To help you prepare for your next doctor’s appointment, print out this Doctor Discussion Guide, answer the questions below, and take it with you.

Describe your symptoms since your last appointment. ____________________________________________________________
_________________________________________________________________________________________________________________________

Have there been any major changes in your life or health recently? ________________________________________________________
_________________________________________________________________________________________________________________________

Are you taking GEODON each day as prescribed? _________________________________________________________________
_________________________________________________________________________________________________________________________

Are you experiencing any side effects that are causing you difficulty or discomfort? __________________________________________
_______________________________________________________________________________________________________________________

Are you taking any new medications, over-the-counter supplements, or herbal remedies, and if so, which ones? ________________
_________________________________________________________________________________________________________________________

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.

You are encouraged to report adverse events related to Pfizer products by calling 1-800-438-1985 (US only). If you prefer, you may contact the US Food and Drug Administration (FDA) directly. Visit http://www.fda.gov/MedWatch or call 1-800-FDA-1088.

GEODON Indications
GEODON is a type of prescription medicine called a psychotrophic, 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 Important Safety Information

**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. 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 page and accompanying Full Prescribing Information, including BOXED WARNING and Patient Information.
Questions for Your Healthcare Team

In the space below, write down any questions you might have for your doctor about your condition and treatment. During your appointment, write down the responses so you can look back at them later.

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>ANSWER</th>
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Additional Questions to Ask Your Doctor

What should I do if I miss a dose of GEODON?
_________________________________________________________________________________

When do I need to come in for a follow-up visit? Date: ___________/___________/___________ Time: ___________:

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.

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.

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.

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

The health information contained herein is provided for educational purposes only and is not intended to replace discussions with a healthcare provider. All decisions regarding patient care must be made with a healthcare provider, considering the unique characteristics of the patient.

The product information provided is intended only for residents of the United States. The products discussed herein may have different product labeling in different countries.

Please see accompanying Full Prescribing Information, including BOXED WARNING and Patient Information.
GEODON® (ziprasidone mesylate) injection for intramuscular use

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

INSTRUCTIONS AND USAGE

GEODON is an atypical antipsychotic. In choosing among treatments, prescribers should be aware of the potential benefits and risks of all available treatments. The overall risk of mortality is increased in elderly patients with dementia-related psychosis treated with antipsychotic drugs. Treatment-specific mortality risks should be considered (5.1). In patients with dementia-related psychosis treated with antipsychotic drugs, the risk of mortality is greatest with the initial few months of treatment. The risk then decreases over time, with the risk for the drug in the dementia population being similar to that in all elderly patients with psychosis treated with antipsychotic drugs (5.1). The overall risk of mortality may be increased at all ages (5.1).

Dosage and Administration

Acute Treatment of Agitation in Schizophrenia

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

- Give oral doses with food.
- Use in patients with known hypersensitivity to ziprasidone (4.2)
- Do not use in patients with uncompensated heart failure (4.1)
- Do not use in patients with recent acute myocardial infarction (4.1)
- Do not use in patients with a known history of QT prolongation (4.1)
- Do not use in patients with known hyperprolactinemia (4.1)
- Do not use in patients with a history of seizures or with conditions that lower seizure threshold (5.12)
- Do not use in patients with known hypersensitivity to ziprasidone (4.2)
- Acute treatment of agitation associated with schizophrenia in elderly patients with dementia-related psychosis (5.1)
- 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)
- Acute treatment of agitation in schizophrenia. (1)

- 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 patients with a history of seizures or with conditions that lower seizure threshold (5.12)
- Do not use in patients with known hypersensitivity to ziprasidone (4.2)

DOSAGE AND ADMINISTRATION

Give oral doses with food.

- Schizophrenia: Initiate at 20 mg twice daily. Daily dosage may be increased 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 disorder: 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)
- Acute treatment of agitation associated with schizophrenia (intramuscular administration): 20 mg/mL single-use vials (3)

- Capsules: 20 mg, 40 mg, 60 mg, and 80 mg (3)
- Intramuscular injection: 20 mg/mL single-use vials (3)

CONTRAINDICATIONS

- Do not use in patients with a known history of QT prolongation (4.1)
- Do not use in patients with recent acute myocardial infarction (4.1)
- Do not use in patients with uncompensated heart failure (4.1)
- Do not use in patients with a history of seizures or with conditions that lower seizure threshold (5.12)
- 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: New cutaneous 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, abdominal pain, 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 cyclohexidinex excipient is cleared by renal filtration. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

9 DRUG ABUSE AND DEPENDENCE

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

13 NONCLINICAL TOXICOLOGY

14 CLINICAL STUDIES

15 PRECAUTIONS

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. GEODON is not approved for the treatment of dementia-related psychosis [see Warnings and Precautions (5.5)].

1 INDICATIONS 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 QTc/QT interval compared to several other antipsychotic drugs [see Warnings and Precautions (5.3)].

Intra-muscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

GEODON is contraindicated in individuals with a known hypersensitivity to the product. Potential for prolongation of the QT interval is associated with ziprasidone. Ziprasidone use should be avoided in combination with other drugs that are known to prolong the QT interval.

In elderly patients with dementia-related psychosis, patients randomized to ziprasidone had 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, Warnings and Precautions (5.5)].

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 dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg twice daily. Dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state 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 previously stabilized with ziprasidone has been conducted. The study was conducted in patients who had been stabilized on a dosing regimen of 10 mg to 80 mg twice daily for 2 weeks. The patients were randomized to 296 mg of sulfobutylether B-cyclodextrin sodium (SECBED), with a mean daily dose of 4.7 mg of methanesulfonic acid solubilized in 294 mg of sulfobutylether B-cyclodextrin sodium (SECBED).

3 DOSAGE FORMS AND STRENGTHS
GEODON Capsules are differentiated by capsule color/size and are imprinted in black ink with “Pfizer and ZDX [dosage strength]” or “Pfizer” and a unique number. GEODON Capsules are supplied for oral administration in 20 mg (blue/purple), 40 mg (blue/green), 60 mg (white/purple), and 80 mg (blue/white) capsules. They are supplied in the following strengths and package configurations:

GEODON Capsules

<table>
<thead>
<tr>
<th>Capsule Strength (mg)</th>
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<th>GEODON Capsules</th>
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<tbody>
<tr>
<td>20</td>
<td>ZDX 20</td>
<td>396</td>
</tr>
<tr>
<td>40</td>
<td>ZDX 40</td>
<td>397</td>
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<td>60</td>
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<td>80</td>
<td>ZDX 80</td>
<td>399</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 (2.5)]. Each mL of ziprasidone mesylate for injection (when reconstituted) affords a colorless to pale pink solution that contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized in 294 mg of sulfobutylether B-cyclodextrin sodium (SECBED).

4 CONTRAINDICATIONS

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

• in patients with a known history of QT prolongation (including congenital long QT syndrome)
• in patients with recent acute myocardial infarction
• in patients with uncompensated heart failure
Pharmacokinetic/pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with:

• dofetilide, sotalol, quinidine, other Class la and III anti-arrhythmics, mesoridazine, trimethadione, haloperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, propranolol or tamsulosin.
• 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, 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 (4.4)].

A study directly comparing the QT/QTc prolongation effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. In the first phase of the trial, ECGs were obtained at the time of maximum plasma concentration when the drug was administered alone. In the second phase of the trial, ECGs were obtained at the time of maximum plasma concentration while the drug was co-administered with an inhibitor of the CYP4503A4 metabolism of the drug.
In the first phase of the study, the mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine.

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

In placebo-controlled trials, oral ziprasidone increased the QTc interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials with oral ziprasidone, the electrocardiograms of 2/988 (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 of ziprasidone, as patients with a history of prolonged QTc and a screening measurement of 489 msec; QTc was 503 msec during ziprasidone treatment. The other patient had a QTc of 391 msec at the end of treatment with ziprasidone and upon switching to thioridazine experienced QTc measurements of 518 and 593 msec.

Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsade de pointes and sudden unexpected death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QTc prolongations may also increase risk, or increase it in susceptible individuals. Although torsade de pointes has not been observed in association with the use of ziprasidone in premarketing experience and is too limited to rule out an increased risk, there have been rare post-marketing reports (in the presence of multiple confounding factors).

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 11.9 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 antipsychotics. In a placebo-controlled trial with a 12-week duration of treatment, the occurrence of torsade de pointes and/or sudden death was one, both in the ziprasidone group (mean QTc interval, including 1) bradycardia; 2) hypokalemia or hypomagnesemia; 3) concomitant use of other drugs that prolong the QTc interval; and 4) presence of congenital prolongation of the QT interval. It is recommended that patients who are considered for ziprasidone treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during ziprasidone treatment. Persistent or prominent prolongation intervals may suggest the need for further evaluation including an electrocardiogram, cardiac history, and symptoms indicative of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac arrhythmia). Ziprasidone should be discontinued in patients who are found to have persistent QT prolongation.

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

5.4 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal syndrome complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Diagnosis of NMS requires a high index of suspicion because of the possibility of coexistence of other medical conditions, including the potential for autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac arrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is prudent to exclude cases in which the patient is experiencing one or more of the following clinical presentations: vomiting, obstipation, autonomic instability, fever, muscle rigidity, hyperpyrexia, tachycardia, diaphoresis, and an increase in creatinine. The differential diagnosis include central anticholinergic toxicity, hyperpyrexia, and neuroleptic malignant syndrome (NMS).

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of specific antipsychotic drugs should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.5 Severe Cutaneous Adverse Reactions

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

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

Other severe cutaneous adverse reactions

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

5.6 Tardive Dyskinesia

A subgroup of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible is believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia. Although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn, Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ziprasidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness (that is, it is known to be responsive) to antipsychotics, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on ziprasidone, discontinuation should be considered. However, some patients may require treatment with ziprasidone despite the presence of the syndrome.

5.7 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. Some of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile. Hyperglycemia and Diabetes Mellitus

Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON. Although fewer patients have been treated with GEODON, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of some metabolic changes, each drug has its own specific risk profile.

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In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline in random glucose for ziprasidone 20-40 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 3: Glucose* Mean Change from Baseline in Short-Term (up to 6 weeks), Placebo-Controlled, Flexible-Dose, Oral Ziprasidone, Monotherapy Trials in Adult Patients with Bipolar Disorder

<table>
<thead>
<tr>
<th>Laboratory Analyte</th>
<th>Category Change (at least once) from Baseline</th>
<th>Treatment Arm</th>
<th>N</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>Normal to High (≥200 mg/dL)</td>
<td>Ziprasidone</td>
<td>125</td>
<td>5.8%</td>
</tr>
<tr>
<td></td>
<td>Borderline to High (≥150 mg/dL)</td>
<td>Placebo</td>
<td>25</td>
<td>1.1%</td>
</tr>
<tr>
<td></td>
<td>Borderline to High (≥150 mg/dL) and &lt;200 mg/dL</td>
<td>Ziprasidone</td>
<td>72</td>
<td>34.8%</td>
</tr>
<tr>
<td></td>
<td>Borderline to High (≥150 mg/dL) and &lt;200 mg/dL</td>
<td>Placebo</td>
<td>71</td>
<td>36.5%</td>
</tr>
</tbody>
</table>

*Fasting

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

<table>
<thead>
<tr>
<th>Laboratory Analyte</th>
<th>Category Change (at least once) from Baseline</th>
<th>Treatment Arm</th>
<th>N</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>Normal to High (≥150 mg/dL and &lt;200 mg/dL)</td>
<td>Ziprasidone</td>
<td>125</td>
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<td>Placebo</td>
<td>71</td>
<td>36.5%</td>
</tr>
</tbody>
</table>

*Fasting

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

<table>
<thead>
<tr>
<th>Laboratory Analyte</th>
<th>Category Change (at least once) from Baseline</th>
<th>Treatment Arm</th>
<th>N</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>Normal to High (≥150 mg/dL)</td>
<td>Ziprasidone</td>
<td>125</td>
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<td></td>
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<td>Placebo</td>
<td>71</td>
<td>36.5%</td>
</tr>
</tbody>
</table>

*Fasting

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

<table>
<thead>
<tr>
<th>Laboratory Analyte</th>
<th>Category Change (at least once) from Baseline</th>
<th>Treatment Arm</th>
<th>N</th>
<th>n (%)</th>
</tr>
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<tbody>
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<td>Placebo</td>
<td>71</td>
<td>36.5%</td>
</tr>
</tbody>
</table>

*Fasting

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

<table>
<thead>
<tr>
<th>Laboratory Analyte</th>
<th>Mean Change from Baseline mg/dL (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>+0.7 (N=85)</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>-8.2 (N=85)</td>
</tr>
</tbody>
</table>

*Fasting

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

<table>
<thead>
<tr>
<th>Laboratory Analyte</th>
<th>Category Change (at least once) from Baseline</th>
<th>Treatment Arm</th>
<th>N</th>
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<td>Placebo</td>
<td>71</td>
<td>36.5%</td>
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</tbody>
</table>

*Fasting

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

<table>
<thead>
<tr>
<th>Laboratory Analyte</th>
<th>Mean Weight (kg) Changes from Baseline (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>+0.3 (N=40)</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>-14.0 (N=104)</td>
</tr>
</tbody>
</table>

*Fasting

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 ≥ 10% 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 ≥ 5% increase in weight from baseline for ziprasidone 20 mg BID was 5.6% (N=72); for ziprasidone 40 mg BID was 2.9% (N=69); for ziprasidone 80 mg BID was 5.7% (N=70) and for placebo was 2.9% (N=70).

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

<table>
<thead>
<tr>
<th>Laboratory Analyte</th>
<th>Mean Weight (kg) Changes from Baseline (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>+0.4 (N=295)</td>
</tr>
<tr>
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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 56% for both ziprasidone and placebo treatment groups who completed the 6 months of observation for relapse. Interpretation of these findings should take into consideration that only patients who adequately tolerated ziprasidone entered the double-blind phase of the study, and there were substantial dropouts during the open label phase.

5.8 Rash

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

5.9 Orthostatic Hypotension

Ziprasidone may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α1-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 leukaemia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukaemia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukaemia/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 decline in WBC in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/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 with a control compound. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density.

5.15 Potential for Cognitive and Motor Impairment

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

5.16 Priapism

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

5.17 Body Temperature Regulation

Although not reported with ziprasidone in premarketing trials, disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ziprasidone for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

5.18 Suicide

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

5.19 Patients with Concomitant Illnesses

Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses is limited [see Use in Specific Populations (8.6), (8.7)]. Ziprasidone has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QTc prolongation and orthostatic hypotension with ziprasidone, caution should be observed in cardiac patients. [see Warnings and Precautions (5.3), (5.9)].

5.20 Laboratory Tests

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical trials for oral ziprasidone included approximately 5700 patients and/or normal subjects exposed to one or more doses of ziprasidone. Of these 5700, over 4800 were patients who participated in multiple-dose effectiveness trials, and their experience corresponded to approximately 1851 patient-years of exposure. These patients include: (1) 4351 patients who participated in multiple-dose trials, predominantly in schizophrenia, representing approximately 1698 patient-years of exposure as of February 5, 2000; and (2) 472 patients who participated in bipolar mania trials representing approximately 133 patient-years of exposure. An additional 127 patients with bipolar disorder participated in a long-term maintenance treatment study representing approximately 74.7 patient-years of exposure to ziprasidone. The conditions and duration of treatment with ziprasidone included open-label and double-blind studies, inpatient and outpatient studies, and short-term and longer-term exposure.

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

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

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

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

The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of 2-week and 4-week fixed-dose trials) and bipolar mania (a pool of 2-week flexible-dose trials) in which ziprasidone was administered in doses ranging from 10 to 200 mg/day.

Commonly Observed Adverse Reactions in Short-Term Placebo-Controlled Trials

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

Schizophrenia trials (see Table 11)

- Somnolence
- Respiratory Tract Infection

Bipolar trials (see Table 12)

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

SCHIZOPHRENIA

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

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

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

Table 11 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy (up to 6 weeks) in predominantly patients with schizophrenia, including only those reactions that occurred in 2% or more of patients treated with ziprasidone and for which the incidence in patients treated with ziprasidone was greater than the incidence in placebo-treated patients.

<table>
<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>5</td>
</tr>
<tr>
<td>Accidental Injury</td>
<td>4</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>3</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2</td>
</tr>
<tr>
<td><strong>Digestive</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
</tr>
<tr>
<td>Constipation</td>
<td>9</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>4</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2</td>
</tr>
<tr>
<td><strong>Nervous</strong></td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal Symptoms*</td>
<td>14</td>
</tr>
<tr>
<td>Somnolence</td>
<td>14</td>
</tr>
<tr>
<td>Akathisia</td>
<td>8</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td>8</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
</tr>
<tr>
<td>Respiratory Tract Infection</td>
<td>8</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4</td>
</tr>
<tr>
<td>Cough Increased</td>
<td>3</td>
</tr>
<tr>
<td><strong>Skin and Appendages</strong></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
</tr>
<tr>
<td>Fungal Dermatitis</td>
<td>2</td>
</tr>
<tr>
<td><strong>Special Senses</strong></td>
<td></td>
</tr>
<tr>
<td>Abnormal Vision</td>
<td>3</td>
</tr>
</tbody>
</table>

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

An analysis for dose response in the schizophrenia 4-study pool revealed an apparent relation of adverse reaction to dose for the following reactions: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dysoria, hypotonia, 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 the short-term, placebo-controlled schizophrenia trials was 14% vs. 8% for placebo. Objectively collected data from those trials on paralysis and twitching for ziprasidone-treated patients in the short-term, placebo-controlled reaction terms extrapyramidal syndrome, hypertonia, 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.

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

Acute Treatment of Manic or Mixed Episodes

Adverse Reactions Observed During the Premarketing Evaluation of Oral Ziprasidone

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

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

**Frequent** - adverse reactions occurring in at least 1/10 patients (≥1.0% of patients) (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing);

**Infrequent** - adverse reactions occurring in 1/100 to 1/1000 patients (in 0.1-1.0% of patients).

**Rare** - adverse reactions occurring in fewer than 1/1000 patients (<0.1% of patients).

### Body as a Whole

**Frequent** - abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident

### Cardiovascular System

**Frequent** - tachycardia, hypertension, postural hypotension

**Infrequent** - bradycardia, angina pectoris, atrial fibrillation

**Rare** - first degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis

### Digestive System

**Frequent** - anorexia, vomiting

**Infrequent** - rectal hemorrhage, dysphagia, tongue edema

**Rare** - gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena

### Endocrine

**Rare** - hypothyroidism, hyperthyroidism, thyroiditis

### Hemic and Lymphatic System

**Infrequent** - anemia, ecchymosis, leukocytosis, leukenopia, eosinophilia, lymphadenopathy

**Rare** - thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphphedema, polycythemia, thrombocytopenia

### Metabolic and Nutritional Disorders

**Infrequent** - thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia

**Rare** - BUN increased, creatinine increased, hyperlipemia, hypercholesteremia, hyperkalemia, hypercholesterolemia, hypoglycemia, hyperproteinemia, glucose tolerance decreased, gout, hypercholesteremia, hyperuricemia, hypocalemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis

### Musculoskeletal System

**Frequent** - myalgia

**Infrequent** - tenosynovitis

**Rare** - myopathy

### Nervous System

**Frequent** - agitation, extrapyramidal syndrome, tremor, dystonia, hyperkinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypophonia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dystarthis, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplegia, incoordination, neuropathy

**Infrequent** - paralysis

**Rare** - myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonus, reflexes increased, trismus

### Respiratory System

**Frequent** - dyspnea

**Infrequent** - pneumonia, epistaxis

**Rare** - hemoptysis, laryngismus

### Skin and Appendages

**Infrequent** - maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash

### Special Senses

**Frequent** - conjunctivitis, dry eyes, tinnitus, blepharitis, catarract, photophobia

**Rare** - eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis

### Urogenital System

**Infrequent** - impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, poluria, urinary retention metrorrhagia, male sexual dysfunction, anorgasia, gynecomastia, vulvodynia

**Rare** - gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage

### Bipolar Disorder

**Acute Treatment of Manic or Mixed Episodes**

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

Approximately 6.5% (18/279) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 3.7% (51/136) on placebo. The most common reactions associated with dropout in the ziprasidone-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these reactions among ziprasidone patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse reactions.
Adverse Reactions Occurring at an Incidence of 2% or More Among Ziprasidone-Treated Patients in Short-Term, Oral, Placebo-Controlled Trials

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

### Table 12: Treatment-Emergent Adverse Reactions Occurring at an Incidence of 1% or More Among Ziprasidone-Treated Patients

<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>Ziprasidone (N=279)</th>
<th>Placebo (N=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Somnolence</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nervous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>Extrapyramidal Symptoms*</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>Dizziness**</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Akathisia</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Speech Disorder</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungal Dermatitis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Special Senses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal Vision</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

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

** Dizziness includes the adverse reaction terms dizziness and lightheadedness.

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

### INTRAMUSCULAR ZIPRASIDONE

Adverse Reactions Occurring at an Incidence of 1% or More Among Ziprasidone-Treated Patients in Short-Term Trials of Intramuscular Ziprasidone

Table 13 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy (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 placebo was greater than the incidence in placebo-treated patients.

### Table 13: Treatment-Emergent Adverse Reaction Incidence in Short-Term Fixed-Dose Intramuscular Trials (cont’d)

<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>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>Asthenia</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>0</td>
<td>2</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: 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 serotoninergic medicinal products), tardive dyskinesia; Psychiatric Disorders: Insomnia, mania/hypomania; Skin and Subcutaneous Tissue Disorders: Allergic reaction (such as allergic dermatitis, angioedema, orofacial edema, urticaria), rash, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); Urogenital System Disorders: Enuresis, urinary incontinence; Vascular Disorders: Postural hypotension, syncope.

7 DRUG INTERACTIONS

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

7.1 Metabolic Pathway

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

7.2 In Vitro Studies

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

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

7.4 Pharmacokinetic Interactions
Carbamazepine
Carbamazepine is an inducer of CYP3A4; administration of 200 mg twice daily for 21 days resulted in a decrease of approximately 35% in the AUC of ziprasidone. This effect may be greater when higher doses of carbamazepine are administered.

Ketocazolone
Ketocazolone, 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.

Cimetidine
Cimetidine at a dose of 800 mg QD for 2 days did not affect ziprasidone pharmacokinetics.

Antacid
The co-administration of 30 mL of Maalox® with ziprasidone did not affect the pharmacokinetics of ziprasidone. 

7.5 Lithium
Ziprasidone at a dose of 40 mg twice daily administered concomitantly with lithium at a dose of 450 mg twice daily for 7 days did not affect the steady-state level or renal clearance of lithium. Ziprasidone dosed adjunctively to lithium in a maintenance trial of bipolar patients did not affect mean therapeutic lithium levels.

7.6 Oral Contraceptives
In vivo studies have revealed no effect of ziprasidone on the pharmacokinetics of estrogen or progestrone 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, dextroxtorph. There was no statistically significant change in the urinary dextromethorphan/dextroxtorph 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 adjutively 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 lorzepam.

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 alterations) 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, embryotial 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 6 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). 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. No antifetal effect 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, hypotonia, 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 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to ziprasidone, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients.

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

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

Intramuscular ziprasidone has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cycloextrin 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 AUC₂₅₀ of 13% and 34% in Childs-Pugh Class A and B, respectively, compared to a matched control group (n=14). A half-life of 7.1 hours was observed in subjects with cirrhosis compared to 4.8 hours in the control group.

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

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

9 DRUG ABUSE AND DEPENDENCE
9.3 Dependence
Ziprasidone has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which ziprasidone will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ziprasidone misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

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

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

10.2 Management of 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 arrhythmogenic 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 α₂ 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.
GEODON Capsules contain a mono hydrochloride, monohydrate salt of ziprasidone. Chemically, ziprasidone hydrochloride monohydrate is C21H21ClN4OS · HCl · H2O and its molecular weight is 467.42. Ziprasidone hydrochloride monohydrate is a white to slightly pink powder.

GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/blue) capsules. GEODON Capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.

GEODON Capsule 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 reconstituted solution contains ziprasidone 6.3 mg and 4.7 mg of methanesulfonic acid solubilized by 294 mL of sulfobutyler 12 cycloexdin sodium (SBCED).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of ziprasidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonism. As with other drugs having efficacy in bipolar disorder, the mechanism of action of ziprasidone in bipolar disorder is unknown.

12.2 Pharmacodynamics

Ziprasidone exhibited high in vitro binding affinity for the dopamine D2, and D3 receptors, the serotonin 5HT2A, 5HT2C, 5HT1A, and 5HT1D receptors, and 5HT1D-adrenergic receptors (K of 4.8, 7.2, 0.4, 1.3, 3.4, 2, and 10 nM, respectively), and moderate affinity for the histamine H1 receptor (K=47 nM). Ziprasidone was found to be an antagonist at the D2, 5HT2A, and 5HT2C receptors, and as an agonist at the 5HT1D receptor. Ziprasidone inhibited synaptic reuptake of serotonin and norepinephrine. No appreciable affinity was exhibited for other receptor/binding sites tested, including the cholinergic muscarinic receptor (IC50 >1 μM). Antagonism at receptors other than dopamine and 5HT, 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.

12.3 Pharmacokinetics

Oral Pharmacokinetics

Ziprasidone's activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of ziprasidone are dose-proportional within the proposed clinical dose range, and ziprasidone accumulation is predictable with multiple dosing. Elimination of ziprasidone is mainly via hepatic metabolism with a mean terminal half-life of about 7 hours within the proposed clinical dose range, and pharmacokinetics of ziprasidone are dose-proportional within the proposed clinical dose range, and pharmacokinetics of ziprasidone are dose-proportional within the proposed clinical dose range.

14 CLINICAL STUDIES

14.1 Schizophrenia

The efficacy of oral ziprasidone in the treatment of schizophrenia was evaluated in 5 placebo-controlled studies, 4 short-term (4- and 6-week) trials and one maintenance trial. All studies were in adult inpatients, most of whom 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 American phase in both trials, this group was never used as a control. In the absence of metabolic activation, positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes, and the in vivo chromosomal aberration assay in mouse bone marrow. There was a reproducible reduction in the in vitro amount of the substance that was used in the carcinogenicity study. The relevance of human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown [see Warnings and Precautions (5.14)].

Metabolism

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 reduction in the in vitro amount of the substance that was used in the carcinogenicity study. The relevance of human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown [see Warnings and Precautions (5.14)].

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, 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 (or 2.5 and 5 times the MRHD on a mg/m2 basis). Ziprasidone had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance of human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown [see Warnings and Precautions (5.14)].

Several instruments were used for assessing psychiatric symptoms and signs in these studies. The Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS) are both multi-item inventories of general psychopathology usually used to evaluate the efficacy of new antipsychotic drugs in schizophrenia. The Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS) are considered useful subset for assessing actively psychotic schizophrenic patients. A second widely used assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing 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 (40 and 80 mg twice daily) with placebo, the 80 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=419) 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.
In a 4-week, placebo-controlled trial (n=200) comparing 3 fixed doses of ziprasidone (5, 20, and 40 mg twice daily), none of the dose groups was statistically superior to placebo on any outcome of interest.

A study was conducted in stable chronic or subchronic (CGI-S = 5 at baseline) schizophrenic inpatients (n=294) who had been hospitalized for not less than two months. After a 3-day single-blind placebo run-in, subjects were randomized to one of 3 fixed doses of ziprasidone (20 mg, 40 mg, or 80 mg twice daily) or placebo and observed and released. Patients were observed for “improving psychotic relapse,” defined as CGI-improvement score of ≥6 (much worse or very much worse) and/or scores ≥6 (moderately severe) on the hostility or uncooperativeness items of the PANSS on 2 consecutive days. Ziprasidone was significantly superior to placebo in time to relapse, with no significant difference between the different dose groups on any of the other variables examined. Examination of population subsets based on gender did not reveal any differential responsiveness.

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 Syndrome subscale (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=265), 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 Therapy

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 criteria for bipolar I disorder. The trial included QT prolongation; risk for significant electrolyte abnormalities; and a history of cardiovascular disease. The primary endpoint of this study was recurrence of a mood episode (manic, mixed, or depressive) during treatment. The mean daily dose of ziprasidone was 132 mg on Day 1 and 112 mg on subsequent days. The mean daily dose of ziprasidone was 132 mg on Day 1 and 112 mg on subsequent days. The mean daily dose of ziprasidone was 132 mg on Day 1 and 112 mg on subsequent days.

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 psychosis subscale: excitement, disorganization, and conceptual disorganization. Efficacy was evaluated by change in the area under the curve (AUC) of the Behavioural Activity Rating Scale (BARS) and Clinical Global Impression (CGI) severity rating. The BARS is a seven point scale with scores ranging from 1 (difficult or unable to rouse) to 7 (violent, requires restraint). Patients’ scores on the BARS at baseline were mostly 5 (signs of excitement or agitation) and determined by investigators, exhibited a degree of agitation that warranted intramuscular therapy. There were few patients with a rating higher than 5 on the BARS, as the most severely agitated patients were generally unable to provide informed consent for participation in a randomized clinical trial.

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 not less than 4 hours. In the other study, the higher dose was 40 mg, which could be given up to 4 times in the 24 hours of the study, at intervals of not less than 4 hours.

The results of the intramuscular ziprasidone trials follow:

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

GEODON Capsules are differentiated by capsule color/size, and are imprinted in black ink with “Pfizer” and “20” [doseage strength] or with “Pfizer” 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/blue) capsules. They are supplied in the following strengths and package configurations:

Bottles of 60
Bottles of 60
Bottles of 60
Unit dose/80
Unit dose/80
Unit dose/80

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GEODON Capsules should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

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 solubilized by 234 mg of sulfobutyl ethers of polyethylene oxide (SBEED).

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Administration with Food

Instruct patients to take GEODON Capsules with food for optimal absorption. The absorption of ziprasidone is increased up to two-fold in the presence of food [see Drug Interactions (7.10) and Clinical Pharmacology (12.3)].

QTc Prolongation

Advise patients to inform their health care providers of the following: History of QT prolongation; recent acute myocardial infarction; uncompensated heart failure; prescription of other drugs that have demonstrated QT prolongation; risk for significant electrolyte abnormalities; and history of cardiac arrhythmia [see Contraindications (4.1) and Warnings and Precautions (5.3)].

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

Severe Cutaneous Adverse Reactions

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

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

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LAB-0273-27.0
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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