
TAKE AN ACTIVE ROLE IN YOUR TREATMENT PLAN

✔ This journal is your personal place to keep track of your treatment experience while taking GEODON

✔ Enter your information and take the completed journal to your next doctor’s appointment

✔ You can print out additional copies of this journal to use as often as you need at www.GEODON.com

GEODON is available in 20-mg, 40-mg, 60-mg, and 80-mg capsules as well as in intramuscular injection in 20-mg/mL single-use vials.

GEODON Important Safety Information and Indications

WARNING: INCREASED DEATH IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
GEODON is not approved for the treatment of patients with dementia-related psychosis. Elderly patients with dementia-related psychosis (having lost touch with reality due to confusion and memory loss) treated with this type of medicine are at an increased risk of death, compared to sugar pill.

GEODON may increase the risk of changes to your heart rhythm. You should not take GEODON if you have certain kinds of heart conditions that change your heart rhythm, a recent heart attack, heart failure, or take certain medicines known to change heart rhythm. It is important to talk to your doctor about this possible side effect. Call your doctor right away if you faint, pass out, or feel a change in your heartbeat.

It is important to tell your doctor about any other medicines that you take, including non-prescription medicines, supplements, and herbal medicines.

Please see additional Important Safety Information and Indications on the following pages and accompanying Full Prescribing Information, including BOXED WARNING and Patient Information.
TRACK YOUR MEDICATIONS

Use this area to keep a record of all the medications you are currently taking. Record how many times per day you take each one and any other instructions your doctor gave you, like whether your medication should be taken with meals. While you are taking GEODON, make sure you check with your doctor before starting any new medications, over-the-counter supplements, or herbal remedies.

<table>
<thead>
<tr>
<th>CURRENT MEDICATIONS (Including medications, over-the-counter supplements, or herbal remedies)</th>
<th>DOSAGE AND TIMES TAKEN PER DAY</th>
<th>SPECIAL INSTRUCTIONS</th>
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Make sure to refill your prescriptions before they run out so you don’t miss a dose.

GEODON Important Safety Information (continued)

If you experience a high fever, stiff muscles, shaking, confusion, sweating, or increased heart rate or blood pressure, tell your doctor right away. These can be signs of a rare but potentially fatal condition called neuroleptic malignant syndrome (NMS).

Delayed-onset drug reaction called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) can occur with ziprasidone. Signs of DRESS may include rash, fever, and swollen lymph nodes. Other severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome, can occur with ziprasidone. Signs of Stevens-Johnson syndrome may include rash with blisters which could include ulcers in mouth, skin shedding, fever, and target-like spots in the skin. DRESS and other SCAR are sometimes fatal; therefore, call your health care professional(s) and seek immediate care if you develop any of these signs or symptoms.

Please see additional Important Safety Information and Indications on the following pages and accompanying Full Prescribing Information, including BOXED WARNING and Patient Information.
**TRACK YOUR TREATMENT EXPERIENCE**

Use this area to record how you are feeling, including symptoms and any side effects you may experience while taking GEODON. Based on the treatment plan you and your doctor have developed, you can track your experiences daily, weekly, or when symptoms occur. Tracking your experience over time may help you and your doctor monitor your illness and treatment plan.

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You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [https://www.fda.gov/medwatch](https://www.fda.gov/medwatch), or call 1-800-FDA-1088.

**GEODON Important Safety Information (continued)**

If you experience abnormal or uncontrollable facial or body movements, notify your doctor. These could be a sign of tardive dyskinesia (TD), a potentially permanent condition whose risk increases with the length of treatment, but which can also occur after brief periods at low doses.

If you have diabetes or have risk factors or symptoms of diabetes, your blood sugar should be monitored. Symptoms include excessive thirst, urination, appetite, and weakness. High blood sugar has been reported with GEODON and medicines like it. In some cases, extreme high blood sugar can lead to coma or death. Increases in cholesterol and weight gain have also been reported with medicines like GEODON.

**Please see additional Important Safety Information and Indications on the following pages and accompanying Full Prescribing Information, including BOXED WARNING and Patient Information.**
## TRACK YOUR TREATMENT EXPERIENCE (continued)

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Taking GEODON as prescribed by your doctor may lessen the chance of your symptoms returning.

**GEODON Important Safety Information (continued)**

Tell your doctor if you are pregnant or intend to become pregnant. Breastfeeding is not recommended.

Antipsychotic drugs (like GEODON) may cause drowsiness, dizziness, or lightheadedness upon standing which could lead to falls, fractures, or other injuries. If you experience these symptoms, tell your doctor.

If you experience a rash or seizures, tell your doctor. Also tell your doctor if you have thoughts of suicide.

Other risks may include decreases in white blood cells (which can be serious), trouble swallowing, high prolactin levels, and impairment in judgment or motor skills. Until you know how GEODON affects you, you should not drive or operate machinery.

Please see additional Important Safety Information and Indications on the following page and accompanying Full Prescribing Information, including BOXED WARNING and Patient Information.
GEODON Important Safety Information (continued)

Do not drink alcohol while taking GEODON. Avoid becoming overheated or dehydrated.

Common side effects of GEODON include:
- Feeling unusually tired or sleepy
- Nausea or upset stomach
- Constipation
- Dizziness
- Restlessness
- Abnormal muscle movements, including tremor, shuffling, and uncontrolled involuntary movements
- Diarrhea
- Rash
- Increased cough/runny nose

In short-term bipolar mania clinical studies, 4.9% of GEODON-treated patients gained significant weight (7% or more of body weight) vs 3.3% for placebo.

In a long-term bipolar maintenance clinical study, patients who tolerated GEODON plus lithium or valproate (Depakote®) for 10-16 weeks were either continued on GEODON or switched to placebo for up to 6 months. During these six months, 5.6% of patients in both groups gained significant weight. These results do not include patients who did not complete the study.

In short-term schizophrenia clinical studies, 10% of GEODON-treated patients gained significant weight vs 4% for placebo.

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

Indications

GEODON is a type of prescription medicine called a psychotropic, also known as an atypical antipsychotic. GEODON can be used to treat symptoms of schizophrenia and acute manic or mixed episodes associated with bipolar disorder. GEODON can also be used as maintenance treatment of bipolar disorder when added to lithium or valproate. GEODON may increase the risk of changes to your heart rhythm. In some cases, these types of changes can be fatal though it is unknown whether this is the case with GEODON. It is important to talk to your doctor about this potential side effect, as your doctor may consider a different medicine first.

GEODON is a registered trademark of Pfizer Inc. Other brands listed are trademarks of their respective owners.

For more information and resources to help with your treatment plan, visit www.GEODON.com. You’ll be able to:
- Learn more about treatment with GEODON
- Download other tools and resources

Please see accompanying Full Prescribing Information, including BOXED WARNING and Patient Information.
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)
• GEODON is not approved for elderly patients with dementia-related psychosis (5.1)

RECENT MAJOR CHANGES
Boxed Warning 11/2018
Dosage and Administration (2.4) Removed 11/2018
Warnings and Precautions (5.1, 5.2) 11/2018

INDICATIONS AND USAGE
GEODON is an atypical antipsychotic. In choosing among treatments, prescribers should be aware of the potential for GEODON to prolong the QT interval and may consider the use of other drugs first (5.3)
• Treatment of schizophrenia. (1)
• Acute treatment as monotherapy of manic or mixed episodes associated with bipolar I disorder. (1)
• Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate. (1)
GEODON as an intramuscular injection is indicated for the:
• Acute treatment of agitation in schizophrenic patients. (1)

DOSAGE AND ADMINISTRATION
Give oral doses with food.
• Schizophrenia: Initiate at 20 mg twice daily. Daily dosage may be adjusted up to 80 mg twice daily. Dose adjustments should occur at intervals of not less than 2 days. Safety and efficacy has been demonstrated in doses up to 100 mg twice daily. The lowest effective dose should be used. (2.1)
• Acute treatment of manic/mixed episodes of bipolar I disorders: Initiate at 40 mg twice daily. Increase to 60 mg or 80 mg twice daily on day 2 of treatment. Subsequent dose adjustments should be based on tolerability and efficacy within the range of 40-80 mg twice daily. (2.2)
• Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate. Continue treatment at the same dose on which the patient was initially stabilized, within the range of 40-90 mg twice daily. (2.2)
• Acute treatment of agitation associated with schizophrenia (intramuscular administration): 10 mg-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. (2.3)

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: GEODON 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 GEODON 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 GEODON 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, asthma, 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 Pfizer Inc at 1-800-438-1985 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 absorption of ziprasidone is increased up to two-fold in the presence of food. (7.10)
• The full prescribing information contains additional drug interactions. (7)

USE IN SPECIFIC POPULATIONS
• Pregnancy: Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk. (8.1)
• Nursing Mothers: Breast feeding is not recommended. (8.3)
• Pediatric Use: Safety and effectiveness 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 and FDA-approved patient labeling.

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Schizophrenia
2.2 Bipolar I Disorder (Acute Mixed or Manic Episodes and Maintenance Treatment as an Adjunct to Lithium or Valproate)
2.3 Acute Treatment of Agitation in Schizophrenia
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 QT Prolongation
4.2 Hypersensitivity
5 WARNINGS AND PRECAUTIONS
5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
5.2 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis
5.3 QT Prolongation and Risk of Sudden Death
5.4 Neuroleptic Malignant Syndrome (NMS)
5.5 Severe Cutaneous Adverse Reactions
5.6 Tardive Dyskinesia
5.7 Metabolic Changes
5.8 Rash
5.9 Orthostatic Hypotension
5.10 Falls
5.11 Leukopenia, Neutropenia, and Agranulocytosis
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Metabolic Pathway
7.2 In Vitro Studies
7.3 Pharmacodynamic Interactions
7.4 Pharmacokinetic Interactions
7.5 Lithium
7.6 Oral Contraceptives
7.7 Dextromethorphan
7.8 Valproate
7.9 Other Concomitant Drug Therapy
7.10 Food Interaction
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
9 DRUG ABUSE AND DEPENDENCE
9.3 Dependence
10 OVERDOSAGE
10.1 Human Experience
10.2 Management of Overdose
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Schizophrenia
14.2 Bipolar I Disorder (Acute Mixed or Manic Episodes and Maintenance Treatment as an Adjunct to Lithium or Valproate)
14.3 Acute Treatment of Agitation in Schizophrenia
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
1 INDICTIONS AND USAGE

GEODON is indicated for the treatment of schizophrenia, as monotherapy for the acute treatment of bipolar manic or mixed episodes, and as an adjunct to lithium or valproate for the maintenance treatment of bipolar disorder. GEODON 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 points-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia, and sudden death. In many cases this would lead to the recommendation that other drugs should be tried first. Whether ziprasidone will cause torsade de points or increase the rate of sudden death is not yet known [see Warnings and Precautions (5.3)].

Schizophrenia

- GEODON is indicated for the treatment of schizophrenia in adults [see Clinical Studies (14.1)].

Bipolar I Disorder (Acute Mixed or Manic Episodes and Maintenance Treatment as an Adjunct to Lithium or Valproate)

- GEODON is indicated as monotherapy for the acute treatment of adults with manic or mixed episodes associated with bipolar I disorder [see Clinical Studies (14.2)].
- GEODON is indicated as an adjunct to lithium or valproate for the maintenance treatment of bipolar I disorder in adults [see Clinical Studies (14.2)].

Acute Treatment of Agitation in Schizophrenia

- GEODON intramuscular is indicated for the treatment of acute agitation in schizophrenic adult patients for whom treatment with ziprasidone is appropriate and who need intramuscular anti-psychotic medication for rapid control of agitation [see Clinical Studies (14.1)]. 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

2.1 Schizophrenia

Dose Selection

GEODON Capsules should be administered at an initial daily dose of 20 mg twice daily with food. In some patients, daily dosages may subsequently be adjusted on the basis of individual clinical status up to 80 mg twice daily. Dosing adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steadystate is achieved within 1 to 3 days. In order to ensure use of the lowest effective dose, patients should ordinarily be observed for improvement for several weeks before upward dosage adjustment.

Efficacy in schizophrenia was demonstrated in a dose range of 20 mg to 100 mg twice daily in short-term, placebo-controlled clinical trials. There were trends toward dose response within the range of 20 mg to 80 mg twice daily, but results were not consistent. An increase to a dose greater than 80 mg twice daily is not generally recommended. The safety of doses above 100 mg twice daily has not been systematically evaluated in clinical trials [see Clinical Studies (14.1)].

Maintenance Treatment

While there is no body of evidence available to answer the question of how long a patient treated with ziprasidone should remain on it, a maintenance study in patients who had been symptomatically improved then randomized to continue ziprasidone or switch to placebo demonstrated a delay in time to relapse for patients receiving GEODON [see Clinical Studies (14.1)]. No additional benefit was demonstrated for doses above 20 mg twice daily. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.2 Bipolar I Disorder (Acute Mixed or Manic Episodes and Maintenance Treatment as an Adjunct to Lithium or Valproate)

Acute Treatment of Manic or Mixed Episodes

Dose Selection-Oral ziprasidone should be administered at an initial daily dose of 40 mg twice daily for 5 days. The dose may then be increased to 80 mg twice daily, if tolerated. On the second day of treatment and subsequently adjusted on the basis of the degree of exacerbation and the response to therapy. In the flexible-dose clinical studies, the mean daily dose administered was 20 mg to 80 mg twice daily, but results were not consistent. An increase to a dose greater than 80 mg twice daily is generally not recommended. The safety of doses above 100 mg twice daily has not been systematically evaluated in clinical trials [see Clinical Studies (14.1)].

Maintenance Treatment (as an adjunct to lithium or valproate)

Continue treatment at the same dose on which the patient was initially stabilized, within the range of 40 mg to 80 mg twice daily with food. Patients should be periodically reassessed to determine the need for maintenance treatment [see Clinical Studies (14.2)].

2.3 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.

GEODON for Injection (ziprasidone mesylate) 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 other than Sterile Water for Injection. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whichever solution and container permit.

3 DOSAGE FORMS AND STRENGTHS

GEODON Capsules are differentiated by capsule color/size and are imprinted in black ink with “PZD” and “ZDX” [dose strength] and a unique number. GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. They are supplied in the following strengths and package configurations:

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<th>GEODON Capsules</th>
<th>Capsule Strength (mg)</th>
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<tr>
<td>20</td>
<td>ZDX 20</td>
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<td>60</td>
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<td>80</td>
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GEODON 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 (2.3)]. 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 solutionized to 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

4 CONTRAINDICATIONS

4.1 QT Prolongation

Because of ziprasidone’s dose-related prolonged QT interval and the known association of fatal arrhythmias with QT prolongation by 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, solatol, quinidine, other Class Ia and III anti-arrhythmics, metoprolol, labetalol, magnesium, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, metoflouquin, pantemidine, arsenic trioxide, levome-thyld acetate, dolaseton mesylate, propranolol or troleandomycin
  - 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. GEODON is not approved for the treatment of dementia-related psychosis. [see Boxed Warning and Warnings and Precautions (5.1)].

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. GEODON is not approved for the treatment of patients with dementia-related psychosis. [see Boxed Warning and Warnings and Precautions (5.2)].

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 (4.1)].

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 QT length was not augmented by the presence of a metabolic inhibitor (ketocanozone 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 GEODON 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 for ziprasidone in the prolongation, a history of prolonged QTc and a screening measurement of 488 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 points or sudden unexpected death. The relationship of QT prolongation to torsade de points 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 points has not been observed in association with the use of ziprasidone in premarketing trials and experience is too limited to rule out an increased risk, there have been rare post-marketing reports (in the presence of metabolic inhibitors) of QT prolongation (5.4).

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 12.3 msec following the second injection. In this study, no patients had a QTc interval exceeding 500 msec.

As with other antipsychotics and placebo, sudden unexpected 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. The mean increase in QTc from baseline for 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.

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It is essential to periodically monitor 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 replaced 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. Persistent or prolonged prolongation of QT interval (including QTc) may be manifestations of cardiac 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 of 500 msecs or more.

For patients taking ziprasidone who experience symptoms that could indicate the occurrence of torsade de points, 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. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is necessary to exclude other illnesses that may mimic NMS (e.g., obesity, family history of diabetes) who are starting treatment with 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 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 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 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 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 be monitored regularly for worsening of glucose control.

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Flexible-Dose, Oral Ziprasidone, Monotherapy Trials in Adult Patients with Bipolar Disorder

Table 4: Glucose* Categorical Changes in Short-Term (up to 6 weeks), Placebo-Controlled,

*Fasting

Table 3: Glucose Mean Change from Baseline in Short-Term (up to 6 weeks), Placebo-Controlled,

change from baseline in random glucose for ziprasidone 20-40 mg BID was -3.4 mg/dL (N=122);
for ziprasidone 60-80 mg BID was +1.3 mg/dL (N=10); and for placebo was +0.3 mg/dL (N=71).

Table 5: Lipid* Mean Change from Baseline in Short-Term (up to 6 weeks), Placebo-Controlled,

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Table 6: Lipid* Categorical Changes in Short-Term (up to 6 weeks), Placebo-Controlled,

Weight Gain

In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean
change from baseline weight for ziprasidone 20-40 mg BID was -2.3 kg (N=124); for ziprasidone 60-80 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 20-40 mg BID was 5.6% (N=124); for ziprasidone 60-80 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 7: Lipid* Mean Change from Baseline in Short-Term (up to 6 weeks), Placebo-Controlled,

- 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 (23-27) 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.

Table 8: Lipid* Categorical Changes in Short-Term (up to 6 weeks), Placebo-Controlled,

Fixed-Dose, Oral Ziprasidone Monotherapy Trials in Adult Patients with Bipolar Disorder

Table 9: Weight Mean Changes in Short-Term (up to 6 weeks), Placebo-Controlled, Fixed-Dose,

Table 10: Summary of Weight Change in Short-Term (up to 6 weeks), Placebo-Controlled,

In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean
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*Note that in the High Dose group, there were 2 subjects with modafinil 200 mg total daily dose and 1 subject with modafinil 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 (23-27) 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-escalation period, probably reflecting its α-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 GEODON) 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 temporarily related to antipsychotic agents. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue GEODON at the first sign of deficit in WBC in the presence 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/mm3) should discontinue GEODON 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 D2 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 patients treated with ziprasidone. Many of these patients included: (1) 4351 patients who participated in multiple-dose trials, predominantly in schizophrenia, representing approximately 1851 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 147 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 of ziprasidone. 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 Reactions Observed in Short-Term, Placebo-Controlled Trials with Oral Ziprasidone
The following findings are based on the short-term placebo-controlled premaketing 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]

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>Respiratory Tract Infection</td>
</tr>
<tr>
<td>Bipolar trials</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Extrapyramidal Symptoms</td>
<td>Akathisia</td>
</tr>
<tr>
<td>Abnormal Vision</td>
<td>Asthenia</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
</tbody>
</table>

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 (5.3), (5.9)].
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

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

* Extrapyramidal Symptoms includes the following adverse reaction terms: extrapyramidal syndrome, dystonia, dyskinesia, hypokinesia, tremor, paroxysm 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 responsiveness in the schizophrenia 4-study pool revealed an apparent relationship of adverse reaction to dose for the following reactions: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypotension, somnolence, tremor, rhinitis, rash, and abnormal vision.

### Extrapyramidal Symptoms (EPS)

The incidence of reported EPS (which included the adverse reaction terms extrapyramidal syndrome, dystonia, dyskinesia, hypokinesia, tremor, paroxysm and twitching) for ziprasidone-treated patients in short-term, placebo-controlled schizophrenia trials was 14% vs. 8% for placebo. Objectively collected data from those trials on extrapyramidal symptoms, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paroxysm and twitching. None of these adverse reactions occurred individually at an incidence greater than 5% in schizophrenia trials.

** Extrapyramidal Symptoms includes the following adverse reaction terms: extrapyramidal syndrome, dystonia, dyskinesia, hypokinesia, tremor, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypotension, somnolence, tremor, rhinitis, rash, and abnormal vision.

### Dystonia

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.

### Vital Sign Changes

Ziprasidone is associated with an increase in the QTc interval.

### Respiratory System

The incidence of reported respiratory adverse reactions was 8% vs. 3% for placebo. The most common reaction 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.

### 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 Related to the Premarketing Evaluation of Oral Ziprasidone

#### Dose Dependency of Adverse Reactions in Short-Term, Fixed-Dose, Placebo-Controlled Trials

An analysis for dose responsiveness in the schizophrenia 4-study pool revealed an apparent relationship of adverse reaction to dose for the following reactions: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypotension, somnolence, tremor, rhinitis, rash, and abnormal vision.

#### Extrapyramidal Symptoms (EPS)

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The incidence of reported respiratory adverse reactions was 8% vs. 3% for placebo. The most common reaction 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

<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>Percentage of Patients Reporting Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>18</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
</tr>
<tr>
<td>Increased Salivation</td>
<td>4</td>
</tr>
<tr>
<td>Tongue Edema</td>
<td>3</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2</td>
</tr>
<tr>
<td>Nervous</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>31</td>
</tr>
<tr>
<td>Extrapyramidal Symptoms*</td>
<td>31</td>
</tr>
<tr>
<td>Dizziness**</td>
<td>16</td>
</tr>
<tr>
<td>Akathisia</td>
<td>10</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Speech Disorder</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td></td>
</tr>
<tr>
<td>Fungal Dermatitis</td>
<td>2</td>
</tr>
<tr>
<td>Special Senses</td>
<td></td>
</tr>
<tr>
<td>Abnormal Vision</td>
<td>6</td>
</tr>
</tbody>
</table>

* Extrapyramidal Symptoms includes the following adverse reaction terms: extrapyramidal syndrome, dystonia, dyskinesia, hypokinesia, tremor, paralyisis 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 associated with the use of intramuscular ziprasidone (incidence of 5% or greater) and observed at a rate on intramuscular ziprasidone (incidence of 1% or more of patients). Table 13 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 13: Treatment-Emergent Adverse Reaction Incidence In Short-Term Fixed-Dose Intramuscular Trials

<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>Ziprasidone 2 mg (N=92)</th>
<th>Ziprasidone 10 mg (N=63)</th>
<th>Ziprasidone 20 mg (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>9</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Flu Syndrome</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Back Pain</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of GEODON. 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 points (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 P-450 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.
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
Ziprasidone 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 Cmax of ziprasidone by 35-40%. Other inhibitors of CYP3A4 would be expected to have similar effects.

Cimetine
Cimetine 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 progestosterone 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.

7.10 Food Interaction
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 [see Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category C
In animal studies ziprasidone demonstrated developmental toxicity, including possible teratogenic effects at doses similar to human therapeutic doses. 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 abnormalities) was observed at a dose of 30 mg/kg/day (3 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m² basis). 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 on a mg/m² basis). 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 on a mg/m² basis) 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 on a mg/m² basis) were associated with maternal toxicity. The developmental no-effect dose was 5 mg/kg/day (0.2 times the MRHD on a mg/m² basis) or greater. A no-effect level was not established for these effects.

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 on a mg/m² basis) or greater. Offspring developmental delays and neurobehavioral functional impairment were observed at doses of 5 mg/kg/day (0.2 times the MRHD on a mg/m² basis) or greater. A no-effect level was not established for these effects.

There are no adequate and well-controlled studies in pregnant women. Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects
Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hyperpyrexia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

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

8.2 Labor and Delivery
The effect of ziprasidone on labor and delivery in humans is unknown.

8.3 Nursing Mothers
It is not known whether ziprasidone or its metabolites are excreted in human milk. It is recommended that women receiving ziprasidone should not breastfeed.

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 or 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 (12.3)].

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, 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 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 hypotension (200/95).

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

10.2 Management of Overdose
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 α1 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

GEODON is available as capsules (ziprasidone hydrochloride) for oral administration and 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 200.24 (free base), with the following chemical name: 5-[2-[4-[[1-(2-benzothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydropyridin-2-yl]amino]-2-pyridone hydrochloride monohydrate is a white to slightly pink powder.

Thus, the potential for drug interactions with ziprasidone due to displacement is minimal.

Metabolism of drugs metabolized by cytochrome P450 enzymes. The metabolism of drugs metabolized by cytochrome P450 enzymes. 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. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vivo chromosomal aberration assay in human lymphocytes, and the in vivo chromosomal aberration assay in mouse bone marrow. There was a reproducible increase in the frequency of sister chromatid exchanges in the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vivo chromosomal aberration assay in human lymphocytes.

11.2 Pharmacodynamics

Ziprasidone exhibited high in vitro binding affinity for the dopamine D2 and D3 receptors, serotonin 5HT2A, 5HT2C, 5HT1A, 5HT1D, and α1-adrenergic receptors (Kd of 4.8, 7.2, 0.4, 1.3, 3.4, 2, and 10 nM, respectively), and moderate affinity for the histamine H1 receptor (Kd=47 nM). Ziprasidone functioned as an antagonist at the D2, D3, 5HT2A, and 5HT2C receptors, and as an agonist at the 5HT1D receptor. Ziprasidone inhibited synaptic uptake of serotonin and norepinephrine. No appreciable affinity was exhibited for other receptor/binding sites tested, including the cholinergic muscarinic receptor (IC50 > 1 μM). Antagonism at receptors other than dopamine and serotonin, with similar receptor affinities may explain some of the other therapeutic and side effects of ziprasidone. Ziprasidone’s antagonism of histamine H1 receptors may explain the somnolence observed with this drug. Ziprasidone’s antagonism of α1-adrenergic receptors may explain the orthostatic hypotension observed with this drug.

11.3 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 terminal half-life of about 7 hours within the proposed clinical dose range. Steady-state concentrations are achieved within three to five 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 80%. 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 α1-acid glycoprotein. The in vitro 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, benzoisothiazole (BITP) sulphoxide, BITP-sulphone, ziprasidone sulphoxide, and S-methylthioziprasidone. 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 radioactivity recovered in the urine. 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 intramuscularally 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 (T1/2) 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 MRHD of 200 mg/day on a mg/m2 basis, 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 on a mg/m2 basis). 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 (2.5 and 5 times the MRHD on an mg/m2 basis). Ziprasidone had no effect on serum prolactin in rats in a 12-week 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 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 increase in the frequency of sister chromatid exchanges in the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vivo 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 on a mg/m2 basis) and in a fertility study in mice (2 to 5 times the MRHD on a mg/m2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m2 basis). 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 on an mg/m2 basis) were mated with untreated females. In an 8-month study in male rats given 200 mg/kg/day (10 times the MRHD on a mg/m2 basis) there were no treatment-related findings observed in the tests.

14 CLINICAL STUDIES

14.1 Schizophrenia

The efficacy of oral ziprasidone in the treatment of schizophrenia was evaluated in 5 placebo-controlled studies, most of which met DSM III-R criteria for schizophrenia. Each study included 2 to 3 fixed doses of ziprasidone as well as placebo. Four of the 5 trials were able to distinguish ziprasidone from placebo; one short-term study did not. Although a single fixed-dose haloperidol arm was included as a comparative treatment in the Amantadine trial, both these groups were superior to placebo on the BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second widely used instrument, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for the Assessment of Negative Symptoms (SANS) was employed for assessing negative symptoms in one trial.

The results of the oral ziprasidone trials in schizophrenia follow:

- In a 4-week, placebo-controlled trial (n=139) comparing 2 fixed doses of ziprasidone (20 and 60 mg twice daily) with placebo, only the 60 mg dose was superior to placebo on the BPRS total score and the CGI severity score. This higher dose group was not superior to placebo on the BPRS psychosis cluster or on the SANS.
- In a 6-week, placebo-controlled trial (n=302) comparing 2 fixed doses of ziprasidone (20 and 60 mg twice daily) with placebo, only the 60 mg dose was superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score and the PANSS total and negative subscale scores. Although 80 mg twice daily had a numerically greater effect than 40 mg twice daily, the difference was not statistically significant.
- In a 12-week, placebo-controlled trial (n=418) comparing 3 fixed doses of ziprasidone (20, 60, and 100 mg twice daily) with placebo, all three dose groups were superior to placebo on the PANSS total score, the BPRS total score, the BPRS psychosis cluster, and the CGI severity score. Only the 100 mg twice daily dose group was superior to placebo on the PANSS negative subscale score. There was no clear evidence for a dose-response relationship within the 20 mg twice daily to 100 mg twice daily dose range.
14.2 Bipolar I Disorder (Acute Mixed or Manic Episodes and Maintenance Treatment as an Adjunct to Lithium or Valproate)

Acute Manic and Mixed Episodes Associated with Bipolar I Disorder

The efficacy of ziprasidone was established in 2 placebo-controlled, double-blind, 3-week monotherapy studies in patients meeting DSM-IV criteria for bipolar I disorder, manic or mixed episode with or without psychotic features. Primary rating instruments used for assessing manic symptoms in these trials were: (1) the Mania Rating Scale (MRS), which is derived from the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-CB) with items grouped as the Manic Subscale syndrome (elevated mood, less need for sleep, excessive energy, excessive activity, grandiosity), the Behavior and Ideation subscale (irritability, motor hyperactivity, accelerated speech, racing thoughts, poor judgment) and impaired insight; and (2) the Clinical Global Impression-Severity of Illness Scale (CGI-S), which was used to assess the clinical significance of treatment response.

The results of the oral ziprasidone trials in adult bipolar I disorder, manic/mixed episode, follow: in a 3-week placebo-controlled trial (n=210), the dose of ziprasidone was 40 mg twice daily on Day 1 and 80 mg twice daily on Day 2. Titration within the range of 40-80 mg twice daily (in 20 mg twice daily increments) was permitted for the duration of the study. Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score. The mean daily dose of ziprasidone in this study was 132 mg. In a second 3-week placebo-controlled trial (n=205), the dose of ziprasidone was 40 mg twice daily on Day 1. Titration within the range of 40-80 mg twice daily (in 20 mg twice daily increments) was permitted for the duration of study (beginning on Day 2). Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score. The mean daily dose of ziprasidone in this study was 112 mg.

Maintenance Treatment

The efficacy of ziprasidone as adjunctive therapy to lithium or valproate in the maintenance treatment of bipolar I disorder was established in a placebo-controlled trial in patients who met DSM-IV-A criteria for bipolar I disorder with the trial included GT personnel. In this post-trial, ziprasidone was mania or mixed, with or without psychotic features. In the open-label phase, patients were required to be stabilized on ziprasidone plus lithium or valproic acid for at least 2 weeks in order to be randomized. In the double-blind randomized phase, patients continued treatment with lithium or valproic acid and were randomized to receive either ziprasidone (administered twice daily: 80 mg to 160 mg twice daily) in the maintenance phase. In the maintenance phase, patients continued on the same dose which they were stabilized during the stabilization phase. The primary endpoint of this study was time to recurrence of a mood episode (manic, mixed or depressed episode) requiring clinical intervention for a mood episode (e.g., initiation of medication or hospitalization), or Mania Rating Scale score of 20 or higher. Ziprasidone was more effective than placebo in reducing the MRS total score and the CGI-S score. The mean daily dose of ziprasidone in this study was 132 mg.

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/or scores of 6 (moderately severe) on the hostility or uncooperativeness items of the PANSS over 2 consecutive days. Ziprasidone was generally unable to provide informed consent for participation in premarketing clinical trials. The results of the intramuscular ziprasidone trials follow:

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 intervals of no less than 4 hours and no more than 10 days. In the other study, the dose was 20 mg, which could be given up to 4 times in the 24 hours of the study, at intervals of no less than 2 hours.

The results of the intramuscular ziprasidone trials follow:

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.

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.
PATIENT SUMMARY OF INFORMATION ABOUT
GEODON® Capsules
(ziprasidone HCl)

Information for patients taking GEODON or their caregivers
This summary contains important information about GEODON. It is not meant to take the place of your doctor's instructions. Read this information carefully before you take GEODON. Ask your doctor or pharmacist if you do not understand any of this information or if you want to know more about GEODON.

What Is GEODON?
GEODON is a type of prescription medicine called a psychotropic, also known as an atypical antipsychotic. GEODON can be used to treat symptoms of schizophrenia and acute manic or mixed episodes associated with bipolar disorder. GEODON can also be used as maintenance treatment of bipolar disorder when added to lithium or valproate.

Who Should Take GEODON?
Only your doctor can know if GEODON is right for you. GEODON may be prescribed for you if you have schizophrenia or bipolar disorder.

Symptoms of schizophrenia may include:
- hearing voices, seeing things, or sensing things that are not there (hallucinations)
- beliefs that are not true (delusions)
- unusual suspiciousness (paranoia)
- becoming withdrawn from family and friends

Symptoms of manic or mixed episodes of bipolar disorder may include:
- extremely high or irritable mood
- increased energy, activity, and restlessness
- racing thoughts or talking very fast
- easily distracted
- little need for sleep

If you show a response to GEODON, your symptoms may improve. If you continue to take GEODON there is less chance of your symptoms returning. Do not stop taking the capsules even when you feel better without first discussing it with your doctor.

It is also important to remember that GEODON capsules should be taken with food.

What is the most important safety information I should know about GEODON?
GEODON is not approved for the treatment of patients with dementia-related psychosis. Elderly patients with a diagnosis of psychosis related to dementia treated with antipsychotics are at an increased risk of death when compared to patients who are treated with placebo (a sugar pill).

GEODON is an effective drug to treat the symptoms of schizophrenia and the manic or mixed episodes of bipolar disorder. However, one potential side effect is that it may change the way the electrical current in your heart works more than some other drugs. The change is small and it is not known whether this will be harmful, but some other drugs that cause this kind of change have in rare cases caused dangerous heart rhythm abnormalities. Because of this, GEODON should be used only after your doctor has considered this risk for GEODON against the risks and benefits of other medications available for treating schizophrenia or bipolar manic and mixed episodes.

Your risk of dangerous changes in heart rhythm can be increased if you are taking certain other medicines and if you already have certain abnormal heart conditions. Therefore, it is important to tell your doctor about any other medicines that you take, including non-prescription medicines, supplements, and herbal medicines. You must also tell your doctor about any heart problems you have or have had.

Who should NOT take GEODON?
Elderly patients with a diagnosis of psychosis related to dementia. GEODON is not approved for the treatment of these patients.

Anything that can increase the chance of a heart rhythm abnormality should be avoided. Therefore, do not take GEODON if:
- You have certain heart diseases, for example, long QT syndrome, a recent heart attack, severe heart failure, or certain irregularities of heart rhythm (discuss the specifics with your doctor)
- You are currently taking medications that should not be taken in combination with ziprasidone, for example, 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.

What To Tell Your Doctor Before You Start GEODON
Only your doctor can decide if GEODON is right for you. Before you start GEODON, be sure to tell your doctor if you:
- have had any problem with the way your heart beats or any heart related illness or disease
- any family history of heart disease, including recent heart attack
- have had any problem with fainting or dizziness
- are taking or have recently taken any prescription medicines
- are taking any over-the-counter medicines you can buy without a prescription, including natural/herbal remedies
- have had any problems with your liver
- are pregnant, might be pregnant, or plan to get pregnant
- are breast feeding
- are allergic to any medicines
- have ever had an allergic reaction to ziprasidone or any of the other ingredients of GEODON capsules. Ask your doctor or pharmacist for a list of these ingredients
- have low levels of potassium or magnesium in your blood

Your doctor may want you to get additional laboratory tests to see if GEODON is an appropriate treatment for you.

GEODON And Other Medicines
There are some medications that may be unsafe to use when taking GEODON, and there are some medicines that can affect how well GEODON works. While you are on GEODON, check with your doctor before starting any new prescription or over-the-counter medications, including natural/herbal remedies.

How To Take GEODON
- Take GEODON only as directed by your doctor.
- Swallow the capsules whole.
- Take GEODON capsules with food.
- It is best to take GEODON at the same time each day.
- GEODON may take a few weeks to work. It is important to be patient.
- Do not change your dose or stop taking your medicine without your doctor's approval.
- Remember to keep taking your capsules, even when you feel better.

Possible Side Effects
Because these problems could mean you’re having a heart rhythm abnormality, contact your doctor IMMEDIATELY if you:
- Faint or lose consciousness
- Feel a change in the way that your heart beats (palpitations)
Common side effects of GEODON include the following and should also be discussed with your doctor if they occur:

- Feeling unusually tired or sleepy
- Nausea or upset stomach
- Constipation
- Dizziness
- Restlessness
- Abnormal muscle movements, including tremor, shuffling, and uncontrolled involuntary movements
- Diarrhea
- Rash
- Increased cough / runny nose

If you develop any side effects that concern you, talk with your doctor. It is particularly important to tell your doctor if you have diarrhea, vomiting, or another illness that can cause you to lose fluids. Your doctor may want to check your blood to make sure that you have the right amount of important salts after such illnesses.

For a list of all side effects that have been reported, ask your doctor or pharmacist for the GEODON Professional Package Insert.

What To Do For An Overdose
In case of an overdose, call your doctor or poison control center right away or go to the nearest emergency room.

Other Important Safety Information
A serious condition called neuroleptic malignant syndrome (NMS) can occur with all antipsychotic medications including GEODON. Signs of NMS include very high fever, rigid muscles, shaking, confusion, sweating, or increased heart rate and blood pressure. NMS is a rare but serious side effect that could be fatal. Therefore, tell your doctor if you experience any of these signs.

Delayed-onset drug reaction called drug reaction with eosinophilia and systemic symptoms (DRESS) can occur with ziprasidone. Signs of DRESS may include rash, fever, and swollen lymph nodes. Other severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome can occur with ziprasidone. Signs of Stevens-Johnson syndrome may include rash with blisters which could include ulcers in mouth, skin shedding, fever and target-like spots in the skin. DRESS and other SCAR are sometimes fatal; therefore, tell your doctor immediately if you experience any of these signs.

Adverse reactions related to high blood sugar (hyperglycemia), sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these reactions. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

Dizziness caused by a drop in your blood pressure may occur with GEODON, especially when you first start taking this medication or when the dose is increased. If this happens, be careful not to stand up too quickly, and talk to your doctor about the problem.

Before taking GEODON, tell your doctor if you are pregnant or plan on becoming pregnant. It is advised that you don’t breast feed an infant if you are taking GEODON.

Because GEODON can cause sleepiness, be careful when operating machinery or driving a motor vehicle.

Since medications of the same drug class as GEODON may interfere with the ability of the body to adjust to heat, it is best to avoid situations involving high temperature or humidity.

It is best to avoid consuming alcoholic beverages while taking GEODON.

Call your doctor immediately if you take more than the amount of GEODON prescribed by your doctor.

GEODON has not been shown to be safe or effective in the treatment of children and teenagers under the age of 18 years old.

Keep GEODON and all medicines out of the reach of children.

How To Store GEODON
Store GEODON capsules at room temperature (59°F to 86°F or 15°C to 30°C).

For More Information About GEODON
This sheet is only a summary. GEODON is a prescription medicine and only your doctor can decide if it is right for you. If you have any questions or want more information about GEODON, talk with your doctor or pharmacist. You can also visit www.geodon.com.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com

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