the Warning Letter have been adequately addressed, and the following conditions have been met:

   a. The firm replied to the Warning Letter with sufficient information to demonstrate that any listed violations have been adequately corrected; or

   b. A follow-up inspection shows that implementation of the corrective actions was adequate, or, based on other verified, appropriate and reliable information, FDA determines that the follow-up inspection is not needed; and

   c. The follow-up inspection (or other appropriate and reliable information) does not reveal other significant violations.

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The issuing office will evaluate the firm's response to the Warning Letter.

Where the district is the issuing office, the following procedure should be followed prior to issuance of a close-out letter. If the district performs an inspection to verify correction, the district may, but need not, ask the center whether it has a comment or objection prior to issuing a close-out letter. If the district decides not to inspect to verify correction, and the Warning Letter required center concurrence, the district will ask the center, via CMS, whether it has a comment or objection prior to issuing a close-out letter. The center will enter any comments or objections to the issuance of a close-out letter (i.e., FDA's conclusion that the firm's corrective actions are adequate to address the violations contained in the Warning Letter), via the center documents tab in CMS within 30 working days. If the center requests more time, an additional 30 working days should be granted. At the end of the 30 (or 60) working day period, the district will review the center's comments or objections, if any, providing deference to the center in areas of the center's expertise, and, where the center has provided comments or objections, will issue the close-out letter only if consensus is reached with the center.

Districts or centers should issue close-out letters within a total of 65 working days of having the necessary information upon which to make a decision. Use the model "close-out letter" in Exhibit 4-2. The issuing district or center is responsible for ensuring that a PDF copy of the final, signed close-out letter is added into CMS.

A close-out letter does not relieve the recipient from their responsibility for taking all necessary steps to assure sustained compliance with the Act, and all other applicable requirements. If a subsequent inspection reveals problems with the adequacy or sustainability of the corrections that were taken in response to the Warning Letter, such violations would be considered serious. If FDA observes violations during subsequent inspections or through other means, we may take enforcement action without further notice.

The issuing district or center will ensure that FDA posts a notice on http://www.fda.gov/foi/warning.htm when a close-out letter is issued.

3. ***Requests to Post Response on Internet***
The agency policy on posting Warning Letter responses on the internet is found at: http://www.fda.gov/foi/warning.htm

In accordance with this policy, when a recipient of a Warning Letter requests that their response to that Warning Letter be posted on FDA's internet site and provides the response electronically in a word processing format, the agency will post that response. The agency has reserved the right not to post certain responses, such as when posting likely would mislead the public about the safety or efficacy of a regulated product.

The office (district or center) that issued the Warning Letter must redact the response to the extent permitted by the Freedom of Information Act, and send a redacted copy of the response to FDA's Division of Freedom of Information, OMP, and the FOI office will then post the response to the above-referenced website. Submissions should be sent to the attention of Brenda Dorsey.

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4. ***Follow-Up Enforcement***
If a firm has been issued a Warning Letter and has been unable or unwilling to correct the violations, districts and centers should consider further administrative and/or regulatory actions. When considering further action, one factor to evaluate is prior notice (see RPM Chapter 10). This evaluation is particularly relevant for firms operating multiple facilities and producing a variety of products when administrative and/or regulatory action involving more than one location is being considered. Although a second Warning Letter to the same firm should not be issued for the same or similar violations, ensuring prior notice through issuance of a second Warning Letter in some situations may best support the agency's objectives.

In determining whether to issue a second Warning Letter, district directors and center issuing officials should consider whether:

a. The products, processes, and/or significant violations are different, taking into account that systems-based inspectional observations may transcend individual products and processes and may, thereby, provide prior notice without an additional Warning Letter;

b. The responsible individual(s) is (are) different; or,

c. The Warning Letter will support the agency's objectives (e.g., letters sent to different facilities within a corporation to achieve correction of corporate-wide problems).

Whether or not a second Warning Letter is issued, any proposed administrative or regulatory action must be supported by adequate evidence (inspectional or other). The Office of Enforcement (Division of Compliance Management and Operations) and center office of compliance contacts can assist districts in evaluating the evidence, the prior notice, and in developing a regulatory approach when multiple facilities are involved. (Also, see section on Ad hoc Committees in Chapter 10.)

Districts and centers also have the option of conducting a meeting with firm's management prior to pursuing an administrative or regulatory action. Such meetings also serve as further prior notice. (See sections on Prior Notice and Regulatory Meetings in Chapter 10.)

5. ***Inspection Classification***
A Warning Letter constitutes official but not final, 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.

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If an OAI classification is based on tissue residue violations, it is not necessary to conduct a follow-up inspection unless additional violations have been reported to the agency by the Department of Agriculture's Food Safety and Inspection Service, or a follow-up inspection is appropriate for other reasons (e.g., to update evidence prior to initiating an enforcement action).

For further information on classification of inspections see Field Management Directive

No. 86, found on the web at http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm061430.htm.

4-1-9 Firm Profile Updates in FACTS

When a profilable firm (i.e., domestic or foreign drug, biologics, or medical device facility) undergoes a Current Good Manufacturing Practice (CGMP) or Quality System (QS) inspection, the inspected profile classes should be updated by the action office (i.e., the district for domestic inspections or the district and the center for foreign inspections) at each stage in the review process. When a Warning Letter is issued as a result of the inspection, the date and type of letter issued should be entered in the Remarks field for the relevant profile classes, and these profile classes should be changed to *unacceptable.* When a Warning Letter close-out letter is issued, the Final Profile for the relevant profile classes should be changed to *acceptable.* For profile procedures, see IOM Exhibit 5-14 or the DCIQA intranet page.

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. Title: "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. The Warning Letter should be addressed to the highest known official in the corporation that includes the facility that was inspected, and a copy should be sent to the highest known official at the facility that was inspected. If you are requesting a separate response from other officials, include them as addressees. Include a suitable notation (e.g., cc, or copy sent to) in the letter and identify each person by name, title, and, if appropriate, address. Issue the letter to each addressee and each person who is identified as having received a copy of the letter, separately and in accordance with the delivery instructions above.
4. The dates of the inspection and a description of the violative condition, practice, or product in brief but sufficient detail to provide the respondent the opportunity to take corrective action. Include citation of the section of the law and, where applicable, the regulation violated. Cite violations of the law using the appropriate section(s) of both the FD&C Act and the U.S. Code, e.g., Section 501(a)(2)(B) of the Act , 21 U.S.C. 351(a)(2)(B). Cite violations of other laws (e.g., the Public Health Service Act) in the same manner.
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 warning statement that failure to achieve prompt correction may result in enforcement

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action without further notice. Examples of such actions may be cited. Do not include a commitment to take enforcement action.

8. A statement in drug Warning Letters (except those issued to IRBs, clinical investigators, sponsors, and monitors involved in clinical trials) about the implications for the award of federal contracts (see paragraph 13 below). If CGMP violations are cited, a statement regarding the potential impact on requests for approval of export certificates and drug applications (see paragraph 13 below.)

9. A statement in device Warning Letters (except those issued to IRBs, clinical investigators, sponsors, and monitors involved in clinical trials) that: "Federal agencies are advised of all Warning Letters about devices so that they may take this information into account when considering the award of contracts."

   For device Warning Letters that include CGMP violations: "Additionally, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the violations have been corrected. Requests for Certificates to Foreign Governments will not be granted until the violations related to the subject devices have been corrected."

10. Instructions, as appropriate, that the response include:

    a. each step that has been or will be taken to completely correct the current violations and to prevent similar violations;

    b. the time within which correction will be completed;

    c. any reason the corrective action has not been completed within the response time; and,

    d. any documentation necessary to show that correction has been achieved.

11. A designated district or center official to whom the response should be addressed.

12. Issued by the district director, division director, or higher agency official. Some program areas will require center concurrence before issuance.

13. For drug Warning Letters, the information in paragraphs 6-8 and 10, above, should be set forth in closing paragraphs as follows (**bold** type indicates optional/alternative language to be used as appropriate):

    The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist **[at your facility/in connection with your product(s)]**. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to assure that **[you/your firm]** comply**[ies]** with all requirements of federal law and FDA regulations.

    You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. **[If cGMP**

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VIOLATIONS ARE CITED: Additionally, FDA may withhold approval of requests for export certificates, or approval of pending new drug applications listing your facility as a *[supplier or manufacturer]* until the above violations are corrected. A reinspection may be necessary.]

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the time within which you will complete the correction. **[If you no longer manufacture or market ____, your response should so indicate, including the reasons that, and the date on which, you ceased production.]**

4-1-11 Warning Letter Distribution

Warning Letter distribution is as follows:

1. Original – Addressee(s)
2. Copy to each person identified in the Warning Letter
3. Blind copy (bcc) to the following:
    a. FDA-MARCS-Compliance Management System (MARCS-CMS) case file. The final, unredacted signed letter should be added to the MARCS-CMS case file under the Final Outcome tab with the file type identified as PDF VERSION Non-Redacted Issued Violation Letter. Once added, this copy becomes available to the full text DOC search within MARCS-CMS. It also serves as an internal copy for FDA that is available through the system to anyone who may need a copy of the issued letter.
    b. Division of Freedom of Information (DFOI) – For more information, see Section 4-1-13 – Freedom of Information (FOI) and the operating instructions within the FOI User's Guide hyperlink in MARCS-CMS located under the User's Guides/Training hyperlink.
        i. Add a PDF version of the redacted Warning Letter into MARCS-CMS. Adobe Acrobat Pro 8 software with the Adobe 8.1.3 patch, or subsequent versions of Adobe (e.g., Pro 9 or greater) should be used. Patched Adobe Pro 8 utilization will:
            - facilitate FDA compliance with the 1996 Electronic FOI Amendments (EFOIA) for posting frequently requested records, and provide the software tool necessary for identifying the location and the extent of every redaction, as required by EFOI, and the statutory exemption which permits the agency to withhold the redacted materials, as required by the Open Government Act of 2007; and
            - facilitate FDA compliance with section 508 of the Americans with Disabilities Act in creating a 508 compliant PDF.

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c. Local Distribution, factory file, WL file, resident post, and appropriate federal and state agencies.

4. One redacted copy of Warning Letters regarding Dietary Supplements to:

Associate Director
Division of Advertising Practices
Federal Trade Commission
600 Pennsylvania Avenue, N.W.
Washington, D.C. 20580

(Or, send a redacted e-copy to: menqle@ftc.gov)

4-1-12 Warning and Untitled Letters Addressed to Importers, Customs Brokers, and Foreign Firms

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.

Districts should address all Warning Letters to the party responsible for the violation. Therefore, before issuing either a Warning Letter or an Untitled Letter, the issuing office must determine the identity and role of the "responsible party." Districts may make this determination by examining the entry documents or the electronic entry data submitted to FDA's OASIS via CBP's ABI/ACS, or both, or other supporting records. It is particularly important to determine whether the firm identified as the importer-of-record is the actual importer, that is, importing for its own account, or whether the importer-of-record is a customs broker acting as the agent for the actual importer. Generally, customs brokers are merely agents for actual importers and therefore are not the responsible parties to whom districts should address Warning Letters. For more information, see "Customs Brokers" below.

Import Alert #00-17 contains a list of Warning Letters issued to importers.

Contact DIOP, Operations and Policy Branch (HFC-172), at 301-443-6553 for assistance in issuing a Warning or Untitled Letter to an importer, consignee, owner, or broker of imported goods

1. ***Importers***
FDA may issue Warning Letters and Untitled Letters to importers, owners, or consignees of FDA-regulated imports when they engage in practices that violate the Act.

2. ***Customs Brokers***
Generally, it is not appropriate to issue a Warning Letter or Untitled Letter to a customs broker unless that broker also is the owner, consignee, or importer responsible for the imported goods. In cases where a customs broker also is the owner, consignee, or importer, that is, the party initiating the importation, or if the broker has authority over the product through prior arrangement with the importer, it may be appropriate to issue a Warning Letter or Untitled Letter to that broker.

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In all cases, districts should ensure that Warning Letters and Untitled Letters are addressed to the party responsible for the violation.

3. ***Foreign Firms***
A Warning Letter or Untitled Letter may be appropriate if FDA has regulatory authority over the company and is prepared to exercise that authority. Firms may be 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 and Untitled Letters should be discussed with the Office of the Chief Counsel. Authorized FDA officials may issue Warning Letters to foreign producers of FDA-regulated products based on establishment inspections or other information. For CBER regulated products, administrative actions may also be considered for licensed foreign establishments.

4-1-13 Freedom of Information (FOI)

1. ***Internet Posting of Warning Letters***

DFOI will obtain the Redacted Warning Letters using the MARCS-Compliance Management System (MARCS-CMS). When the Action Taken Date (i.e., date on the letter) is entered into MARCS-CMS, an FOI section in the electronic case file for the Warning Letter opens. Identify the district or center FOI officer redacting the letter. After the FOI officer for the issuing district or Center redacts the Warning Letter, add (scan or upload) a redacted PDF version of the letter into MARCS-CMS. ***Do not include "bcc" information, or the "credit page" related to drafting sequence, etc., on the redacted copies.***

MARCS-CMS sends an alert to DFOI that a new, redacted letter is ready for final DFOI review and Internet posting when a redacted violation letter file is added.

For more information, see the operating instructions within the FOI User's Guide hyperlink in MARCS-CMS.

2. ***FOI Requests for Warning Letters***

All FDA-issued Warning Letters (redacted) should be posted on FDA's Warning Letters internet page and thus the public can obtain a copy directly without the need to submit a formal FOIA request. If FDA has not yet posted the Warning Letter on the Warning Letter Internet page, the requester should fax the request for a copy of the Warning Letter to DFOI to answer. By following this procedure, the agency will comply with its "first in, first out" policy. Do not disclose a copy of a Warning Letter to the public unless your office receives the FOIA request through DFOI.

DFOI will obtain the issued letter from within MARCS-CMS or DFOI will notify the Office of Enforcement's Division of Compliance Management and Operations if the final letter is not contained in the MARCS-CMS case file per established regulatory procedures.

Refer the public to FDA's procedures in the agency's "Handbook" for submitting a Freedom of Information Act (FOIA) request at: <<http://www.fda.gov/opacom/backgrounders/foiahand.html>>. The Handbook includes

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DFOI's mailing address and fax number. Generally, do not accept electronic or telephone requests for records, including Warning Letters.

4-1-14 Center For Biologics Evaluation And Research (CBER)

The compliance programs for CBER regulated products are located at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/CompliancePrograms/default.htm. Evaluate violations to decide if they are of regulatory significance. 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) that handles warning letter recommendations is the Division of Case Management, HFM-610. They can be reached at (301) 827-6201.

1. ***CBER Program Warning Letters***

   a. 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.

   b. The lists of deviations (those that may lead to enforcement action if not promptly and adequately corrected) serve as guides for determining the recommended course of action. Any significant deviation, whether repetitive or an isolated occurrence, may warrant the issuance of a Warning Letter.

   c. 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.

   d. 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.

   e. Send copies of all Warning Letters to Division of Case Management (HFM-610).

   f. 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 or the sharing is

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authorized by law. See Chapter 3 for commissioning procedures.

2. ***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.

3. ***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.

4. ***Warning Letters Recommendations***
Send Warning Letter recommendations to CBER's Office of Compliance and Biologics Quality

   a. For Blood, Plasma and HCT/Ps:
   Chief, Blood and Tissue Compliance Branch
   Division of Case Management, HFM-614

   b. For Biological Drugs and Devices:
   Chief, Biological Drug and Device Compliance Branch
   Division of Case Management, HFM-624 (Except for therapeutic biological drugs, which are submitted to CDER for concurrence.)

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.

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4-1-15 Center For Drug Evaluation And Research (CDER)

1. ***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, NDAs, BLAs) 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 and the issue(s) affect marketed products or the inspection has extended to marketed

products which are included on the FDA 483. 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."

2. ***Surveillance Inspections For Assessing Conformance With Adulteration Provisions of the Act, Including CGMP***
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 adulteration provisions of the Act, including CGMP. See Standard Charge i, in Section 3, below. The lists of deviations (those that may lead to enforcement action if not promptly and adequately corrected) serve as guides for determining the recommended course of action. Any significant deviation, whether repetitive or an isolated occurrence, may warrant the issuance of a Warning Letter. In therapeutic biologic drugs, operations to assess their conformance to the adulteration provisions, including CGMP, will be conducted by appropriately trained investigators, preferable Level III certified drug investigators. These drugs will be subject to the same regulatory procedures and actions as other drugs regulated by CDER. If there is a question of which center presides over a therapeutic biologic drug, contact the Branch Chief, Manufacturing and Pre-Approval Compliance Branch, Division of Manufacturing and Product Quality, CDER, at 301-796-3275.

3. ***Standard CDER Charges***

   a. Grandfather New Drug Charge: The charge for drugs that claim to have been on the market before 1938 or before 1962:

      505(a), 21 U.S.C. 355(a) - The articles are new drugs within the meaning of Section 201(p) of the Act, 21 U.S.C. 321(p), and approval of an application filed under Section 505(b) of the Act, 21 U.S.C. 355(b), is not effective for such drugs and a Notice of Claimed Investigational Exemption under Section 505(i) of the Act, 21 U.S.C. 355(j), and 21 CFR Part 312 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.

   b. 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), 21 U.S.C. 352(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, 21 U.S.C. 321(p), and no approval of an application filed pursuant to Sections 505(b) and 505(j) of the Act, 21 U.S.C. 355(b) and (j), is effective for this drug.

      A 502(f)(1) charge is appropriate for OTC drugs for which the directions are

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"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 21 CFR 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.)

c. When the product is not a new drug, the simple misbranding charge should read:

502(f)(1), 21 U.S.C. 352(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.

d. Prescription Drug Where There Is No Labeling Bearing Directions for Use
The charge is as follows:

502(f)(1), 21 U.S.C. 352(f)(1) - The article(s), (DRUG NAME), is subject to the provisions of Section 503(b)(1) of the Act, 21 U.S.C. 353(b)(1), and it is not exempt from Section 502(f)(1) of the Act, 21 U.S.C. 352(f)(1), 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.

e. 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), 21 U.S.C. 352(o) - The articles, (DRUG NAMES), are misbranded in that they were manufactured in an establishment not duly registered under Section 510 of the Act, 21 U.S.C. 360, and the articles have not been listed as required by Section 510(j) of the Act, 21 U.S.C. 360(j).

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f. 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) 21 U.S.C. 353(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:

i. For a prescription drug:
503(b)(4)(A), 21 U.S.C. 353(b)(4)(A) - The article of drug, (DRUG NAME), is subject to Section 503(b)(1) of the Act, 21 U.S.C. 353(b)(1), and is misbranded in that its label fails to bear the symbol, "Rx only."

ii. For an OTC drug that is not to bear the symbol, "Rx only":
503(b)(4)(B), 21 U.S.C. 353(b)(4)(B) - The article of drug, (Drug name), is not subject to Section 503(b)(1) of the Act, 21 U.S.C. 353(b)(1), and is misbranded in that its label bears the symbol, "Rx only" and it is not entitled to bear such symbol.

g. The following straight UNAPPROVED NEW DRUG charge may be used when there is interstate movement of the finished, labeled drug product.

505(a), 21 U.S.C. 355(a) - The article of drug, (DRUG NAME), is a drug within the meaning of Section 201(g) of the Act, 21 U.S.C. 321(g), which may not be introduced or delivered for introduction into Interstate commerce under Section 505(a) of the Act, 21 U.S.C. 355(a), since it is a new drug within the meaning of Section 201(p) of the Act, 21 U.S.C. 321(p), and no approval of an application filed pursuant to Section 505(b) of the Act, 21 U.S.C. 355(b), is effective for such drug.

h. For information regarding health fraud issues, contact the Internet and Health Fraud Team at (301) 796-3342.

i. Adulteration Due To Inadequate Conformance with CGMP

The charge is as follows:

501(a)(2)(B), 21 U.S.C. 351(a)(2)(B) - The article(s), (DRUG NAME), is (are) adulterated within the meaning of Section 501(a)(2)(B) of the Act, 21 U.S.C. 351(a)(2)(B), 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].

j. Adverse Drug Experience Reporting Violations and NDA Field Alerts Reporting Violations

The charge is as follows:

505(k)(1), 21 U.S.C. 355(k)(1) – Your firm failed to establish and maintain records and report data relating to clinical experience, along with other data or information for drugs for which an approved application is in effect, as required by Section 505(k)(1) of the Act, 21 U.S.C. 355(k)(1). Failure to comply with Section 505(k) is a prohibited act under Section 301(e) of the Act, 21 U.S.C. 331(e).

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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.

4-1-16 Center For Devices And Radiological Health (CDRH)

1. ***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.)

   Most Level 1 and repeat Level 2 inspection observations will not result in Warning Letters (see Part V of the Compliance Program).

   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.

2. ***Sample Wording For Charges***

   a. Adulteration Charges

      i. Section 501(f)(1)(B), 21 U.S.C. 351(f)(1)(B), in that it is a Class III device under Section 513(f), 21 U.S.C. 360c(f), and does not have an approved application for premarket approval in effect pursuant to Section 515(a), 21 U.S.C. 360e(a), or an approved application for an investigational device exemption under Section 520(g), 21 U.S.C. 360j(g).

      ii. Section 501(c), 21 U.S.C. 351(c), in that its strength, purity, or quality falls below that which it purports or is represented to possess.

      iii. Section 501(h), 21 U.S.C. 351(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.

      iv. Section 501(i), 21 U.S.C. 351(i), in that it is a device for which an exemption has been granted under section 520(g), 21 U.S.C. 360j(g), for investigational use and the person who was granted such exemption or an investigator who has used the device under such exemption has failed to comply with a requirement imposed by or under such section.

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b. Misbranding Charges

i. Section 502(a), 21 U.S.C. 352(a), 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.

ii. Section 502(b), 21 U.S.C. 352(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.

iii. Section 502(f)(1), 21 U.S.C. 352(f)(1), 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.)

iv. Section 502(f)(1), 21 U.S.C. 352(f)(1), in that the labeling for the device fails to bear adequate directions for use because the labeling does not contain an expiration date based upon the stated storage instructions, as required by 21 CFR 809.10.

v. Section 502(o), 21 U.S.C. 352(o), in that the device was manufactured, prepared, propagated, compounded, or processed in an establishment not duly registered under Section 510, 21 U.S.C. 360, was not included in a list required by Section 510(j), 21 U.S.C. 360(j),, and a notice or other information respecting the device was not provided to FDA as required by Section 510(k), 21 U.S.C. 360(k).

vi. Section 502(o), 21 U.S.C. 352(o), 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).

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.

3. ***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

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1968) of Chapter V of the Act requires the Secretary to notify the assembler/manufacturer concerning noncompliant or defective radiation emitting devices and solicit follow-up corrective action by the assembler/manufacturer 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, Diagnostic X-Ray Devices Branch, HFZ-240, 240-276-3332.

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.

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.

Districts should ***only*** submit recommendations, coupled with their supporting evidence, to CFSAN via the Compliance Management System (CMS), an electronic case submission system. This system is available from the IT Applications page on FDA's intranet site.

4-1-18 Tracking

1. ***Identification Of Warning Letters***
   All Warning Letters must be entered into the Compliance Management System (CMS); whether they are generated by a district or center, and whether they are approved and issued or not. Every Warning Letter that is issued should bear the CMS-assigned number or a sequential code number assigned by the issuing district or center. If a district or center assigned number is used, this number should be recorded in CMS to facilitate tracking.

2. ***Updating Firm Profile Status in FACTS***

   When a violation letter is the result of a Current Good Manufacturing Practice (CGMP) or Quality System (QS) inspection of a domestic or foreign drug, biologics, or medical device facility, the firm's profile status information in the Field Accomplishment and Compliance Tracking System (FACTS) is to be appropriately updated at each stage in the review process. The action office (i.e., the district or center initiating the recommendation) is responsible for entering the status of the violation letter into FACTS. (See Exhibit 4-1, 5.4, and Chapter 4 "Firm Profile Updates in FACTS" for more information.)"

4-2 UNTITLED LETTERS

4-2-1 Policy

An Untitled Letter cites violations that do not meet the threshold of regulatory significance for Warning Letter. Therefore, the format and content of an Untitled Letter should clearly distinguish it from a Warning Letter. For example:

1. The letter is not titled.

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2. 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.
3. The letter does not include a warning statement that failure to take prompt correction may result in enforcement action.
4. The letter does not evoke a mandated district follow-up.
5. 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.

4-2-2 Center Concurrence and Letters Issued By Centers

Center concurrence is required prior to issuing Untitled Letters in the areas listed in section 4-1-4, or the Untitled 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.

4-2-3 Tracking

1. ***Identification Of Untitled Letters***
   All Untitled Letters must be entered into the Compliance Management System (CMS); whether they are generated by a district or center, and whether they are approved and issued or not. Every Untitled Letter that is issued should bear the CMS-assigned number or a sequential code number assigned by the issuing district or center. If a district or center assigned number is used, this number should be recorded in CMS to facilitate tracking.

2. ***Updating Firm Profile Status in FACTS***

   When a profilable firm (i.e., domestic or foreign drug, biologics, or medical device facility) undergoes a Current Good Manufacturing Practice (CGMP) or Quality System (QS) inspection, the inspected profile classes should be updated by the action office (i.e., the district for domestic inspections or the district and the center for foreign inspections) at each stage in the review process. When an Untitled Letter is issued as a result of the inspection, the date and type of letter issued should be entered in the Remarks field for the relevant profile classes. For profile procedures, see IOM Exhibit 5-14 or the DCIQA intranet page.

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4-3 USE OF STATE EVIDENCE FOR FDA WARNING LETTERS AND UNTITLED LETTERS

Evidence obtained by state personnel may be sufficient to support the issuance of Warning Letters and Untitled Letters if the standards and criteria used by state personnel provide

reliable support for regulatory actions the agency may take consistent with the agency's guidance on regulatory actions and laboratory procedures.

1. If state evidence involves inspectional observations made solely by state personnel, factors that indicate that the standards and criteria used are reliable for these purposes include, but are not limited to, the following:

   a. The state inspector made the inspectional observations during an inspection conducted pursuant to an agency contract inspection program or a joint inspection program in which FDA participates; or

   b. The state inspector made the inspectional observations after receiving training in relevant law and any specific requirements applicable to the inspection and the establishment or commodity being inspected; or

   c. The state inspector received an "acceptable" rating if audited by a qualified FDA or state auditor under FMD 76, "State Contracts – Evaluation of Inspectional Performance" (or other applicable audit program); or

   d. The state inspector detected and documented the observations in the manner set forth in FDA's inspectional procedures, such as the Investigations Operations Manual, guides to inspections, or comparable inspectional approaches.

2. If state evidence involves laboratory data, factors that indicate that the laboratory data and the methods and procedures used to collect and analyze the sample are valid and reliable include the following:

   a. The procedures involved in the sample collection have been analyzed and found to be reliable in that the sample was collected, handled, and analyzed using procedures that assure sample integrity and chain of custody and a sample size and test method the Director, Division of Field Science (DFS), HFC-141, determines to be appropriate; or

   b. The Director, DFS, designates that the laboratory data from state facilities meet the criteria and standards appropriate for compliance decision-making; or

   c. The Director, DFS, has reviewed and endorsed the state laboratory findings through an evaluation of the laboratory operations, methods, sampling, and evidence documentation.

3. Except for state inspections of retailers to determine compliance with the provisions of the Family Smoking and Tobacco Control Act and its implementing regulations, the district office must review and endorse the state evidence as meeting the criteria for the issuance of a Warning Letter or Untitled Letter in accordance with district procedures and agency compliance policy. Warning Letters and Untitled Letters relating exclusively to state inspections of retailers to determine compliance with the provisions of the Family Smoking and Tobacco Control Act and its implementing regulations will be drafted by the Center for Tobacco Products based on sufficient evidence collected and documented by state personnel.

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4. The FDA product center with primary jurisdiction over the establishment or commodities inspected and the Office of Chief Counsel concurs with the use of the evidence obtained by state personnel.

5. This section is not applicable where a proposal for a Warning Letter or Untitled Letter is based on FDA-developed evidence to demonstrate the current condition of the commodity or establishment, and evidence obtained by state personnel is used to solely demonstrate prior compliance history.

4-4 EXHIBITS

4-1 Procedures for Clearing FDA Warning Letters and Untitled Letters

4-2 Warning Letter Close-Out Letter

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Exhibit 4-1

Procedures for Clearing FDA Warning Letters and Untitled Letters

March 2010

Contents

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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.

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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.

4. Definitions

For the purpose of these procedures:

4.1 A ***Warning Letter*** 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. 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 section 6.3 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 the Compliance Management System (CMS or MARC-CMS). This application replaces the AIMS Violation Letter Tracking Systems (VLTS). CMS provides the capability to enter and track Warning and Untitled Letters through the approval process. The action office (i.e. the District or Center initiating the recommendation) is responsible for entering all violation letters into CMS; as well as updating data related to their submissions. The issuing office of the violation letter is also responsible for ensuring that a PDF copy of the final, signed violation letter is added into CMS.

Instructions for using CMS are available in the User's Guide link within the application and further information is available within the link to Frequently Asked Questions.

5.4 When a violation letter is the result of a Current Good Manufacturing Practice (CGMP) or Quality System (QS) inspection of a domestic or foreign drug, biologics, or medical device facility, the firm's profile status information in the Field Accomplishment and

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Compliance Tracking System (FACTS) is to be appropriately updated at each stage in the review process. The action office (i.e., the District or Center initiating the recommendation) is responsible for entering the Final Profile Status in FACTS. (See Chapter 4 "Firm Profile Updates in FACTS" for more information.)

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 recommits 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.

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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

All Warning Letters and Untitled Letters must be entered into the Compliance Management System (CMS or MARC-CMS), where they are available for review.

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 via CMS to OCC for concurrence.

(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 via CMS to OCC for concurrence.

(3) To facilitate OCC's review of the Warning or Untitled Letters, ensure that the violation letter documents within CMS include 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.

(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 and also added into the case file for the proposed action within CMS. The review clock will stop when OCC is notified and restart upon OCC's receipt of the Form FDA 483 response and the

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District's assessment. Any changes to the proposed letter as a result of the FDA-483 response will be discussed with the initiating office.

(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, add a PDF signed copy of the Warning or Untitled Letter into the Final Outcome tab for the action within CMS. Distribute additional copies in accordance with any applicable Compliance Program and 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 and the district's compliance officer who proposed the action, along with a copy of the draft "final" letter with any edits (the District can then issue the letter).

(3) If ***non***concurrence or the letter is flagged because it raises significant issues, contact the District, and state ***in writing*** the reason for nonconcurrence.

(c) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued and actively monitor CMS to identify missing letters, if any.

6.2.2. <u>General Procedures for Warning and Untitled Letters Pursuant to a Foreign Inspection</u>

(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 via CMS to OCC for concurrence.

(4) To facilitate OCC's review of the Warning or Untitled Letters, ensure that the violation letter documents within CMS include 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.

(5) If there is no Form FDA 483 or EIR, send the evidence to OCC that supports the

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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, and should also be added into the case file for the proposed action within CMS. 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.

(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, add a PDF signed copy of the Warning or Untitled Letter into the Final Outcome tab for the action within CMS. Send a copy to ORA's Office of Regional Operations (ORO), Division of Field Investigations (DFI), and distribute additional copies in accordance with any applicable Compliance Program and 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) 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 Warning and Untitled Letters that have been issued and actively monitor CMS to identify missing letters, if any.

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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 through CMS.

(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 through CMS.

(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, ensure that the violation letter documents within CMS include all evidence necessary to support issuance of the letter or other relevant information. For example, the Form FDA 483, the endorsement page of the EIR or the FACTS coversheet, the narrative portion of the EIR, the relevant exhibits, product labels and labeling, and, if applicable, the summary of any sample analysis.

(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 and also added into the case file for the proposed action within CMS. 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.

(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, add a PDF signed copy of the Warning or Untitled Letter into the Final Outcome tab for the action within CMS. Distribute additional copies in accordance with any applicable Compliance Program and 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 and add a copy of the Center decision document for the violation letter into the Center documents tab in CMS.

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(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 and add a copy of the Center decision document for the violation letter into the Center documents tab in CMS.

(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's "final" letter with any edits should be added to the Center documents tab in CMS and clearly identified via the document description that it is for OCC review and concurrence. For instance, the description field within CMS should indicate "FOR OCC REVIEW."

(4) To facilitate OCC's review of the Warning or Untitled Letters, ensure that the violation letter documents within CMS include 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.

(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 and OCC of its decision within 15 working days. 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. The Center will add a copy of its Center decision memorandum for the violation letter into the Center documents tab in CMS.

(7) If the Untitled Letter recommendation is ***not*** approved, the Center will notify the District's Director of the Compliance Branch, and OCC, of its decision within 45 working days. 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. The Center will add a copy of its Center decision memorandum for the violation letter into the Center documents tab in CMS.

(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 and the district's compliance officer who proposed the action, along with a copy of the draft "final" letter with any edits (the District can then issue the letter).

(4) If nonconcurrence or the letter is flagged because it raises significant issues, contact the Center involved and the District, and state in writing the reason for nonconcurrence.

(d) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued and actively

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monitor CMS to identify missing letters, if any.

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 via CMS to OCC.

(3) To facilitate OCC's review of the Warning or Untitled Letters, ensure that the violation letter documents within CMS include 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.

(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, and also added into the case file for the proposed action within CMS. 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.

(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, add a PDF signed copy of the Warning or Untitled Letter into the Final Outcome tab for the action within CMS. Send a copy to the District's Director of the Compliance Branch where the recipient of the letter is located and distribute additional copies in accordance with any applicable Compliance Program and RPM Chapter 4.

(10) In the case of nonconcurrence 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.

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(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) 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 Warning and Untitled Letters that have been issued and actively monitor CMS to identify missing letters, if any.

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 via CMS to OCC for concurrence.

(3) To facilitate OCC's review of the Warning or Untitled Letter, ensure that the violation letter documents within CMS include the evidence that supports the issuance of the letter.

(4) If OCC concurs, issue the letter.

(5) Upon issuance, add a PDF signed copy of the Warning or Untitled Letter into the Final Outcome tab for the action within CMS. Distribute additional copies in accordance with any applicable Compliance Program and 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) 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, and actively monitor CMS to identify missing letters, if any.

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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/AboutFDA/CentersOffices/CBER/ucm133463.htm. Additional information can be found at:
http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm136265.htm.

Recommendations and other correspondence related to 6.3.1 – 6.3.3 (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 via CMS to OCC within the 3 working day period.

(3) To facilitate OCC's review of the letter, ensure that the documents within CMS include the Health Hazard Evaluation and the pertinent evidence that establishes that a danger to health exists.

(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, add a PDF signed copy of the letter into the Final Outcome tab for the action within CMS. Distribute additional copies in accordance with any applicable Compliance Program and 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) 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 License Suspension Letters that have been issued and actively monitor CMS to identify missing letters, if any.

6.3.2 License Revocation (For Cause)

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(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 via CMS to OCC for their concurrence.

(3) To facilitate OCC's review of the letter, ensure that the documents within CMS include the recommendation and any additional supporting documents.

(4) If OCC concurs, issue the letter.

(5) Upon issuance, add a PDF signed copy of the letter into the Final Outcome tab for the action within CMS.

(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) 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 License Revocation Letters that have been issued and actively monitor CMS to identify missing letters, if any.

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 via CMS to OCC for their concurrence.

(3) If OCC concurs, issue the letter.

(4) Upon issuance, add a PDF signed copy of the letter into the Final Outcome tab for the action within CMS.

(5) In the case of ***non***concurrence or the letter is flagged because it raises significant issues, the Center will work with OCC.

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(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) 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 NOIR Letters that have been issued and actively monitor CMS to identify missing letters, if any.

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

Audit letters are automatically identified by the Compliance Management System (CMS), using the audit schedules in 6.4.1 based on the nationwide count of that category of letter. The system will automatically indicate those letters subject to OCC review while the remaining letters in that audit category may be issued without such review. The model letters must be followed for all letters under this audit review program issued on or after the associated effective date.

If the same model is used for both Warning Letters and Untitled Letters, such as the model letter for x-ray assemblers, the audit schedule must be followed for each type of letter. This means that for x-ray assembler letters, every fifth Untitled Letter and every fifth Warning Letter are to be submitted for OCC review using the procedures in this document.

At the discretion of the issuing office, 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.

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(b) District Responsibilities

Use the relevant model letter for all letters to be issued under the audit program. Once the action is added into Compliance Management System (CMS), the district must identify the OCC audit program under which the letter falls in order to determine whether the letter is subject to audit submission to OCC. For letters that require Center concurrence,

the district should likewise identify that the proposed action letter falls within one of the OCC audit programs and follow the routine procedures in this document. For direct reference letters, submit audit letters to OCC for review using the procedures in this document. The other letters may issue without OCC review but must still be added into CMS in order for the agency to keep accurate accounting for the issuance of the letter.

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

Use the relevant model letter for all letters to be issued under the audit program. Once the action is added into Compliance Management System (CMS), the Center must identify the OCC audit program under which the letter falls in order to determine whether the letter is subject to audit submission to OCC. In most instances, this information should be completed by the recommending district; however, Centers will review as well to ensure an audit program is identified when appropriate. For letters for which the Center is responsible for obtaining OCC concurrence, submit audit letters to OCC for review using the procedures in this document. The other letters may issue without OCC review.

When a Center submits an "audit letter" to OCC for review, the transmittal memo approving the recommendation will contain the notation "Audit Letter – OCC concurrence is required" under the heading "Warning Letter – Approved." This identifies the letter as one that requires OCC review and concurrence under the audit review program before it can be issued.

Centers 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.

(d) OCC Responsibilities

Review Untitled Letter and Warning Letter recommendations submitted by a District or Center, representing the audit letters of that type to be issued by that District or Center on or after the effective date of the model (shown below) in accordance with the routine procedures in this document. Determine conformity with the model letter. Report any perceived problems to the Office of Enforcement.

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(e) OE Responsibilities

Maintain a repository of all Untitled Letters and Warning Letters issued and actively monitor CMS to identify any missing letters. Review conformance with these procedures as part of the periodic evaluation.

6.4.1 Model Letters and Audit Schedules

The following model letters and audit schedules have been approved for use under this audit review program. The links to these letters can be found in the Warning Letter page on the Office of Enforcement's intranet site.

Center	Type of Letter	Audit Schedule
CDRH	Notification to X-Ray Assemblers of Defect or Noncompliance as the Result of Field Testing. The effective date for use of this letter is March 1, 2004.	Every Fifth Letter
CDRH	MQSA (Mammography Quality Standards Act) Warning Letter. The effective date for use of this letter is December 7, 2004.	Every Fifth Letter
CDRH	CDRH Foreign Warning Letter – with Detention. The effective date for use of this letter is December 7, 2004.	Every Fifth Letter
CDRH	CDRH Foreign Warning Letter – without Detention. The effective date for use of this letter is December 7, 2004.	Every Fifth Letter
CDRH	CDRH Foreign Untitled Letter The effective date for use of this letter is July 18, 2006.	Every Fifth Letter
CFSAN	Seafood HACCP Warning Letter – Domestic Processors. The effective date for use of this letter is September 12, 2005.	Every Fifth Letter

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Center	Type of Letter	Audit Schedule
CFSAN	Seafood HACCP Warning Letter – Importers. The effective date for use of this letter is December 15, 2005.	Every Fifth Letter
CFSAN	Seafood HACCP Warning Letter – Combination Importer-Domestic Processor. The effective date for use of this letter is April 26, 2005.	Every Fifth Letter
CFSAN	Seafood HACCP Untitled Letter – Domestic Processors. The effective date for use of this letter is September 12, 2005.	Every Fifth Letter
CFSAN	Seafood HACCP Untitled Letter – Combination Importer-Domestic Processor. The effective date for use of this letter is April 26, 2005.	Every Fifth Letter
CFSAN	Food Registration Untitled Letter. The effective date for use of this letter is October 30, 2006.	Every Tenth Letter
CVM	Tissue Residues Warning Letter for Producers who Medicate Animals (For letters requiring center concurrence only. Direct reference letters are not included in the audit program at this time.) The effective date for use of this letter is June 18, 2008.	Every Fifth Letter

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Exhibit 4-2

WARNING LETTER CLOSE-OUT LETTER

Mr. John Doe, President
J.D. Laboratories, Inc.
Somewhere, USA

Dear Mr. Doe:

The Food and Drug Administration has completed an evaluation of (your/your firm's) corrective actions in response to our Warning Letter [insert WL # and Date]. Based on our evaluation, it appears that you have addressed the violation(s) contained in this Warning Letter. Future FDA inspections and regulatory activities will further assess the adequacy and sustainability of these corrections.

This letter does not relieve you or your firm from the responsibility of taking all necessary steps to assure sustained compliance with the Federal Food, Drug, and Cosmetic Act and its implementing regulations or with other relevant legal authority. The Agency expects you and your firm to maintain compliance and will continue to monitor your state of compliance. This letter will not preclude any future regulatory action should violations be observed during a subsequent inspection or through other means.

Sincerely,

Official [issuing district/office]

bcc: Establishment File
Home District of Corporate HQ (or of receiving firm if issued by a Center)
FOI Office for Posting (typically no redaction needed; electronic through CMS)
CMS case file (electronic copy)

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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. **Alan Wilson,** in his capacity as Attorney General of the State of South Carolina,	Civil Action No.: 2007-CP-42-1438
PLAINTIFF,	
v.	**PLAINTIFF THE STATE OF SOUTH CAROLINA'S MOTION TO EXCLUDE THE EXPERT TESTIMONY OF SHELDON BRADSHAW**
ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA, INC., and/or JANSSEN, L.P., AND JOHNSON & JOHNSON, INC.	
DEFENDANTS.	

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

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Plaintiff, the State of South Carolina, *ex rel.* Alan Wilson[1], in his capacity as Attorney General of the State of South Carolina (hereinafter, "the State"), by and through the undersigned counsel, hereby submits its Motion to Exclude the Testimony of Sheldon Bradshaw, seeking the Court's order excluding the testimony of defense attorney, Sheldon Bradshaw, untimely designated to render "expert opinions regarding the U.S. Food and Drug Administration ("FDA" or the "Agency") and FDA regulatory matters" by Defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. f/k/a Janssen Pharmaceutica, Inc., and/or Janssen, L.P., and Johnson & Johnson, Inc., (collectively, "Janssen" or "Defendant") from the trial of this matter as the testimony is irrelevant and unfairly prejudicial.

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

I.
SUMMARY OF THE ARGUMENT

> *The basis of expert capacity, according to Wigmore (§ 555) may 'be summed up in the term "experience"'. But, experience is hardly a qualification for construing a document for its legal effect when there is a knowledgeable gentleman in a robe whose exclusive province it is to instruct the jury on the law.*[1]

Far from the myriad qualifications of the State's regulatory expert, pharmacologist, toxicologist, and FDA regulatory specialist, Dr. Laura M. Plunkett, Ph.D., DABT, Defendant's "expert," defense attorney and former FDA attorney, Sheldon Bradshaw, lacks the requisite specialized knowledge, skill, experience, training or education to advance the opinions set forth in his Report[2] served on the eve of trial. As a threshold matter, he cannot be qualified as an expert under S.C. R. Evid. 702. Additionally, he lacks the personal knowledge required of a witness under S.C. R. Evid. 602, and his testimony is prejudicial and in violation of S.C. R. Evid. 403. His testimony is also unreliable by virtue of the egregiously biased and inaccurate information he employed and the process by which he synthesized the information to develop his final opinion relative to the intent and motivation of FDA regulators and prescription drug labeling.

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Perhaps most offensive is Bradshaw's advancement of improper legal conclusions by his opinion, which do more to invade the province of the Court and the jury than assist the fact finder in its determination. Bradshaw's testimony is not designed to assist the trier of fact but, rather, is *admitted* legal argument regarding the "legal effect of FDA letters," and other communications and why the Court should rule, as a matter of law, the "Risperdal label and

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1 *Adalman v. Baker*, 807 F.2d 359, 367 (4th Cir. 1986) (quoting *Marx & Co., Inc. v. Diners' Club, Inc.* 550 F.2d 505 (2d Cir. 1977), *cert. denied* 434 U.S. 861 (1977)).

2 *See* Expert Report of Sheldon T. Bradshaw, J.D., Partner, Hunton & Williams LLP, Dec. 30, 2010, (hereinafter, "Report"), a true and correct copy of which is attached hereto as Exhibit A.

November 10 medical communication were [not] 'false' and 'misleading.'" (Report at 4, 13.) Such testimony indisputably falls outside the scope of Rule 702, is categorically prohibited under all applicable law, and, therefore, must be excluded.

Assuming *arguendo* Bradshaw could be qualified as an expert and his testimony was sufficiently reliable and helpful to the fact finder to overcome Rule 702 preconditions, it is nevertheless prejudicial for the additional reason that in serving Bradshaw's Report, Defendant ignored this Court's pretrial deadlines and the South Carolina Rules governing discovery in untimely propounding his opinions at the close of a more than three-year long discovery period. As in the past and throughout the Court's pretrial program, Defendant has willfully flouted the Court's pretrial deadlines and discovery orders, and unfairly prejudiced the State. By Defendant's unwarranted delay, the State has been prevented from participating in expert-based discovery relative to the opinions Bradshaw now advances and, in particular, has been prevented from deposing Bradshaw.[3]

For the reasons set forth herein, Bradshaw's testimony must be excluded.

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II.
STATEMENT OF THE CASE

On April 23, 2007, the State initiated this action against Janssen, manufacturer of the atypical antipsychotic drug Risperdal, to recover, *inter alia*, civil penalties pursuant to S.C. Code Ann. § 39-5-110(a) for Janssen's willful, deceptive and unfair course of conduct in its product labeling. On March 19, 2010, the State filed its Second Amended Civil Action Complaint, (hereinafter, "Amended Complaint"), petitioning the Court to assess against Janssen such

[3] Although the State does not contend that the prejudice caused by Defendants' delay and related failure to comply with discovery deadlines could be cured by the deposition of Dr. Bradshaw on the eve of trial, the State hereby reserves the right to supplement its Motion to further address Dr. Bradshaw's deposition testimony if he is deposed.

penalties in an amount up to five thousand dollars for each "method, act or practice declared unlawful by § 39-5-20" and the willful use thereof. S.C. Code Ann. § 39-5-110(a). The State's Amended Complaint alleges, in brief, that Janssen: (1) "willfully engaged in a protracted, deceptive and unfair course of conduct in violation of SCUTPA" through its "labeling of Risperdal, which willfully, deceptively, and unfairly minimized, misrepresented, and/or concealed the drug's dangerous side effects"; (2) "had actual knowledge that Risperdal causes weight gain," and "other severe adverse effects," upon product launch, but "failed to include a warning of the potential for weight gain and the possible development of diabetes as a result of the use of Risperdal in its U.S. labeling for many years," and "failed to warn adequately of these adverse effects," in all subsequent label changes; (3) was "chastised by the FDA for being brazenly 'false' and 'misleading'" in its Dear Doctor Letters by "[f]ailing to disclose the addition of information relating to hyperglycemia and diabetes mellitus to the labeling; [m]inimizing the risks of potentially fatal hyperglycemia-related adverse events;[4] [f]ailing to recommend regular glucose control monitoring to identify diabetes mellitus as soon as possible; and [m]isleadingly claiming that Risperdal is safer than other atypical antipsychotics"; and, (4) "made, and continue[s] to make, orally and in writing, false, misleading or deceptive representations," and "continue[s] to disseminate false, misleading, or deceptive information to the public . . . regarding the health risks and benefits associated with using Risperdal." (Pl.'s Second Am. Compl. ¶¶ 8, 13, 24, 26, 45, 46, 57, 58.)

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[4] FDA DDMAC's April 2004 Warning Letter to Janssen at 1, a true and correct copy of which is attached hereto as Exhibit B; *see also* FDA DDMAC's January 1999 Notice of Violation to Janssen, a true and correct copy of which is attached hereto as Exhibit C.

III.
ARGUMENT

A. Standard.

South Carolina Rule of Evidence 702 provides: "If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise." Under South Carolina law, "[a]ll expert testimony must satisfy the Rule 702 criteria, and that includes the trial court's gatekeeping function in ensuring the proposed expert testimony meets a reliability threshold for the jury's ultimate consideration." *State v. White*, 676 S.E.2d 684, 686 (S.C. 2009) (citing S.C. R. Evid. 702). In discharging its gatekeeping role, the "'trial court must assess the threshold foundational requirements of qualification and reliability and further find that the proposed evidence will assist the trier of fact[, and] . . . only after the trial court has vetted the matters of qualifications and reliability and admitted the evidence' may challenges be potentially dismissed as going to the weight rather than admissibility." *State v. Tapp*, 691 S.E.2d 165, 166 (S.C. App. 2010) (quoting *White*, 676 S.E.2d at 688-89).

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Indeed, "[r]eliability is a central feature of Rule 702 admissibility." *Id.* (citing *State v. Jones*, 541 S.E.2d 813, 818 (2001); *State v. Council*, 515 S.E.2d 508, 518 (1999)). Likewise, the relevant inquiry cannot focus solely on the reliability of the witness himself but must also assess the reliability of the process by which he derived his opinion. *See Tapp*, 691 S.E.2d at 170; *see also id.* (noting that *Council* factors "may be quite relevant" in the case of experience-based expert testimony) (citing *State v. Council*, 515 S.E.2d 508, 517 (1999); *State v. Jones*, 259 S.E.2d 120, 124-25 (1979)).

While "[t]he test for qualification of an expert is a relative one that is dependent on the particular witness's reference to the subject[,]" it demands that "the witness has acquired by study or practical experience such knowledge of the subject matter of his testimony as would enable him to give guidance and assistance to the jury in resolving a factual issue which is beyond the scope of the jury's good judgment and common knowledge," and that he "be better qualified than the fact finder to form an opinion on the particular subject." *State v. White*, 642 S.E.2d 607, 612 (S.C. Ct. App. 2007). It is the offering party's burden to show that "the witness possesses the necessary learning, skill, or practical experience to enable the witness to give opinion testimony." *Id.*

When admitting evidence under Rule 702, the Court must additionally determine if its probative value is outweighed by its prejudicial effect as prescribed by Rule 403 which provides, in pertinent part, that "evidence may be excluded if its probative value is substantially outweighed by the danger of unfair prejudice, confusion of the issues, or misleading the jury, or by considerations of undue delay, waste of time, or needless presentation of cumulative evidence." S.C. R. Evid. 403.

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B. <u>Sheldon Bradshaw Should Be Precluded From Rendering Opinions Regarding The Intent And Motivation Of FDA Regulators And Regarding Prescription Drug Labeling, Because He Is Not Qualified To Render Such Opinions, And His Opinions Are Speculative, Unreliable, And Not Based On Sufficient Facts Or Data.</u>

In an effort to defeat the State's claims and otherwise minimize the impact of the FDA's classification of Risperdal labeling as "false" and "misleading," Defendant has tendered defense attorney, Bradshaw, as an "expert" witness to testify regarding the intent and motivation of the FDA in sending Warning Letters, untitled letters, and Notices of Violation, *inter alia*, to Defendant regarding its "false" and "misleading" labeling of Risperdal, more specifically, and regarding prescription drug labeling, more generally. (FDA DDMAC's January 1999 Notice of

Violation at 1-4 (Ex. C); FDA DDMAC's April 2004 Warning Letter at 1 (Ex. B); *see generally* Rep.) Bradshaw, however, lacks requisite specialized knowledge, skill, experience, training or education to advance the opinions set forth in his Report, and because his opinions are both unreliable and prejudicial, his testimony should be excluded.

More particularly, Bradshaw's opinions relative to the intent and motivation of FDA regulators and prescription drug labeling, generally, are speculative, unreliable, and not based on sufficient facts or data. Rather, Bradshaw's opinions draw from his experience and practice as a corporate defense attorney and, through inference upon inference, Bradshaw ultimately speculates that certain FDA communications "are not legally binding and should not be considered to reflect the Agency's conclusive determination regarding Janssen's promotional efforts or labeling for *Risperdal*"; and, contrary to FDA regulators' express reprimands of Defendant, Bradshaw concludes that "Janssen has never been found to have falsely or misleadingly represented the risks associated with *Risperdal*." (*Compare* Rep. at 9-10 (emphasis in original), *with* FDA DDMAC's April 2004 Warning Letter to Janssen at 1 ("The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a 'Dear Healthcare Provider' (DHCP) Letter for Risperdal® (risperidone) disseminated by Janssen Pharmaceutica, Inc. on November 10, 2003[,] and "***DDMAC has concluded that the DHCP letter is false or misleading in violations of*** Sections 502(a) and 201(n) of ***the Federal Food, Drug, and Cosmetic Act (Act)*** (21 U.S.C. 352(a) and 321(n)) . . ." (emphases added) (Ex. B), *and with* FDA DDMAC's January 1999 Notice of Violation to Janssen, at 1 ("This letter concerns [Janssen's] promotional materials and activities for the marketing of Risperdal (risperidone) Tablets that have been reviewed by [DDMAC] as part of its monitoring and surveillance program[,] and "***DDMAC has concluded that these materials are false, misleading, and/or***

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lacking in fair balance, and in violation of the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder.") (emphasis added) (Ex. C.).)

Bradshaw appears to base his "expert" opinion that the FDA did not intend to convey "the Agency's conclusive determination, regarding Janssen's promotional efforts or labeling for *Risperdal*," in disseminating Warning Letters, Untitled Letters, or Notices of Violations, because the FDA did not also invoke one of its other "enforcement tools . . . including making a referral for criminal prosecution, seeking injunctive relief, or seizure" against Defendant. (Rep. at 9-10 (emphasis in original).) His testimony, however, is a transparent attempt to soften the blow of the FDA DDMAC's January 1999 Notice of Violation to Defendant for its "false" and "misleading" campaign to promote Risperdal to elderly patients, as well as the FDA DDMAC's Warning Letter of April 2004, chastising Defendant's November 2003 Dear Doctor Letter as brazenly "false" and "misleading" in failing to disclose the addition of information relating to hyperglycemia and diabetes mellitus to the labeling, *inter alia*. (*See* Pl.'s Second Am. Compl. ¶ 46; *see also id.* at ¶¶ 40-48; FDA DDMAC's April 2004 Warning Letter to Janssen (Ex. B); FDA DDMAC's January 1999 Notice of Violation to Janssen (Ex. C.).) It ignores that the FDA, by its April 2004 communication, demanded that Janssen immediately cease the dissemination of promotional materials for Risperdal containing claims similar to the foregoing and provide a plan of action to correct the effects of its "false" and "misleading" Dear Doctor Letter. (*Id.*) Likewise, it fails to address the FDA's warning that the violations detailed above did not constitute an exhaustive list, and that it was continuing to "evaluate other aspects" of Janssen's promotional campaign for Risperdal and could determine that "additional measures" would be necessary to "fully correct the false or misleading messages resulting from your [Janssen's] violative conduct." (*Id.*)

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In sum, his opinions are wholly unreliable with respect to his own capacity to provide reliable testimony as an attorney hired by Defendant who does not specialize in regulatory matters, and relative to the speculative process by which he derived his opinion without sufficient, or even accurate, facts or data.

Even if Bradshaw's opinions were reliable and could assist the trier of fact, he is not qualified to render opinions regarding the intent or motivation of FDA regulators, or regarding prescription drug labeling, more generally. Bradshaw has never been employed as a regulator by the FDA or in any capacity other than as legal counsel. (*See* Rep. at 2-3.) His opinions regarding the intent and motivation of FDA regulators in addressing prescription drug labeling and in related correspondence, as well as prescription drug labeling as a whole, can only be based on his limited role as legal counsel to the FDA and not based on experience as a member of the FDA's regulatory department, or any expertise relative to the regulatory issues addressed in his Report.

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In addition, because Bradshaw is an attorney acting on Defendant's behalf, his testimony is inadmissible because it is violative of Rule 403 as unduly prejudicial. *See Bates v. Firestone Tire & Rubber Co., Inc.*, 83 F.R.D. 535, 538 (D. S.C. 1979) (reasoning that evidence of letters written by attorneys was inadmissible when attorneys sought to advance position of one party). Thus, "[t]estimony by attorneys," such as Bradshaw, "engaged in making self-serving statements and advancing conclusions of law," should be "withheld from the jury . . . on the ground that their prejudicial effect outweighs their probative value in regard to the issue to which they were directed." *Id.* at 538 (quoting *Gardner v. Q.H.S.*, 448 F.2d 238, 244 (4th Cir. 1971)).

Based on the foregoing, Bradshaw should be precluded from rendering opinions regarding the intent and motivation of FDA regulators and regarding prescription drug labeling

because he is not qualified to render such opinions, as well as because his opinions are speculative, unreliable, and not based on sufficient facts or data.

C. **Sheldon Bradshaw's Opinions Regarding The Legal Effect Of FDA Communications And Defendant's Labeling Do Not Assist The Trier Of Fact, But, Rather, Are Impermissible Legal Arguments Designed To Substitute The Judgment Of Defendant For That Of This Court And Jury.**[5]

In addition to opining regarding the intent and motivation of FDA regulators and prescription drug labeling, more generally, Defendant has tendered defense attorney, Bradshaw, as an "expert" witness to testify, more specifically, as to his opinions that certain of Defendant's communications and promotional activities were not "false" or "misleading" or otherwise violative of SCUTPA or some other, unidentified legal standard. (Rep. at 4, 8, 9, 13, 16—18.) Detailing the purported "reason that FDA letters do not establish legal violations," why, allegedly, "FDA warning letters, untitled letters, and advisory letters have no legal effect," in addition to opining generally on "the legal effect" of FDA communications, the Risperdal labeling, and a host of Janssen-sponsored promotional activities relative to Risperdal, Bradshaw has rendered an opinion gravely violative of the South Carolina Rules of Evidence. (Rep. at 13, 16; *see generally* Rep.) Bradshaw's Report is undeniably wrought with impermissible legal conclusions and interpretation, advancing in each section of his report a deliberate commentary on the law. (*See generally* Rep.) Bradshaw's testimony is inadmissible as his entire opinion is premised expressly on his own interpretation of the law, as a hired lawyer, including the legal effect and interpretation of Defendant's labeling and related FDA communications.

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[5] Despite its proffer of such testimony, Defendant apparently agrees that "it is the court's responsibility to explain the legal standards and requirements to the jury," and "not the proper function for an expert." (Def.'s Memo. of Law in Support of Mot. *in Limine* to Exclude Expert Testimony of Laura Plunkett, Ph.D. at 12 (citations omitted).) Although misplaced as to Dr. Plunkett who is not a defense attorney hired to interpret Janssen's communications as violative under SCUTPA or otherwise render legal conclusions, Defendant's argument is instructive to the determination of admissibility of Bradshaw's testimony and, likewise, advocates in favor of his exclusion.

Accordingly, under all applicable law and legal precedent, Bradshaw's testimony must be excluded.

In particular, the South Carolina Supreme Court has made clear that "[s]uch 'testimony' falls outside of Rule 702, SCRE" and must be excluded. *Green v. State*, 569 S.E.2d 318, 325 (S.C. 2002) (even in case of claim of ineffective assistance of counsel, criminal defense attorney "expert" witness was not permitted to testify ***where "his opinion, assuming certain facts***, [that] trial counsel's actions fell below acceptable legal standards of competence[,] . . . ***was legal argument*** why the PCR court should rule . . . trial counsel's actions fell below an acceptable legal standard of competence," ***and otherwise "not designed to assist the PCR court to understand certain facts"***) (emphases added). Indeed, Rule 702 permits expert testimony *only* "where it will assist the trier of fact." S.C. R. Evid. 702; *see* Fed. R. Evid. 702.[6] Accordingly, ***"the use of expert testimony is not permitted if it will usurp either the role of the trial judge in instructing the jury as to the applicable law or the role of the jury in applying that law to the facts before it."*** *See United States v. Chapman*, 209 Fed. Appx. 253, 269 (4th Cir. 2006) (quoting *United States v. Duncan*, 42 F.3d 97, 101 (2d Cir. 1994)), *cert. denied*, 550 U.S. 949 (2007) (emphasis added). "When an expert undertakes to tell the jury what result to reach, this does not *aid* the jury in making a decision, but rather attempts to substitute the expert's judgment for the jury's." *Id.* (citations and internal quotation marks omitted in original) (emphasis in original).

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The South Carolina Supreme Court has further instructed that "expert testimony on issues of law is inadmissible," particularly when generated by an expert witness *lawyer*.

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[6] When interpreting the South Carolina Rules of Evidence, South Carolina courts have routinely relied on federal case law interpreting the same. *See, e.g., Dawkins v. Fields*, 580 S.E.2d 433, 437 (S.C. 2003); *see also* S.C. R. Evid. 702 cmt. ("The rule is identical to the federal rule[.]"); S.C. R. Evid. 704 cmt. ("It is identical to the federal rule as it existed prior to the 1984 amendment which added subsection (b) to the rule to prohibit expert testimony on the ultimate issue of whether a criminal defendant is insane.").

Dawkins v. Fields, 580 S.E.2d 433, 436-37 (S.C. 2003) (emphasis in original); *see also O'Quinn v. Beach Assocs.*, 249 S.E.2d 734, 739-40 (S.C. 1978) (holding that the trial court properly excluded professor's expert testimony ***where it was offered to relate to the court "his understanding of the law and his interpretation of the law that would be applicable to the facts and issues***" of the case and otherwise render legal conclusions, diminishing the court's judgment and invading its "exclusive province") (emphasis added). In *Dawkins*, the South Carolina Supreme Court held that the trial court correctly excluded respondents' expert affidavit regarding the propriety of stock issuances, as it "contained legal opinions and conclusions rather than specific facts," and, thus, "constituted an opinion on the law which improperly invaded the trial court's own role." *Id.* at 436. In so holding, the court considered that although "'an opinion . . . is not objectionable because it embraces an ultimate issue to be decided by the trier of fact,'" pursuant to S.C. R. Evid. 704, it must be excluded where it "inappropriately attempt[s] to usurp the trial court's role in determining [dispositive questions]." *Id.* at 437 (quoting *O'Quinn*, 249 S.E.2d at 739-40). The *Dawkins* court found *Green* particularly instructive in view of the similarities between petitioner Green's proposed expert testimony of a criminal defense attorney on whether trial counsel was deficient and respondents' expert affidavit regarding stock issuances relatives to respondents' claims for breach of fiduciary duty, violation of statutory standards for directors, corporate oppression and violation of preemptive rights. *Id.* (citing *Green*, 569 S.E.2d at 325). Like Green's proffered expert testimony, respondents' expert affidavit in *Dawkins* "read[] as if it could have been *respondents'* oral argument to the trial court"; and, although it "arguably offered some helpful, factual information, the overwhelming majority of [the] affidavit [was] simply legal argument as to why summary judgment should be

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denied." *Id.* (emphasis added). For those reasons, the court correctly refused to consider the testimony. *Id.* (citing *Green*, 569 S.E.2d at 325; *O'Quinn*, 249 S.E.2d at 739-40).

Similarly, the United States Court of Appeals for the Fourth Circuit and the United States District Court for the District of South Carolina have consistently excluded expert testimony concerning applicable legal standards as improper. *See, e.g., Adalman v. Baker*, 807 F.2d 359, 366-68 (4th Cir. 1986); *Hermitage Indus. v. Schwerman Trucking Co.*, 814 F. Supp. 484, 485-86 (D. S.C. 1993). In *Adalman*, the issue presented was to what extent could the parties call expert witnesses, lawyers, to testify regarding the applicable law and what it may mean, what it requires or does not require. 807 F.2d at 366. Affirming the district court's exclusion of defense attorney's expert testimony, the court analyzed the issue as follows:

> While this case turns on the applicability and meaning of the securities laws, the issue as just stated obviously has a far broader reach than securities cases. If such experts are to testify to the meaning and applicability of securities laws, what line is to be drawn to exclude tort lawyers from offering their expert opinions to the jury as to the meaning and applicability of the laws governing tort litigation? Examples of this sort could be multiplied across the gamut of litigation.
>
> The analysis here begins with the proposition that under our system it is the responsibility – and the duty – of the court to state to the jury the meaning and applicability of the appropriate law, leaving to the jury the task of determining the facts which may or may not bring the challenged conduct within the scope of the court's instruction as to the law.
>
> ***Under circumstances involving domestic law, this court can conceive of no circumstances which should shift this burden from the court to the jury, where the jury judgment would be influenced, if not made, on the basis of expert witness testimony which would undoubtedly follow the usual pattern of conflicting expert opinions. Permitting such testimony as to legal conclusions gives cogent meaning to the apprehensions that jurors will turn to the expert, rather than to the judge, for guidance on the applicable law.***

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Id. (citation and internal quotation marks omitted) (emphasis added).

Relying on *Adalman* and a plethora of additional authority excluding opinion testimony in the form of legal conclusions or interpretations, the *Hermitage* court also excluded expert testimony stating opinions as to legal conclusions and, correspondingly, rejected defendant's contention that the proffered expert testimony was admissible as an opinion on an ultimate issue under S.C. R. Evid. 704(a). 814 F. Supp. at 485-86 ("Other federal circuit courts of appeals have concluded that opinion testimony in the form of a legal conclusion is inadmissible. *See, e.g., Hygh v. Jacobs*, 961 F.2d 359, 363 (2d Cir. 1992); *Phillips v. Calhoun*, 956 F.2d 949, 952 (10th Cir. 1992); *Montgomery v. Aetna Cas. & Sur. Co.*, 898 F.2d 1537, 1541 (11th Cir. 1990); *Shahid v. City of Detroit*, 889 F.2d 1543, 1547-48 (6th Cir. 1989); *Owen* [*v. Kerr-McGee Corp.*], 698 F.2d [236,] . . . 239-40 [(5th Cir. 1983)]. The South Carolina Supreme Court has also held that expert testimony embracing a legal conclusion is inadmissible. *See, e.g., O'Quinn*[,] . . . 249 S.E.2d . . . [at] 739-40[.]"). The court described the various reasons advanced in excluding such testimony: "it allows a witness to tell the jury what verdict to reach"; "it tends to confuse jurors"; and, as noted in *Adalman*, "it increases the likelihood that jurors will look to the witness rather than the trial judge for guidance as to the law." *Id.* at 486.

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Most significantly, on August 31, 2010, in a litigation similar to the State's, the United States District Court for the Central District of California granted, in its entirety, defendant Welch Foods, Inc.'s Motion *in Limine* to Exclude Testimony and Report of Sheldon Bradshaw where Bradshaw's purported "expert rebuttal report" was characterized as a "legal brief" or "treatise" intended to "instruct [the] Court and the jury on pure matters of law," and defendant emphasized that "[i]t would be hard to find a more striking example of 'legal conclusions' than those presented by Mr. Bradshaw." ([Public Redacted] Defendant Welch Food Inc.'s Notice of

Motion and Motion *in Limine* to Exclude Testimony and Report of Sheldon Bradshaw ("Motion *in Limine*"), *POM Wonderful, LLC v. Welch Foods, Inc.*, 2:09-cv-00567, slip op. at 1-3 (C.D. Ca. July 26, 2010), a true and correct copy of which is attached hereto as Exhibit D; *see* Civil Minutes – General, *POM Wonderful, LLC v. Welch Foods, Inc.*, 2:09-cv-00567, slip op. at 3 (C.D. Ca. Aug. 31, 2010) (in case involving claims for false and deceptive advertising under California consumer protection law, *inter alia*, granting defendant's Motion *in Limine* to Exclude Testimony and Report of Sheldon Bradshaw), a true and correct copy of which is attached hereto as Exhibit E; *see also* Complaint, *POM Wonderful, LLC v. Welch Foods, Inc.*, 2:09-cv-00567 (C.D. Ca. Jan. 23, 2009), a true and correct copy of which is attached hereto as Exhibit F.) Specifically, the court refused to admit Bradshaw's testimony or related "expert rebuttal report" regarding topics similar to those he now advances in this case, including to rebut portions of defendant's regulatory-based expert report regarding the legal effect of certain FDA Warning Letters issued to POM, as well as legal conclusions relative to FDA regulators. (*See* Motion *in Limine*, at 1-5 (Ex. D.); *see also* Civil Minutes – General (Ex. E).) In so ruling, the court concluded that "Bradshaw's testimony offers legal conclusions that are ***unnecessary and impermissible.***" (Civil Minutes – General (emphasis added) (Ex. E.).)

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Consistent with the foregoing authorities, Bradshaw's testimony constitutes impermissible and prejudicial legal opinion and interpretation that, like the excluded expert opinion by the defense attorney in *Adalman*, would not only "***allow [Bradshaw] to tell the jury what verdict to reach***" and "***confuse the jurors***," but also "***increase the likelihood that jurors will look to [Bradshaw] rather than [this Court] for guidance as to the law***," prohibitively invading the province of the Court and jury. *Adalman*, 814 F. Supp. at 486 (emphases added).

Also similar to the proffered expert testimony of lawyers in *Green* and *Dawkins, supra* at 11-12, and his own prior testimony in *POM*, supra at 14-15, Bradshaw's Report reads as if it could be Janssen's opening statement at trial; and, even if his Report had contained some potentially helpful, factual information relative to "FDA regulatory matters"—the topic about which he was purportedly hired to opine—"the overwhelming majority of his [Report] is simply legal argument" on the ultimate issue in this case and, therefore, inadmissible. *Dawkins*. 580 S.E.2d (citing *Green*, 569 S.E.2d at 325; *O'Quinn*, 249 S.E.2d at 739-40). (*See also* Civil Minutes – General (Ex. E).)

In short, Bradshaw's testimony is not designed to assist the trier of fact, but, rather, is admitted legal argument why the Court should rule, as a matter of law, the "Risperdal label and November 10 medical communication were [not] 'false' and 'misleading,'" and regarding the "legal effect" of FDA letters, Risperdal labeling and other promotional activities of Defendant relative to Risperdal. (Rep. at 4, 8, 9, 13, 16—18.) Apart from the egregious bias he advances as an *attorney* hired by Defendant and the fact that his highly prejudicial conclusions are erroneous, Bradshaw's Report does nothing more than render legal conclusions which are not likely to assist the trier of fact in its determination. (*See id.*) Bradshaw's testimony is, in fact, more likely to confuse the jury by outlining *his* (and Janssen's) interpretation of the operative legal standard under SCUTPA and attempting to tell jurors what result to reach with respect to whether certain alleged violations of SCUTPA were, in fact, "false" and "misleading." (*Id.*; *see* Pl.'s Second Am. Compl. ¶ 58 (alleging violations of SCUTPA.) Furthermore, to the extent Bradshaw opines about whether a SCUTPA violation exists, that is, whether certain of Defendant's communications were "false" and "misleading," the legal definition and explanation will be presented to the jury through the Court's instructions. While Defendant might have been

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permitted to present lay testimony from FDA regulators who were parties to the correspondence about which Bradshaw opines, regarding what they believed to be the intent or the motivation of the FDA, the Court should not admit the testimony Defendant now advances as it would not only intrude upon the province of the Court in interpreting the law but also upon the province of the jury in allowing their witness to present what would amount to an expert opinion that Defendant did not violate the law.

D. Sheldon Bradshaw's Opinions Should Be Excluded Because They Were Not Timely Disclosed In Advance Of Trial And Are, Therefore, Prejudicial.

Since the inception of this Court's discovery program, Defendant's vast discovery deficiencies have been the subject of various motions to compel by the State and related Orders by the Court compelling the production of documentation and depositions that are relevant and necessary to the State's claims. Defendant has had numerous opportunities to comply with its discovery obligations as well as the rules of this Court but has remained inscrutably defiant in its reaction to the Court's discovery and other pretrial Orders. Defendant's refusal to comply with existing Orders has most recently caused the State to inure significantly prejudice on the eve of trial as further described below.

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Despite the Court's long-standing Case Scheduling Order requiring parties to serve all expert reports by May 14, 2010 and otherwise complete expert-based discovery by December 31, 2010, Defendant disclosed putative expert Bradshaw's opinions on December 30, 2010, at the close of what has been a more than three-year long discovery period, *more than seven months after the Court's related deadline*, and, also, more than seven months after producing reports generated by eleven timely designated expert witnesses,[7] without seeking relief from the

[7] *See* Def.'s letter of May 14, 2010, identifying its expert witnesses (with the exception of Drs. Jebaily and Wecker and Sheldon Bradshaw) and enclosing expert reports, a true and correct copy of which is attached hereto as Exhibit G.

operative Order or explanation otherwise.[8] As a result, the State has been unable to meaningfully participate in expert discovery and, likewise, prevented from deposing Bradshaw. In addition, the State has been unable to adequately prepare its case for trial, as Defendant has withheld certain discoverable liability information relative to its expert witness in failing to make requisite disclosures timely. The State has suffered and will continue to suffer significant prejudice should Bradshaw's opinions be admitted at the trial. Accordingly, Rule 403 mandates their exclusion. *See* S.C. R. Evid. 403.

Indeed, "[t]he gist and gravaman of the discovery rules mandate full and fair disclosure to prevent a trial from becoming a guessing game," and likewise, "the rights of discovery articulated by the rules give the attorney the means to prepare for trial." *Scott v. Greenville Housing Auth.*, 579 S.E.2d 151, 158 (S.C. Ct. App. 2003) (citing *South Carolina State Highway Dep't v. Booker*, 195 S.E.2d 615, 617, 619 (S.C. 1973)). Because "discovery is the quintessence of preparation for trial, . . . when discovery rights are trampled, prejudice must be presumed." *Id.*

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Furthermore, if such testimony was admitted, the Court would then be required to determine what sanction to impose for Defendant's failure to disclose discoverable information during the discovery process, including "weigh[ing] the nature of the interrogatories, the discovery posture of the case, willfulness, and the degree of prejudice." *Samples v. Mitchell*, 495 S.E.2d 213, 216 (S.C. Ct. App. 1997) (reversing and remanding where defendant failed to timely disclose evidence that was "clearly relevant" to plaintiff's claim during the discovery period, and trial judge admitted such evidence without first weighing the requisite factors for determining what sanction to impose "for failure to disclose evidence during the discovery process"). "Even

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[8] *See* Def.'s letter of December 30, 2010, identifying Sheldon Bradshaw as expert witness and enclosing report, a true and correct copy of which is attached hereto as Exhibit H.

though the imposition of sanctions is usually left to the sound discretion of the trial judge, whatever sanction the judge imposes should serve to protect the rights of discovery provided by the Rules," bearing in mind that "[o]verly lenient sanctions are to be avoided." *Id.* (citing *Downey v. Dixon*, 362 S.E.2d 317, 318-19 (S.C. Ct. App. 1987)) (internal quotation marks omitted).

In sum, "[a]ppellate courts have routinely upheld, as within the discretion of the trial court, the exclusion of witnesses and evidentiary exhibits based on a party's failure to comply with discovery deadlines." *Adalman*, 807 F.2d at 369; *see also Samples*, 495 S.E.2d at 216-18; *Downey*, 362 S.E.2d at 319-19. Because Defendant has willfully failed to comply with the Court's deadlines relative to expert discovery and caused the State to incur significant prejudice, Bradshaw's opinions must be excluded.

IV.
CONCLUSION

For the foregoing reasons, the State's Motion to Exclude the Testimony of Sheldon Bradshaw should be granted, and Defendant should be precluded from offering the above referenced testimony in its entirety.

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Respectfully submitted,

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