ZIPRASIDONE MESYLATE- ziprasidone mesylate injection, powder, lyophilized, for solution
Dr.Reddy's Laboratories, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZIPRASIDONE MESYLATE FOR INJECTION safely and effectively. See full prescribing information for ZIPRASIDONE MESYLATE FOR INJECTION.
ZIPRASIDONE MESYLATE for injection, for intramuscular use
Initial U.S. Approval: 2001

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 (5.1)**
- **Ziprasidone mesylate for injection is not approved for the treatment of patients with dementia-related psychosis (5.1)**

INDICATIONS AND USAGE

Ziprasidone mesylate for injection is an atypical antipsychotic. In choosing among treatments, prescribers should be aware of the capacity of ziprasidone mesylate for injection to prolong the QT interval and may consider the use of other drugs first (5.3)
Ziprasidone mesylate for injection as an intramuscular injection is indicated for the:
- Acute treatment of agitation in schizophrenic patients. (1)

DOSAGE AND ADMINISTRATION

- Acute treatment of agitation associated with schizophrenia (intramuscular administration): 10 mg to 20 mg up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every 2 hours. Doses of 20 mg may be administered every 4 hours. (2.4)

DOSAGE FORMS AND STRENGTHS

- For injection: 20 mg/mL single-use vials (3)

CONTRAINDICATIONS

- Do not use in patients with a known history of QT prolongation (4.1)
- Do not use in patients with recent acute myocardial infarction (4.1)
- Do not use in patients with uncompensated heart failure (4.1)
- Do not use in combination with other drugs that have demonstrated QT prolongation (4.1)
- Do not use in patients with known hypersensitivity to ziprasidone (4.2)

WARNINGS AND PRECAUTIONS

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack). (5.2)
- *QT Interval Prolongation*: Ziprasidone mesylate for injection use should be avoided in patients with bradycardia, hypokalemia or hypomagnesemia, congenital prolongation of the QT interval, or in combination with other drugs that have demonstrated QT prolongation. (5.3)
- *Neuroleptic Malignant Syndrome* (NMS): Potentially fatal symptom complex has been reported with antipsychotic drugs. Manage with immediate discontinuation of drug and close monitoring. (5.4)
- *Severe Cutaneous Adverse Reactions*, such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson syndrome has been reported with ziprasidone exposure. DRESS and other Severe Cutaneous Adverse Reactions (SCAR) are sometimes fatal. Discontinue ziprasidone mesylate for injection if DRESS or SCAR are suspected. (5.5)
- *Tardive Dyskinesia:* May develop acutely or chronically. (5.6)

- *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. (5.7)
- *Hyperglycemia and Diabetes Mellitus (DM):* Monitor all patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients with DM risk factors should undergo blood glucose testing before and during treatment. (5.7)
- *Dyslipidemia:* Undesirable alterations have been observed in patients treated with atypical antipsychotics. (5.7)
- *Weight Gain*: Weight gain has been reported. Monitor weight gain. (5.7)
- *Rash*: Discontinue in patients who develop a rash without an identified cause. (5.8)
- *Orthostatic Hypotension:* Use with caution in patients with known cardiovascular or cerebrovascular disease. (5.9)
- *Leukopenia, Neutropenia, and Agranulocytosis* has 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 should discontinue ziprasidone mesylate for injection at the first sign of a decline in WBC in the absence of other causative factors. (5.11)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower seizure threshold. (5.12)
- *Potential for Cognitive and Motor impairment:* Patients should use caution when operating machinery. (5.13)
- *Suicide*: Closely supervise high-risk patients. (5.18)

ADVERSE REACTIONS

Commonly observed adverse reactions (incidence ≥5% and at least twice the incidence for placebo) were:

• *Schizophrenia*: Somnolence, respiratory tract infection. (6.1)

• *Manic and Mixed Episodes Associated with Bipolar Disorder*: Somnolence, extrapyramidal symptoms, dizziness, akathisia, abnormal vision, asthenia, vomiting. (6.1)

• *Intramuscular administration* (≥5% and at least twice the lowest intramuscular ziprasidone group): Headache, nausea, somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Dr. REDDY'S LABORATORIES Inc., at 1-888-375- 3784 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Ziprasidone should not be used in combination with other drugs that have demonstrated QT prolongation. (4.1, 7.3)
- The full prescribing information contains additional drug interactions. (7).

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
- *Pediatric Use*: Safety and effectiveness for pediatric patients has not been established. (8.4)
- *Renal Impairment:* Intramuscular ziprasidone should be administered with caution to patients with impaired renal function as the cyclodextrin excipient is cleared by renal filtration. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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. Ziprasidone mesylate for injection is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)].*

1 INDICATIONS AND USAGE

Ziprasidone mesylate for injection intramuscular is indicated for acute agitation in schizophrenic patients. When deciding among the alternative treatments available for the condition needing treatment, the prescriber should consider the finding of ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs *[see Warnings and Precautions (5.3)].* Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia, and sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether ziprasidone will cause torsade de pointes or increase the rate of sudden death is not yet known *[see Warnings and Precautions (5.3)]*

Acute Treatment of Agitation in Schizophrenia

- Ziprasidone mesylate for injection intramuscular is indicated for the treatment of acute agitation in schizophrenic adult patients for whom treatment with ziprasidone is appropriate and who need intramuscular antipsychotic medication for rapid control of

agitation.

Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

2 DOSAGE AND ADMINISTRATION

2.4 Acute Treatment of Agitation in Schizophrenia

Intramuscular Dosing
The recommended dose is 10 mg to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every two hours; doses of 20 mg may be administered every four hours up to a maximum of 40 mg/day. Intramuscular administration of ziprasidone for more than three consecutive days has not been studied.

If long-term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as soon as possible.

Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

Ziprasidone intramuscular is intended for intramuscular use only and should not be administered intravenously.

Intramuscular Preparation for Administration
Ziprasidone mesylate for injection should only be administered by intramuscular injection and should not be administered intravenously. Single-dose vials require reconstitution prior to administration.

Add 1.2 mL of Sterile Water for Injection to the vial and shake vigorously until all the drug is dissolved. Each mL of reconstituted solution contains 20 mg ziprasidone. To administer a 10 mg dose, draw up 0.5 mL of the reconstituted solution. To administer a 20 mg dose, draw up 1.0 mL of the reconstituted solution. Any unused portion should be discarded. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final solution. This medicinal product must not be mixed with other medicinal products or solvents other than Sterile Water for Injection. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

3 DOSAGE FORMS AND STRENGTHS

Ziprasidone mesylate for injection is available in a single-dose vial as ziprasidone

mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions) *[see Dosage and Administration (2.4)].* Each mL of ziprasidone mesylate for injection (when reconstituted) affords a colorless to pale pink solution that contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

4 CONTRAINDICATIONS

4.1 QT Prolongation

Because of ziprasidone's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone is contraindicated:

- in patients with a known history of QT prolongation (including congenital long QT syndrome)
- in patients with recent acute myocardial infarction
- in patients with uncompensated heart failure

Pharmacokinetic/pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with:

- dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus.
- other drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning *[see Warnings and Precautions (5.3)].*

4.2 Hypersensitivity

Ziprasidone is contraindicated in individuals with a known hypersensitivity to the product.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. 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. Ziprasidone mesylate for injection is not approved for the treatment of patients with dementia-related psychosis. *[see Boxed Warning, Warnings and Precautions (5.2)].*

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

In placebo-controlled trials in elderly subjects with dementia, patients randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. Ziprasidone mesylate for injection is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)].*

5.3 QT Prolongation and Risk of Sudden Death

Ziprasidone use should be avoided in combination with other drugs that are known to prolong the QTc interval *[see Contraindications (4.1) and Drug Interactions (7.4)].* Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QTc interval. Such drugs should not be prescribed with ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias *[see Contraindications (4)].*

A study directly comparing the QT/QTc prolonging effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. In the first phase of the trial, ECGs were obtained at the time of maximum plasma concentration when the drug was administered alone. In the second phase of the trial, ECGs were obtained at the time of maximum plasma concentration while the drug was co-administered with an inhibitor of the CYP4503A4 metabolism of the drug.

In the first phase of the study, the mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine.

In the second phase of the study, the effect of ziprasidone on QTc length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg twice daily).

In placebo-controlled trials, oral ziprasidone increased the QTc interval compared to

placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials with oral ziprasidone, the electrocardiograms of 2/2988 (0.06%) patients who received ziprasidone mesylate for injection and 1/440 (0.23%) patients who received placebo revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone. One patient had a history of prolonged QTc and a screening measurement of 489 msec; QTc was 503 msec during ziprasidone treatment. The other patient had a QTc of 391 msec at the end of treatment with ziprasidone and upon switching to thioridazine experienced QTc measurements of 518 and 593 msec.
Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QTc prolongations may also increase risk, or increase it in susceptible individuals. Although torsade de pointes has not been observed in association with the use of ziprasidone in premarketing studies and experience is too limited to rule out an increased risk, there have been rare post-marketing reports (in the presence of multiple confounding factors) *[see Adverse Reactions (6.2)].*

A study evaluating the QT/QTc prolonging effect of intramuscular ziprasidone, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of ziprasidone (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular ziprasidone is 50% higher than the recommended therapeutic dose. The mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QTc from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patients had a QTc interval exceeding 500 msec.

As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking ziprasidone at recommended doses. The premarketing experience for ziprasidone did not reveal an excess risk of mortality for ziprasidone compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, ziprasidone's larger prolongation of QTc length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for ziprasidone than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products *[see Indications and Usage (1)].*

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

It is recommended that patients being considered for ziprasidone treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or

hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during ziprasidone treatment. Persistently prolonged QTc intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, ziprasidone should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec.

For patients taking ziprasidone who experience symptoms that could indicate the occurrence of torsade de pointes, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, e.g., Holter monitoring may be useful.

5.4 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. 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 (CNS) 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.

5.5 Severe Cutaneous Adverse Reactions

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with Ziprasidone exposure. DRESS consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. DRESS is sometimes fatal. Discontinue ziprasidone if DRESS is suspected.

Other severe cutaneous adverse reactions

Other severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, have been reported with ziprasidone exposure. Severe cutaneous adverse reactions are sometimes fatal. Discontinue ziprasidone if severe cutaneous adverse reactions are suspected.

5.6 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment 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, ziprasidone 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 ziprasidone, drug discontinuation should be considered. However, some patients may require treatment with ziprasidone despite the presence of the syndrome.

5.7 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 and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with ziprasidone mesylate for injection. Although fewer patients have been treated with ziprasidone mesylate for injection, it is not known if this more limited experience is the sole reason for the paucity of such reports. 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 reactions is not completely understood. Precise risk estimates for hyperglycemia-related adverse reactions 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 antidiabetic treatment despite discontinuation of the suspect drug.

Pooled data from short-term, placebo-controlled studies in schizophrenia and bipolar disorder are presented in Tables 1 to 4. Note that for the flexible dose studies in both schizophrenia and bipolar disorder, each subject is categorized as having received either low (20 to 40 mg BID) or high (60 to 80 mg BID) dose based on the subject’s modal daily dose. In the tables showing categorical changes, the percentages (% column) are calculated as 100x(n/N).

Table 1: Glucose* Mean Change from Baseline in Short-Term (up to 6 weeks), Placebo-Controlled, Fixed-Dose, Oral Ziprasidone, Monotherapy Trials in Adult Patients with Schizophrenia

Mean Random Glucose Change from Baseline mg/dL (N)						
Ziprasidone						Placebo
5 mg BID	20 mg BID	40 mg BID	60 mg BID	80 mg BID	100 mg BID	
-1.1 (N=45)	+2.4 (N=179)	-0.2 (N=146)	-0.5 (N=119)	-1.7 (N=104)	+4.1 (N=85)	+1.4 (N=260)

*"Random" glucose measurements—fasting/non-fasting status unknown

Table 2: Glucose* Categorical Changes in Short-Term (up to 6 weeks), Placebo-Controlled, Fixed-Dose, Oral Ziprasidone, Monotherapy Trials in Adult Patients with Schizophrenia

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	N	n (%)
Random Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Ziprasidone	438	77 (17.6%)
		Placebo	169	26 (15.4%)
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Ziprasidone	159	54 (34.0%)
		Placebo	66	22 (33.3%)

*"Random" glucose measurements – fasting/non-fasting status unknown

In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline in random glucose for ziprasidone 20 to 40 mg BID was -3.4 mg/dL (N=122); for ziprasidone 60 to 80 mg BID was +1.3 mg/dL (N=10); and for placebo was +0.3 mg/dL (N=71).

Table 3: Glucose* Mean Change from Baseline in Short-Term (up to 6 weeks), Placebo-Controlled, Flexible-Dose, Oral Ziprasidone, Monotherapy Trials in Adult Patients with Bipolar Disorder

Mean Fasting Glucose Change from Baseline mg/dL (N)		
Ziprasidone		Placebo
Low Dose: 20 to 40 mg		

Low Dose: 20 to 40 mg BID	High Dose: 60 to 80 mg BID	
+0.1 (N=206)	+1.6 (N=166)	+1.4 (N=287)

*Fasting

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Table 4: Glucose* Categorical Changes in Short-Term (up to 6 weeks), Placebo-Controlled, Flexible-Dose, Oral Ziprasidone, Monotherapy Trials in Adult Patients with Bipolar Disorder

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	N	n (%)
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Ziprasidone	272	5 (1.8%)
		Placebo	210	2 (1.0%)
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Ziprasidone	79	12 (15.2%)
		Placebo	71	7 (9.9%)

*Fasting

Dyslipidemia
Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Pooled data from short-term, placebo-controlled studies in schizophrenia and bipolar disorder are presented in Tables 5 to 8.

Table 5: Lipid* Mean Change from Baseline in Short-Term (up to 6 weeks), Placebo-Controlled, Fixed-Dose, Oral Ziprasidone Monotherapy Trials in Adult Patients with Schizophrenia

Mean Lipid Change from Baseline mg/dL (N)							
Laboratory Analyte	Ziprasidone						Placebo
	5 mg BID	20 mg BID	40 mg BID	60 mg BID	80 mg BID	100 mg BID	
Triglycerides	-12.9 (N=45)	-9.6 (N=181)	-17.3 (N=146)	-0.05 (N=120)	-16.0 (N=104)	+0.8 (N=85)	-18.6 (N=260)
Total Cholesterol	-3.6 (N=45)	-4.4 (N=181)	-8.2 (N=147)	-3.6 (N=120)	-10.0 (N=104)	-3.6 (N=85)	-4.7 (N=261)

*"Random" lipid measurements, fasting/non-fasting status unknown

Table 6: Lipid* Categorical Changes in Short-Term (up to 6 weeks), Placebo-Controlled, Fixed-Dose, Oral Ziprasidone Monotherapy Trials in Adult Patients

with Schizophrenia

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	N	n (%)
Triglycerides	Increase by ≥50 mg/dL	Ziprasidone	681	232 (34.1%)
		Placebo	260	53 (20.4%)
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Ziprasidone	429	63 (14.7%)
		Placebo	152	12 (7.9%)
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Ziprasidone	92	43 (46.7%)
		Placebo	41	12 (29.3%)
Total Cholesterol	Increase by ≥40 mg/dL	Ziprasidone	682	76 (11.1%)
		Placebo	261	26 (10.0%)
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Ziprasidone	380	15 (3.9%)
		Placebo	145	0 (0.0%)
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Ziprasidone	207	56 (27.1%)
		Placebo	82	22 (26.8%)

*"Random"lipid measurements, fasting/non-fasting status unknown

In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline in random triglycerides for ziprasidone 20 to 40 mg BID was +26.3 mg/dL (N=15); for ziprasidone 60 to 80 mg BID was -39.3 mg/dL (N=10); and for placebo was +12.9 mg/dL (N=9). In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline in random total cholesterol for ziprasidone 20 to 40 mg BID was +2.5 mg/dL (N=14); for ziprasidone 60 to 80 mg BID was -19.7 mg/dL (N=10); and for placebo was -28.0 mg/dL (N=9).

Table 7: Lipid* Mean Change from Baseline in Short-Term (up to 6 weeks), Placebo-Controlled, Flexible-Dose, Oral Ziprasidone Monotherapy Trials in Adult Patients with Bipolar Disorder

Laboratory Analyte	Mean Change from Baseline mg/dL (N)		
	Ziprasidone		Placebo
	Low Dose: 20 to 40 mg BID	High Dose: 60 to 80 mg BID	
Fasting Triglycerides	+0.95 (N=206)	-3.5 (N=165)	+8.6 (N=286)
Fasting Total Cholesterol	-2.8 (N=206)	-3.4 (N=165)	-1.6 (N=286)
Fasting LDL Cholesterol	-3.0 (N=201)	-3.1 (N=158)	-1.97 (N=270)
Fasting HDL Cholesterol	-0.09 (N=206)	+0.3 (N=165)	-0.9 (N=286)

*Fasting

Table 8: Lipid* Categorical Changes in Short-Term (up to 6 weeks), Placebo-Controlled, Flexible-Dose, Oral Ziprasidone Monotherapy Trials in Adult Patients with Bipolar Disorder

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	N	n (%)
Fasting Triglycerides	Increase by ≥50 mg/dL	Ziprasidone	371	66 (17.8%)
		Placebo	286	62 (21.7%)
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Ziprasidone	225	15 (6.7%)
		Placebo	179	13 (7.3%)
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Ziprasidone	58	16 (27.6%)
		Placebo	47	14 (29.8%)
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Ziprasidone	371	30 (8.1%)
		Placebo	286	13 (4.5%)
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Ziprasidone	204	5 (2.5%)
		Placebo	151	2 (1.3%)
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Ziprasidone	106	10 (9.4%)
		Placebo	87	15 (17.2%)
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Ziprasidone	359	39 (10.9%)
		Placebo	270	17 (6.3%)
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Ziprasidone	115	0 (0%)
		Placebo	89	1 (1.1%)
	Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL)	Ziprasidone	193	18 (9.3%)
		Placebo	141	14 (9.9%)
Fasting HDL	Normal (>=40 mg/dL) to Low (<40 mg/dL)	Ziprasidone	283	22 (7.8%)
		Placebo	220	24 (10.9%)

*Fasting

Weight Gain
Weight gain has been observed with atypical antipsychotic use. Monitoring of weight is recommended. Pooled data from short-term, placebo-controlled studies in schizophrenia and bipolar disorder are presented in Tables 9 to 10.

Table 9: Weight Mean Changes in Short-Term (up to 6 weeks), Placebo-Controlled, Fixed-Dose, Oral Ziprasidone Monotherapy Trials in Adult Patients with Schizophrenia

Ziprasidone						Placebo
					100 mg	

5 mg BID	20 mg BID	40 mg BID	60 mg BID	80 mg BID	100 mg BID	Placebo
Mean Weight (kg) Changes from Baseline (N)						
+0.3 (N=40)	+1.0 (N=167)	+1.0 (N=135)	+0.7 (N=109)	+1.1 (N=97)	+0.9 (N=74)	-0.4 (227)
Proportion of Patients with ≥7% Increase in Weight from Baseline (N)						
0.0% (N=40)	9.0% (N=167)	10.4% (N=135)	7.3% (N=109)	15.5% (N=97)	10.8% (N=74)	4.0% (N=227)

In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline weight for ziprasidone 20 to 40 mg BID was -2.3 kg (N=124); for ziprasidone 60 to 80 mg BID was +2.5 kg (N=10); and for placebo was -2.9 kg (N=72). In the same long-term studies, the proportion of subjects with ≥ 7% increase in weight from baseline for ziprasidone 20 to 40 mg BID was 5.6% (N=124); for ziprasidone 60 to 80 mg BID was 20.0% (N=10), and for placebo was 5.6% (N=72). In a long-term (at least 1 year), placebo-controlled, fixed-dose study in schizophrenia, the mean change from baseline weight for ziprasidone 20 mg BID was -2.6 kg (N=72); for ziprasidone 40 mg BID was -3.3 kg (N=69); for ziprasidone 80 mg BID was -2.8 kg (N=70) and for placebo was -3.8 kg (N=70). In the same long-term fixed-dose schizophrenia study, the proportion of subjects with ≥ 7% increase in weight from baseline for ziprasidone 20 mg BID was 5.6% (N=72); for ziprasidone 40 mg BID was 2.9% (N=69); for ziprasidone 80 mg BID was 5.7% (N=70) and for placebo was 2.9% (N=70).

Table 10: Summary of Weight Change in Short-Term (up to 6 weeks), Placebo-Controlled, Flexible-Dose, Oral Ziprasidone Monotherapy Trials in Adult Patients with Bipolar Disorder:

Ziprasidone		Placebo
Low Dose: 20 to 40 mg BID	**High Dose*: 60 to 80 mg BID**	
Mean Weight (kg) Changes from Baseline (N)		
+0.4 (N=295)	+0.4 (N=388)	+0.1 (N=451)
Proportion of Patients with ≥ 7% Increase in Weight from Baseline (N)		
2.4% (N=295)	4.4% (N=388)	1.8% (N=451)

* Note that in the High Dose group, there were 2 subjects with modal 200 mg total daily dose and 1 subject with modal 100 mg total daily dose.

Schizophrenia -The proportions of patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of four 4-and 6-week placebo-controlled schizophrenia clinical trials, revealing a statistically significantly greater incidence of weight gain for ziprasidone (10%) compared to placebo (4%). A median weight gain of 0.5 kg was observed in ziprasidone patients compared to no median weight change in placebo patients. In this set of clinical trials, weight gain was reported as an adverse reaction in 0.4% and 0.4% of ziprasidone and placebo patients, respectively. During long-term therapy with ziprasidone, a categorization of patients at baseline on the basis

of body mass index (BMI) revealed the greatest mean weight gain and highest incidence of clinically significant weight gain (> 7% of body weight) in patients with low BMI (<23) compared to normal (23 to 27) or overweight patients (>27). There was a mean weight gain of 1.4 kg for those patients with a “low” baseline BMI, no mean change for patients with a “normal” BMI, and a 1.3 kg mean weight loss for patients who entered the program with a “high” BMI.

Bipolar Disorder – During a 6-month placebo-controlled bipolar maintenance study in adults with ziprasidone as an adjunct to lithium or valproate, the incidence of clinically significant weight gain (≥ 7% of body weight) during the double-blind period was 5.6% for both ziprasidone and placebo treatment groups who completed the 6 months of observation for relapse. Interpretation of these findings should take into consideration that only patients who adequately tolerated ziprasidone entered the double-blind phase of the study, and there were substantial dropouts during the open label phase.

5.8 Rash

In premarketing trials with ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to dose of ziprasidone, although the finding might also be explained by the longer exposure time in the higher dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly with adjunctive treatment with antihistamines or steroids and/or upon discontinuation of ziprasidone, and all patients experiencing these reactions were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, ziprasidone should be discontinued.

5.9 Orthostatic Hypotension

Ziprasidone 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 antagonist properties. Syncope was reported in 0.6% of the patients treated with ziprasidone.

Ziprasidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

5.10 Falls

Antipsychotic drugs (which include ziprasidone mesylate for injection) may cause somnolence, postural hypotension, and motor and sensory instability, which could lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.11 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents. Agranulocytosis (including fatal cases) 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 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 should discontinue ziprasidone mesylate for injection 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 ziprasidone mesylate for injection and have their WBC followed until recovery.

5.12 Seizures

During clinical trials, seizures occurred in 0.4% of patients treated with ziprasidone. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. As with other antipsychotic drugs, ziprasidone 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.

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. Ziprasidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia *[see Boxed Warning].*

5.14 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, ziprasidone elevates prolactin levels in humans. Increased prolactin levels were also observed in animal studies with this compound, and were associated with an increase in mammary gland neoplasia in mice; a similar effect was not observed in rats *[see Nonclinical Toxicology (13.1)]*. 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. 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.

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. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density.

5.15 Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse reaction in patients treated with ziprasidone. In the 4-and 6-week placebo-controlled trials, somnolence was reported in 14% of patients on ziprasidone compared to 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since ziprasidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that ziprasidone therapy does not affect them adversely.

5.16 Priapism

One case of priapism was reported in the premarketing database. While the relationship of the reaction to ziprasidone use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that ziprasidone may share this capacity. Severe priapism may require surgical intervention.

5.17 Body Temperature Regulation

Although not reported with ziprasidone in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ziprasidone 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.

5.18 Suicide

The possibility of a suicide attempt is inherent in psychotic illness or bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ziprasidone should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose.

5.19 Patients with Concomitant Illnesses

Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses is limited *[see Use in Specific Populations (8.6),(8.7)].*

Ziprasidone 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 QTc prolongation and orthostatic hypotension with ziprasidone, caution should be observed in cardiac patients. *[see Warnings and Precautions (5.3), (5.9)].*

5.20 Laboratory Tests

Patients being considered for ziprasidone treatment that are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be replaced before proceeding with treatment. Patients who are started on diuretics during Ziprasidone therapy need periodic monitoring of serum potassium and magnesium. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec *[see Warnings and Precautions (5.3)].*

6 ADVERSE REACTIONS

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 the rates observed in practice.

Clinical trials for oral ziprasidone included approximately 5700 patients and/or normal subjects exposed to one or more doses of ziprasidone. Of these 5700, over 4800 were patients who participated in multiple-dose effectiveness trials, and their experience corresponded to approximately 1831 patient-years. These patients include: (1) 4331 patients who participated in multiple-dose trials, predominantly in schizophrenia, representing approximately 1698 patient-years of exposure as of February 5, 2000; and (2) 472 patients who participated in bipolar mania trials representing approximately 133 patient-years of exposure. An additional 127 patients with bipolar disorder participated in a long-term maintenance treatment study representing approximately 74.7 patient-years of exposure to ziprasidone. The conditions and duration of treatment with ziprasidone included open-label and double-blind studies, inpatient and outpatient studies, and short-term and longer-term exposure.

Clinical trials for intramuscular ziprasidone included 570 patients and/or normal subjects who received one or more injections of ziprasidone. Over 325 of these subjects participated in trials involving the administration of multiple doses.

Adverse reactions during exposure were obtained by collecting voluntarily reported adverse experiences, as well as results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

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.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with Oral Ziprasidone

The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which ziprasidone was administered in doses ranging from 10 to 200 mg/day.

Commonly Observed Adverse Reactions in Short Term Placebo-Controlled Trials

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

Schizophrenia trials *(see Table 11)*

- Somnolence
- Respiratory Tract Infection

Bipolar trials *(see Table 12)*

- Somnolence
- Extrapyramidal Symptoms which includes the following adverse reaction terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse reactions occurred individually at an incidence greater than 10% in bipolar mania trials.
- Dizziness which includes the adverse reaction terms dizziness and lightheadedness.
- Akathisia
- Abnormal Vision
- Asthenia
- Vomiting

SCHIZOPHRENIA

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials of Oral Ziprasidone

Approximately 4.1% (29/702) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 2.2% (6/273) on placebo. The most common reaction associated with dropout was rash, including 7 dropouts for rash among ziprasidone patients (1%) compared to no placebo patients *[see Warnings and Precautions (5.8)].*

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

Table 11 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy (up to 6 weeks) in predominantly patients with schizophrenia, including only those reactions that occurred

in 2% or more of patients treated with ziprasidone and for which the incidence in patients treated with ziprasidone was greater than the incidence in placebo-treated patients.

Table 11: Treatment-Emergent Adverse Reaction Incidence In Short-Term

Oral Placebo-Controlled Trials – Schizophrenia

	Percentage of Patients Reporting Reaction	
Body System/Adverse Reaction	**Ziprasidone (N=702)**	**Placebo (N=273)**
Body as a Whole		
Asthenia	5	3
Accidental Injury	4	2
Chest Pain	3	2
Cardiovascular		
Tachycardia	2	1
Digestive		
Nausea	10	7
Constipation	9	8
Dyspepsia	8	7
Diarrhea	5	4
Dry Mouth	4	2
Anorexia	2	1
Nervous		
Extrapyramidal Symptoms*	14	8
Somnolence	14	7
Akathisia	8	7
Dizziness**	8	6
Respiratory		
Respiratory Tract Infection	8	3
Rhinitis	4	2
Cough Increased	3	1
Skin and Appendages		
Rash	4	3
Fungal Dermatitis	2	1
Special Senses		
Abnormal Vision	3	2

* Extrapyramidal Symptoms includes the following adverse reaction terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse reactions occurred individually at an incidence greater than 5% in schizophrenia trials.
** Dizziness includes the adverse reaction terms dizziness and lightheadedness.

Dose Dependency of Adverse Reactions in Short-Term, Fixed-Dose, Placebo-Controlled Trials
An analysis for dose response in the schizophrenia 4-study pool revealed an apparent relation of adverse reaction to dose for the following reactions: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness,

dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision.

Extrapyramidal Symptoms (EPS) -The incidence of reported EPS (which included the adverse reaction terms extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching) for ziprasidone-treated patients in the short-term, placebo-controlled schizophrenia trials was 14% vs. 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) did not generally show a difference between ziprasidone and placebo.

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.

Vital Sign Changes -Ziprasidone is associated with orthostatic hypotension *[see Warnings and Precautions (5.9)]*

ECG Changes -Ziprasidone is associated with an increase in the QTc interval *[see Warnings and Precautions (5.3)].* In the schizophrenia trials, ziprasidone was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients.

Other Adverse Reactions Observed During the Premarketing Evaluation of Oral Ziprasidone

Following is a list of COSTART terms that reflect treatment-emergent adverse reactions as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with ziprasidone in schizophrenia trials at multiple doses >4 mg/day within the database of 3834 patients. All reported reactions are included except those already listed in Table 11 or elsewhere in labeling, those reaction terms that were so general as to be uninformative, reactions reported only once and that did not have a substantial probability of being acutely life-threatening, reactions that are part of the illness being treated or are otherwise common as background reactions, and reactions considered unlikely to be drug-related. It is important to emphasize that, although the reactions reported occurred during treatment with ziprasidone, they were not necessarily caused by it.

Adverse reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions:

Frequent adverse reactions occurring in at least 1/100 patients (≥1.0% of patients) (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing);
Infrequent adverse reactions occurring in 1/100 to 1/1000 patients (in 0.1 to 1.0% of patients)
Rare adverse reactions occurring in fewer than 1/1000 patients (<0.1% of

patients).

Body as a Whole
Frequent abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident

Cardiovascular System
Frequent tachycardia, hypertension, postural hypotension
Infrequent bradycardia, angina pectoris, atrial fibrillation
Rare first degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis

Digestive System
Frequent anorexia, vomiting
Infrequent rectal hemorrhage, dysphagia, tongue edema
Rare gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena

Endocrine
Rare hypothyroidism, hyperthyroidism, thyroiditis

Hemic and Lymphatic System
Infrequent anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy
Rare thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia

Metabolic and Nutritional Disorders
Infrequent thirst, transaminase increased, peripheral edema, hyperglycemia, creatin, phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia
Rare BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemicreaction, hypomagnesemia, ketosis, respiratory alkalosis

Musculoskeletal System
Frequent myalgia
Infrequent tenosynovitis
Rare myopathy

Nervous System
Frequent agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy
Infrequent paralysis

Rare myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus

Respiratory System
Frequent dyspnea
Infrequent pneumonia, epistaxis
Rare hemoptysis, laryngismus

Skin and Appendages
Infrequent maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash

Special Senses
Frequent fungal dermatitis
Infrequent conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia
Rare eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis

Urogenital System
Infrequent impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria
Rare gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage

BIPOLAR DISORDER

Acute Treatment of Manic or Mixed Episodes

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

Approximately 6.5% (18/279) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 3.7% (5/136) on placebo. The most common reactions associated with dropout in the ziprasidone-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these reactions among ziprasidone patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse reactions.

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

Table 12 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy (up to 3 weeks) in patients with bipolar mania, including only those reactions that occurred in 2% or more of patients treated with ziprasidone and for which the incidence in patients treated with ziprasidone was greater than the incidence in placebo-treated patients.

Table 12: Treatment-Emergent Adverse Reactions Incidence In Short-Term Oral Placebo-Controlled Trials –Manic and Mixed Episodes Associated with Bipolar Disorder

	Percentage of Patients Reporting Reaction	
Body System/Adverse Reaction	**Ziprasidone (N=279)**	**Placebo (N=136)**
Body as a Whole		
Headache	18	17
Asthenia	6	2
Accidental Injury	4	1
Cardiovascular		
Hypertension	3	2
Digestive		
Nausea	10	7
Diarrhea	5	4
Dry Mouth	5	4
Vomiting	5	2
Increased Salivation	4	0
Tongue Edema	3	1
Dysphagia	2	0
Musculoskeletal		
Myalgia	2	0
Nervous		
Somnolence	31	12
Extrapyramidal Symptoms*	31	12
Dizziness**	16	7
Akathisia	10	5
Anxiety	5	4
Hypesthesia	2	1
Speech Disorder	2	0
Respiratory		
Pharyngitis	3	1
Dyspnea	2	1
Skin and Appendages		
Fungal Dermatitis	2	1
Special Senses		
Abnormal Vision	6	3

* Extrapyramidal Symptoms includes the following adverse reaction terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse reactions occurred individually at an incidence greater than 10% in bipolar mania trials.
**Dizziness includes the adverse reaction terms dizziness and lightheadedness.

Explorations for interactions on the basis of gender did not reveal any clinically meaningful differences in the adverse reaction occurrence on the basis of this demographic factor.

INTRAMUSCULAR ZIPRASIDONE
Adverse Reactions Occurring at an Incidence of 1% or More Among

Ziprasidone-Treated Patients in Short-Term Trials of Intramuscular Ziprasidone

Table 13 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy with intramuscular ziprasidone in 1% or more of patients.

In these studies, the most commonly observed adverse reactions associated with the use of intramuscular ziprasidone (incidence of 5% or greater) and observed at a rate on intramuscular ziprasidone (in the higher dose groups) at least twice that of the lowest intramuscular ziprasidone group were headache (13%), nausea (12%), and somnolence (20%).

Table 13: Treatment-Emergent Adverse Reaction Incidence In Short-Term Fixed-Dose Intramuscular Trials

-

	Percentage of Patients Reporting Reaction		
Body System/Adverse Reaction	**Ziprasidone 2 mg (N=92)**	**Ziprasidone 10 mg (N=63)**	**Ziprasidone 20 mg (N=41)**
Body as a Whole			
Headache	3	13	5
Injection Site Pain	9	8	7
Asthenia	2	0	0
Abdominal Pain	0	2	0
Flu Syndrome	1	0	0
Back Pain	1	0	0
Cardiovascular			
Postural Hypotension	0	0	5
Hypertension	2	0	0
Bradycardia	0	0	2
Vasodilation	1	0	0
Digestive			
Nausea	4	8	12
Rectal Hemorrhage	0	0	2
Diarrhea	3	3	0
Vomiting	0	3	0
Dyspepsia	1	3	2
Anorexia	0	2	0
Constipation	0	0	2
Tooth Disorder	1	0	0
Dry Mouth	1	0	0
Nervous			
Dizziness	3	3	10
Anxiety	2	0	0
Insomnia	3	0	0
Somnolence	8	8	20

Akathisia	0	2	0
Agitation	2	2	0
Extrapyramidal Syndrome	2	0	0
Hypertonia	1	0	0
Cogwheel Rigidity	1	0	0
Paresthesia	0	2	0
Personality Disorder	0	2	0
Psychosis	1	0	0
Speech Disorder	0	2	0
Respiratory			
Rhinitis	1	0	0
Skin and Appendages			
Furunculosis	0	2	0
Sweating	0	0	2
Urogenital			
Dysmenorrhea	0	2	0
Priapism	1	0	0

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ziprasidone mesylate for injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reaction reports not listed above that have been received since market introduction include rare occurrences of the following : *Cardiac Disorders*: Tachycardia, torsade de pointes (in the presence of multiple confounding factors), *[see Warnings and Precautions (5.3)]; Digestive System Disorders*: Swollen Tongue; *Reproductive System and Breast Disorders*: Galactorrhea, priapism; *Nervous System Disorders*: Facial Droop, neuroleptic malignant syndrome, serotonin syndrome (alone or in combination with serotonergic medicinal products), tardive dyskinesia; *Psychiatric Disorders*: Insomnia, mania/hypomania; *Skin and subcutaneous Tissue Disorders*: Allergic reaction (such as allergic dermatitis, angioedema, orofacial edema, urticaria), rash, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); *Urogenital System Disorders*: Enuresis, urinary incontinence; *Vascular Disorders*: Postural hypotension, syncope.

7 DRUG INTERACTIONS

Drug-drug interactions can be pharmacodynamic (combined pharmacologic effects) or pharmacokinetic (alteration of plasma levels). The risks of using ziprasidone in combination with other drugs have been evaluated as described below. All interactions studies have been conducted with oral ziprasidone. Based upon the pharmacodynamic and pharmacokinetic profile of ziprasidone, possible interactions could be anticipated:

7.1 Metabolic Pathway

Approximately two-thirds of ziprasidone is metabolized via a combination of chemical reduction by glutathione and enzymatic reduction by aldehyde oxidase. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase. Less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation.

7.2 In Vitro Studies

An *in vitro* enzyme inhibition study utilizing human liver microsomes showed that ziprasidone had little inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and thus would not likely interfere with the metabolism of drugs primarily metabolized by these enzymes. There is little potential for drug interactions with ziprasidone due to displacement *[see Clinical Pharmacology (12.3)].*

7.3 Pharmacodynamic Interactions

Ziprasidone should not be used with any drug that prolongs the QT interval *[see Contraindications (4.1)].*
Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs.
Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents.
Ziprasidone may antagonize the effects of levodopa and dopamine agonists.

7.4 Pharmacokinetic Interactions

Carbamazepine
Carbamazepine is an inducer of CYP3A4; administration of 200 mg twice daily for 21 days resulted in a decrease of approximately 35% in the AUC of ziprasidone. This effect may be greater when higher doses of carbamazepine are administered.
Ketoconazole
Ketoconazole, a potent inhibitor of CYP3A4, at a dose of 400 mg QD for 5 days, increased the AUC and C_{max} of ziprasidone by about 35 to 40%. Other inhibitors of CYP3A4 would be expected to have similar effects.
Cimetidine
Cimetidine at a dose of 800 mg QD for 2 days did not affect ziprasidone pharmacokinetics.
Antacid
The co-administration of 30 mL of Maalox® with ziprasidone did not affect the pharmacokinetics of ziprasidone.

7.5 Lithium

Ziprasidone at a dose of 40 mg twice daily administered concomitantly with lithium at a dose of 450 mg twice daily for 7 days did not affect the steady-state level or renal

clearance of lithium. Ziprasidone dosed adjunctively to lithium in a maintenance trial of bipolar patients did not affect mean therapeutic lithium levels.

7.6 Oral Contraceptives

In vivo studies have revealed no effect of ziprasidone on the pharmacokinetics of estrogen or progesterone components. Ziprasidone at a dose of 20 mg twice daily did not affect the pharmacokinetics of concomitantly administered oral contraceptives, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg).

7.7 Dextromethorphan

Consistent with *in vitro* results, a study in normal healthy volunteers showed that ziprasidone did not alter the metabolism of dextromethorphan, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio.

7.8 Valproate

A pharmacokinetic interaction of ziprasidone with valproate is unlikely due to the lack of common metabolic pathways for the two drugs. Ziprasidone dosed adjunctively to valproate in a maintenance trial of bipolar patients did not affect mean therapeutic valproate levels.

7.9 Other Concomitant Drug Therapy

Population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including ziprasidone mesylate for injection, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary
Neonates exposed to antipsychotic drugs, including ziprasidone mesylate for injection, during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical Considerations)*. Overall available data from published epidemiologic studies of pregnant women exposed to ziprasidone have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal

outcomes *(see Data)*. There are risks to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics, including ziprasidone mesylate for injection, during pregnancy *(see Clinical Considerations)*.

In animal studies, ziprasidone administration to pregnant rats and rabbits during organogenesis caused developmental toxicity at doses similar to recommended human doses, and was teratogenic in rabbits at 3 times the maximum recommended human dose (MRHD). Rats exposed to ziprasidone during gestation and lactation exhibited increased perinatal pup mortality and delayed neurobehavioral and functional development of offspring at doses less than or similar to human therapeutic doses. *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

There is risk to the mother from untreated schizophrenia or bipolar I disorder, including increased risk of relapse, hospitalization, and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Fetal/neonatal adverse reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including ziprasidone mesylate for injection, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Data

Human Data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects.

Animal Data

When ziprasidone was administered to pregnant rabbits during the period of organogenesis, an increased incidence of fetal structural abnormalities (ventricular septal defects and other cardiovascular malformations, and kidney alterations) was observed at a dose of 30 mg/kg/day (3 times the MRHD of 200 mg/day based on mg/m^2 body surface area). There was no evidence to suggest that these developmental effects were secondary to maternal toxicity. The developmental no effect dose was 10 mg/kg/day (equivalent to the MRHD based on a mg/m^2 body surface area). In rats, embryofetal toxicity (decreased fetal weights, delayed skeletal ossification) was observed following administration of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD

based on mg/m^2 body surface area) during organogenesis or throughout gestation, but there was no evidence of teratogenicity. Doses of 40 and 160 mg/kg/day (2 and 8 times the MRHD based on mg/m^2 body surface area) were associated with maternal toxicity. The developmental no-effect dose is 5 mg/kg/day (0.2 times the MRHD based on mg/m^2 body surface area).

There was an increase in the number of pups born dead and a decrease in postnatal survival through the first 4 days of lactation among the offspring of female rats treated during gestation and lactation with doses of 10 mg/kg/day (0.5 times the MRHD based on mg/m^2 body surface area) or greater. Offspring developmental delays (decreased pup weights) and neurobehavioral functional impairment (eye opening air righting) were observed at doses of 5 mg/kg/day (0.2 times the MRHD based on mg/m^2 body surface area) or greater. A no-effect level was not established for these effects.

8.2 Lactation

Risk Summary

Limited data from a published case report indicate the presence of ziprasidone in human milk. Although there are no reports of adverse effects on a breastfed infant exposed to ziprasidone via breast milk, there are reports of excess sedation, irritability, poor feeding, and extrapyramidal symptoms (tremors and abnormal muscle movements) in infants exposed to other atypical antipsychotics through breast milk *(see Clinical Considerations)*. There is no information on the effects of ziprasidone on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ziprasidone mesylate for injection and any potential adverse effects on the breastfed child from ziprasidone mesylate for injection or from the mother's underlying condition.

Clinical Considerations

Infants exposed to ziprasidone mesylate for injection should be monitored for excess sedation, irritability, poor feeding, and extrapyramidal symptoms (tremors and abnormal muscle movements).

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the pharmacologic action of ziprasidone (D2 antagonism), treatment with ziprasidone mesylate for injection may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential *[see Warnings and Precautions (5.15) and Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use

The safety and effectiveness of ziprasidone in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of ziprasidone, 2.4 percent were 65 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. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to ziprasidone, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients.

Ziprasidone intramuscular has not been systematically evaluated in elderly patients (65 years and over).

8.6 Renal Impairment

Because ziprasidone is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a major impact on the pharmacokinetics of ziprasidone. The pharmacokinetics of ziprasidone following 8 days of 20 mg twice daily dosing were similar among subjects with varying degrees of renal impairment (n=27), and subjects with normal renal function, indicating that dosage adjustment based upon the degree of renal impairment is not required. Ziprasidone is not removed by hemodialysis.

Intramuscular ziprasidone has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function *[see Clinical Pharmacology (12)].*

8.7 Hepatic Impairment

As ziprasidone is cleared substantially by the liver, the presence of hepatic impairment would be expected to increase the AUC of ziprasidone; a multiple-dose study at 20 mg twice daily for 5 days in subjects (n=13) with clinically significant (Childs-Pugh Class A and B) cirrhosis revealed an increase in AUC $_{0\text{-}12}$ of 13% and 34% in Childs-Pugh Class A and B, respectively, compared to a matched control group (n=14). A half-life of 7.1 hours was observed in subjects with cirrhosis compared to 4.8 hours in the control group.

8.8 Age and Gender Effects

In a multiple-dose (8 days of treatment) study involving 32 subjects, there was no difference in the pharmacokinetics of ziprasidone between men and women or between elderly (>65 years) and young (18 to 45 years) subjects. Additionally, population pharmacokinetic evaluation of patients in controlled trials has revealed no evidence of clinically significant age or gender-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for age or gender are, therefore, not recommended.

8.9 Smoking

Based on *in vitro* studies utilizing human liver enzymes, ziprasidone is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of ziprasidone. Consistent with these *in vitro* results, population pharmacokinetic evaluation has not revealed any significant pharmacokinetic differences between smokers and nonsmokers.

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

Ziprasidone 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 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 ziprasidone 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 ziprasidone misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

In premarketing trials involving more than 5400 patients and/or normal subjects, accidental or intentional overdosage of oral ziprasidone was documented in 10 patients. All of these patients survived without sequelae. In the patient taking the largest confirmed amount, 3,240 mg, the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (200/95).

Adverse reactions reported with ziprasidone overdose included extrapyramidal symptoms, somnolence, tremor, and anxiety. *[see Adverse Reactions (6.2)]*

10.2 Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Intravenous access should be established, and gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical

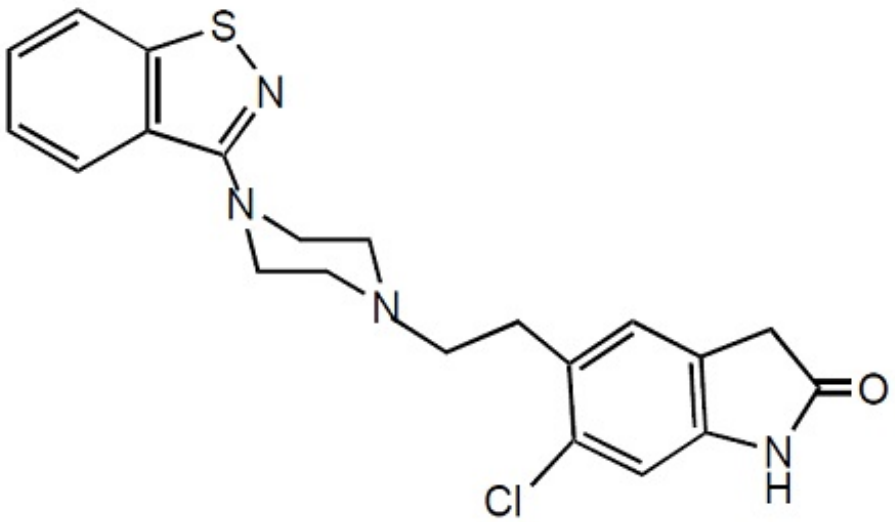
hazard of additive QT-prolonging effects that might be additive to those of ziprasidone.

Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. If sympathomimetic agents are used for vascular support, epinephrine and dopamine should not be used, since beta stimulation combined with α_1 antagonism associated with ziprasidone may worsen hypotension. Similarly, it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of ziprasidone, resulting in problematic hypotension.

In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. There is no specific antidote to ziprasidone, and it is not dialyzable. The possibility of multiple drug involvement should be considered. Close medical supervision and monitoring should continue until the patient recovers.

11 DESCRIPTION

Ziprasidone mesylate for injection is an atypical antipsychotic available as an injection (ziprasidone mesylate) for intramuscular use only. Ziprasidone is a psychotropic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. It has a molecular weight of 412.94 (free base), with the following chemical name: 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one. The empirical formula of $C_{21}H_{21}ClN_4OS$ (free base of ziprasidone) represents the following structural formula:



Ziprasidone mesylate for injection contains a lyophilized form of ziprasidone mesylate trihydrate. Chemically, ziprasidone mesylate trihydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, methanesulfonate,

trihydrate. The empirical formula is $C_{21}H_{21}ClN_4OS \cdot CH_3SO_3H \cdot 3H_2O$ and its molecular weight is 563.09.

Ziprasidone mesylate for injection is available in a single-dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions) *[see Dosage and Administration (2.4)].* Each mL of ziprasidone mesylate for injection (when reconstituted) contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of ziprasidone in the treatment of the listed indications could be mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism.

12.2 Pharmacodynamics

Ziprasidone binds with relatively high affinity to the dopamine D_2 and D_3, serotonin $5HT_{2A}$, $5HT_{2C}$, $5HT_{1A}$, $5HT_{1D}$, and α_1-adrenergic receptors (K_i s of 4.8, 7.2, 0.4, 1.3, 3.4, 2, and 10 nM, respectively), and with moderate affinity to the histamine H_1 receptor (K_i=47 nM). Ziprasidone is an antagonist at the D_2, $5HT_{2A}$, and $5HT_{1D}$ receptors, and as agonist at the $5HT_{1A}$ receptor. Ziprasidone inhibited synaptic reuptake of serotonin and norepinephrine. No appreciable affinity was exhibited for other receptor/binding sites tested, including the cholinergic muscarinic receptor (IC_{50} >1 μM).

12.3 Pharmacokinetics

Oral Pharmacokinetics
Ziprasidone's activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of ziprasidone are dose-proportional within the proposed clinical dose range, and ziprasidone accumulation is predictable with multiple dosing. Elimination of ziprasidone is mainly via hepatic metabolism with a mean terminal half-life of about 7 hours within the proposed clinical dose range. Steady-state concentrations are achieved within one to three days of dosing. The mean apparent systemic clearance is 7.5 mL/min/kg. Ziprasidone is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Ziprasidone is well absorbed after oral administration, reaching peak plasma concentrations in 6 to 8 hours. The absolute bioavailability of a 20 mg dose under fed conditions is approximately 60%. The absorption of ziprasidone is increased up to two-fold in the presence of food.

Distribution: Ziprasidone has a mean apparent volume of distribution of 1.5 L/kg. It is greater than 99% bound to plasma proteins, binding primarily to albumin and α_1-acid glycoprotein. The *in vitro* plasma protein binding of ziprasidone was not altered by warfarin or propranolol, two highly protein-bound drugs, nor did ziprasidone alter the binding of these drugs in human plasma. Thus, the potential for drug interactions with

ziprasidone due to displacement is minimal.

Metabolism and Elimination: Ziprasidone is extensively metabolized after oral administration with only a small amount excreted in the urine (<1%) or feces (<4%) as unchanged drug. Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benzisothiazole (BITP) sulphoxide, BITP-sulphone, ziprasidone sulphoxide, and S-methyldihydroziprasidone. Approximately 20% of the dose is excreted in the urine, with approximately 66% being eliminated in the feces. Unchanged ziprasidone represents about 44% of total drug-related material in serum. *In vitro* studies using human liver subcellular fractions indicate that S-methyldihydroziprasidone is generated in two steps. These studies indicate that the reduction reaction is mediated primarily by chemical reduction by glutathione as well as by enzymatic reduction by aldehyde oxidase and the subsequent methylation is mediated by thiol methyltransferase. *In vitro* studies using human liver microsomes and recombinant enzymes indicate that CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone. CYP1A2 may contribute to a much lesser extent. Based on *in vivo* abundance of excretory metabolites, less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation and approximately two-thirds via reduction. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase.

Intramuscular Pharmacokinetics
Systemic Bioavailability: The bioavailability of ziprasidone administered intramuscularly is 100%. After intramuscular administration of single doses, peak serum concentrations typically occur at approximately 60 minutes post-dose or earlier and the mean half-life ($T_{½}$) ranges from two to five hours. Exposure increases in a dose-related manner and following three days of intramuscular dosing, little accumulation is observed.

Metabolism and Elimination: Although the metabolism and elimination of IM ziprasidone have not been systematically evaluated, the intramuscular route of administration would not be expected to alter the metabolic pathways.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Lifetime carcinogenicity studies were conducted with ziprasidone in Long Evans rats and CD-1 mice. Ziprasidone was administered for 24 months in the diet at doses of 2, 6, or 12 mg/kg/day to rats, and 50, 100, or 200 mg/kg/day to mice (0.1 to 0.6 and 1 to 5 times the maximum recommended human dose (MRHD) of 200 mg/day based on mg/m^2 body surface area, respectively). In the rat study, there was no evidence of an increased incidence of tumors compared to controls. In male mice, there was no increase in incidence of tumors relative to controls. In female mice, there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested (50 to 200 mg/kg/day or 1 to 5 times the MRHD based on mg/m^2 body surface area). Proliferative changes in the pituitary and mammary glands of rodents have been observed following chronic

administration of other antipsychotic agents and are considered to be prolactin-mediated. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice at 100 and 200 mg/kg/day (or 2.5 and 5 times the MRHD based on mg/m^2 body surface area). Ziprasidone had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown *[see Warnings and Precautions (5.14)].*

Mutagenesis
Ziprasidone was tested in the Ames bacterial mutation assay, the *in vitro* mammalian cell gene mutation mouse lymphoma assay, the *in vitro* chromosomal aberration assay in human lymphocytes, and the *in vivo* chromosomal aberration assay in mouse bone marrow. There was a reproducible mutagenic response in the Ames assay in one strain of S. *typhimurium* in the absence of metabolic activation. Positive results were obtained in both the *in vitro* mammalian cell gene mutation assay and the *in vitro* chromosomal aberration assay in human lymphocytes.

Impairment of Fertility
Ziprasidone was shown to increase time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day based on mg/m^2 body surface area). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD based on mg/m^2 body surface area). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD based on mg/m^2 body surface area). The effect on fertility appeared to be in the female since fertility was not impaired when males given 160 mg/kg/day (8 times the MRHD based on mg/m^2 body surface area) were mated with untreated females.

14 CLINICAL STUDIES

14.3 Acute Treatment of Agitation in Schizophrenia

The efficacy of intramuscular ziprasidone in the management of agitated schizophrenic patients was established in two short-term, double-blind trials of schizophrenic subjects who were considered by the investigators to be “acutely agitated” and in need of IM antipsychotic medication. In addition, patients were required to have a score of 3 or more on at least 3 of the following items of the PANSS: anxiety, tension, hostility and excitement. Efficacy was evaluated by analysis of the area under the curve (AUC) of the Behavioural Activity Rating Scale (BARS) and Clinical Global Impression (CGI) severity rating. The BARS is a seven point scale with scores ranging from 1 (difficult or unable to rouse) to 7 (violent, requires restraint). Patients' scores on the BARS at baseline were mostly 5 (signs of overt activity [physical or verbal], calms down with instructions) and as determined by investigators, exhibited a degree of agitation that warranted intramuscular therapy. There were few patients with a rating higher than 5 on the BARS, as the most severely agitated patients were generally unable to provide informed consent for participation in premarketing clinical trials.

Both studies compared higher doses of ziprasidone intramuscular with a 2 mg control dose. In one study, the higher dose was 20 mg, which could be given up to 4 times in the 24 hours of the study, at interdose intervals of no less than 4 hours. In the other

study, the higher dose was 10 mg, which could be given up to 4 times in the 24 hours of the study, at interdose intervals of no less than 2 hours.

The results of the intramuscular ziprasidone trials follow:
(1) In a one-day, double-blind, randomized trial (n=79) involving doses of ziprasidone intramuscular of 20 mg or 2 mg, up to QID, ziprasidone intramuscular 20 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 4 hours, and by CGI severity at 4 hours and study endpoint.

(2) In another one-day, double-blind, randomized trial (n=117) involving doses of ziprasidone intramuscular of 10 mg or 2 mg, up to QID, ziprasidone intramuscular 10 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 2 hours, but not by CGI severity.

16 HOW SUPPLIED/STORAGE AND HANDLING

Ziprasidone mesylate for injection is available in a single-dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions) *[see Dosage and Administration (2.4)]*. Each mL of ziprasidone mesylate for injection (when reconstituted) affords a colorless to pale pink solution that contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

Ziprasidone mesylate for injection		
Package	**Concentration**	**NDC Code**
Single-Dose Vials (carton of 10 vials)	20 mg/mL	NDC 43598-**061**-58 Contains 10 of NDC 43598-**061**-11

Ziprasidone mesylate for injection should be stored at 20° to 25°C (68° to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] in dry form. Protect from light. Following reconstitution, Ziprasidone mesylate for injection can be stored, when protected from light, for up to 24 hours at 15°C to 30°C (59°F to 86°F) or up to 7 days refrigerated, 2°C to 8°C (36°F to 46°F).

17 PATIENT COUNSELING INFORMATION

QTc Prolongation
Advise patients to inform their health care providers of the following: History of QT prolongation; recent acute myocardial infarction; uncompensated heart failure; prescription of other drugs that have demonstrated QT prolongation; risk for significant

electrolyte abnormalities; and history of cardiac arrhythmia *[see Contraindications (4.1) and Warnings and Precautions (5.3)].*

Instruct patients to report the onset of any conditions that put them at risk for significant electrolyte disturbances, hypokalemia in particular, including but not limited to the initiation of diuretic therapy or prolonged diarrhea. In addition, instruct patients to report symptoms such as dizziness, palpitations, or syncope to the prescriber *[see Warnings and Precautions (5.3)]*.

Severe Cutaneous Adverse Reactions
Instruct patients to report to their health care provider at the earliest onset any signs or symptoms that may be associated with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or with severe cutaneous adverse reactions, such as Stevens-Johnson syndrome *[see Warnings and Precautions (5.5)]*.

Pregnancy
Advise pregnant women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with ziprasidone mesylate for injection. Advise patients that ziprasidone mesylate for injection may cause extrapyramidal and/or withdrawal symptoms (agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) in a neonate. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ziprasidone mesylate for injection during pregnancy *[see Use in Specific Populations (8.1)].*

Lactation
Advise breastfeeding women using ziprasidone mesylate for injection to monitor infants for excess sedation, irritability, poor feeding, and extrapyramidal symptoms (tremors, and abnormal muscle movements) and to seek medical care if they notice these signs *[see Use in Specific Populations (8.2)].*

Infertility
Advise females of reproductive potential that ziprasidone mesylate for injection may impair fertility due to an increase in serum prolactin levels. The effects on fertility are reversible *[see Warnings and Precautions (5.15)and Use in Specific Populations (8.3)]*.

Distributor:

Dr.Reddy's Laboratories Inc.,

Princeton, NJ 08540

Made in India

Revised: 0721

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

10 Single-Dose Vials NDC 43598-061-58

Ziprasidone

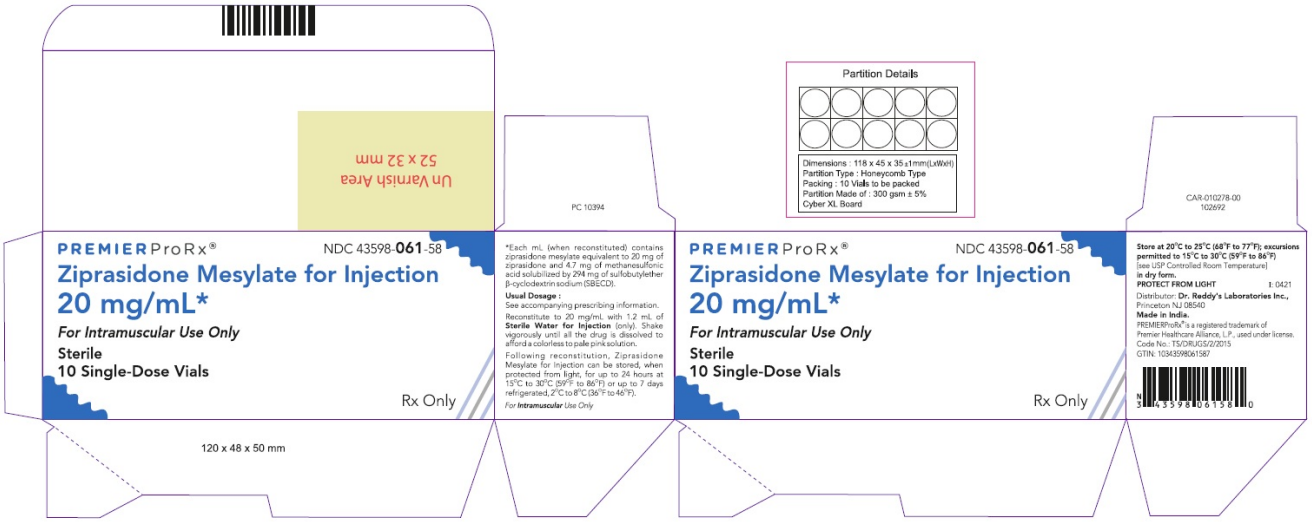
Mesylate for Injection
20 mg/mL*

For Intramuscular Use Only

Sterile

Rx only

Carton Label:



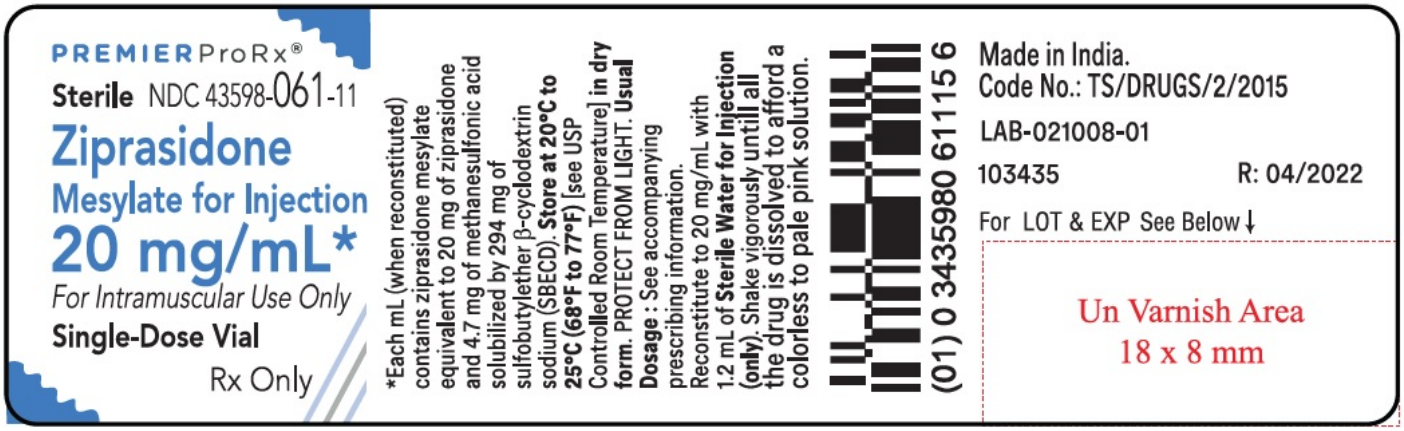
Sterile NDC 43598-**061**-11

Ziprasidone

Mesylate for Injection
20 mg/mL*
For Intramuscular Use Only
Single-dose Vial

Rx only

Vial Label:



ZIPRASIDONE MESYLATE

ziprasidone mesylate injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43598-061
Route of Administration	INTRAMUSCULAR		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ZIPRASIDONE MESYLATE (UNII: 3X6SAX83JZ) (ZIPRASIDONE - UNII:6UKA5VEJ6X)	ZIPRASIDONE	20 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
METHANESULFONIC ACID (UNII: 12EH9M7279)	4.7 mg in 1 mL
BETADEX SULFOBUTYL ETHER SODIUM (UNII: 2PP9364507)	294 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43598-061-58	1 in 1 CARTON	03/22/2022	
1	NDC:43598-061-11	1 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA211908	03/22/2022	

Labeler - Dr.Reddy's Laboratories, Inc. (802315887)

Registrant - Gland Pharma Limited (918601238)

Establishment

Name	Address	ID/FEI	Business Operations
Gland Pharma Limited		858971074	analysis(43598-061) , manufacture(43598-061)

Revised: 7/2021 Dr.Reddy's Laboratories, Inc.