Use these tips along with your GEODON Savings Card when picking up your brand-name prescription.

Begin at your doctor’s office.

Remind your doctor to indicate “Dispense As Written” (“DAW”) or “No Substitutions,” as per your state’s requirement if your doctor has decided to prescribe brand-name GEODON.

Ask for brand-name GEODON at the pharmacy, and tell your pharmacist your GEODON Savings Card does not work with the generic.

Notify the pharmacist right away if you did not receive brand-name GEODON or your savings at pick-up.

Don’t forget your GEODON Savings Card each time you visit the pharmacy.

*Terms and conditions apply. See below.

If you didn’t get the brand-name savings that come with your GEODON Savings Card and you meet all eligibility requirements, check to make sure:

- You received brand-name GEODON in your prescription bag. Your card works only with brand-name GEODON
- Your GEODON Savings Card details were entered correctly
- Your pharmacist called 1-800-725-9655 for help processing the card for this brand

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.

*Eligibility required. Terms and conditions apply. Full terms and conditions can be found at GEODON.com/about-copay#terms. Card accepted only at participating pharmacies. Card is not health insurance. No membership fees. Maximum benefit of $3,000 per year. The Card is not valid for prescriptions that are eligible to be reimbursed in whole or in part, by Medicaid, Medicare, or other federal or state healthcare programs. The Card is not valid for prescriptions that are eligible to be reimbursed in whole by private insurance plans or other health or pharmacy benefit programs. For more information, call 1-800-725-9655, visit www.GEODON.com, or write: Attn: GEODON Savings Card: 2250 Perimeter Park Drive, Suite 300, Morrisville, NC 27560.

Please see accompanying Full Prescribing Information, including BOXED WARNING and Patient Information.
FULL PRESCRIBING INFORMATION: CONTENTS*

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

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REVISED: 2/2017
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 schizophrenia patients. When deciding among the alternative treatments available for the condition needing treatment, the prescriber should consider the finding of ziprasidone’s greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs [see Warnings and Precautions (5.2)]. Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia, and sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether ziprasidone will cause torsade de pointes or increase the rate of sudden death is not yet known [see Warnings and Precautions (5.2)].

1.1 Schizophrenia
GEODON is indicated for the treatment of schizophrenia. The efficacy of oral ziprasidone was established in four short-term (4- and 6-week) controlled trials of adult schizophrenic inpatients and in one maintenance trial of stable adult schizophrenic inpatients [see Clinical Studies (14.1)].

1.2 Bipolar I Disorder (Acute Mixed or Manic Episodes and Maintenance Treatment as an Adjunct to Lithium or Valproate)
GEODON is indicated as monotherapy for the acute treatment of manic or mixed episodes associated with bipolar I disorder. Efficacy was established in 2-3 week monotherapy studies in adult patients [see Clinical Studies (14.2)].

GEODON is indicated as an adjunct to lithium or valproate for the maintenance treatment of bipolar I disorder. Efficacy was established in a maintenance trial in adult patients. The efficacy of GEODON as monotherapy for the maintenance treatment of bipolar I disorder has not been systematically evaluated in controlled clinical trials [see Clinical Studies (14.2)].

1.3 Acute Treatment of Agitation in Schizophrenia
GEODON intramuscular is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with ziprasidone is appropriate and who need intramuscular antipsychotic medication for rapid control of agitation. The efficacy of intramuscular ziprasidone for acute agitation in schizophrenia was established in single day controlled trials of agitation schizophrenic inpatients [see Clinical Trials (14.1)].

“Psychomotor agitation” is defined in DSM-IV as “excessive motor activity associated with a feeling of inner tension”. Schizophrenic patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation. Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended. Ziprasidone intramuscular is intended for intramuscular use only and should not be administered intravenously.

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 1 week and should be based on 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 100 mg twice daily, but data were not consistent. An increase to a dose greater than 80 mg twice daily is not generally recommended. The safety of doses above 100 mg twice daily has not been systematically evaluated in clinical trials [see Clinical Studies (14.1)].

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

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

Acute Treatment of Manic or Mixed Episodes
Dose Selection-Oral ziprasidone should be administered at an initial daily dose of 40 mg twice daily, with food. The dose may then be increased to 60 mg or 80 mg twice daily on the second day of treatment and subsequently adjusted on the basis of tolerance and efficacy within the range of 40 mg-80 mg twice daily. In the flexible-dose clinical trials, the mean daily dose administered was approximately 120 mg [see Clinical Studies (14.2)].

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

2.3 Acute Treatment of Agitation in Schizophrenia

Intramuscular Dosing
The recommended dose is 10 mg to 20 mg administered as required up to a maximum dose of 40 mg per day. GEODON may be administered every 2 days; doses of 20 mg may be administered every four hours up to a maximum of 40 mg/day. Intramuscular administration of ziprasidone for more than three consecutive days has not been studied. If long-term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as soon as possible.

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

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

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

2.4 Dosing in Special Populations

Oral: Dosage adjustments are generally not required on the basis of age, gender, race, or renal or hepatic impairment. GEODON is not approved for use in children or adolescents. Intramuscular: Ziprasidone intramuscular has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclohexidine excitant is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function. Dosing adjustments are not required on the basis of gender or race [see Use in Specific Populations (8)].

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 “PZ” and a unique number. GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/white), 60 mg (white/white), and 80 mg (blue/white) capsules. They are supplied in the following strengths and package configurations:

<table>
<thead>
<tr>
<th>GEODON Capsules</th>
<th>OR</th>
<th>GEODON Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsule Strength (mg)</td>
<td>Imprint</td>
<td>Capsule Strength (mg)</td>
</tr>
<tr>
<td>20</td>
<td>ZDX 20</td>
<td>20</td>
</tr>
<tr>
<td>40</td>
<td>ZDX 40</td>
<td>40</td>
</tr>
<tr>
<td>60</td>
<td>ZDX 60</td>
<td>60</td>
</tr>
<tr>
<td>80</td>
<td>ZDX 80</td>
<td>80</td>
</tr>
</tbody>
</table>

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 294 mg of sulfobutylether b-cyclodextrin sodium (SBEDC).

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

• dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thiadorzidine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, melofloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dalogastone mesylate, or propylthiouracil, or halothane, or 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 (5.2)].

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 seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of 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 were considered to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. GEODON (ziprasidone) is not approved for the treatment of patients with Dementia-Related Psychosis [see Warnings and Precautions (5.1)].
5.2 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), 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 (e.g., sick sinus syndrome). Be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.4 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.

5.5 Tardive Dyskinesia

A syndrome characterized by involuntary, 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 not clear.

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

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may, in some patients, partially or completely resolve following drug discontinuation. However, some patients may require treatment with ziprasidone despite the presence of the syndrome.

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON. Although all antipsychotics have been reported to cause weight gain and hyperglycemia, the risk associated with ziprasidone should be considered for patients who are at increased risk for diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with ziprasidone are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing at some time during treatment. If symptoms of hyperglycemia develop while on antipsychotic treatment, the drug should be discontinued. Patients may require treatment with antipsychotics and glucose lowering medications. Some cases, treatment is a hospitalization. Antipsychotic therapy should be discontinued; however, some patients require continuation of antidiabetic treatment despite discontinuation of the suspected drug.

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

<table>
<thead>
<tr>
<th>Glucose* Mean Change from Baseline mg/dL (N)</th>
<th>Ziprasidone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg BID</td>
<td>20 mg BID</td>
<td>40 mg BID</td>
</tr>
<tr>
<td>+1.1 (N=45)</td>
<td>+2.4 (N=179)</td>
<td>-0.2 (N=146)</td>
</tr>
</tbody>
</table>

Random glucose measurements—fasting/non-fasting status unknown.
Table 2: Glucose* Categorical Changes in Short-Term (up to 6 weeks), Placebo-Controlled, Fixed-Dose, Oral Ziprasidone, Monotherapy Trials in Adult Patients with Schizophrenia

<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>Glucose</td>
<td>Random Glucose</td>
<td>Ziprasidone</td>
<td>438</td>
<td>77 (17.6%)</td>
</tr>
<tr>
<td></td>
<td>Normal to High (&lt;100 mg/dL to ≥126 mg/dL)</td>
<td>Placebo</td>
<td>169</td>
<td>26 (15.4%)</td>
</tr>
<tr>
<td></td>
<td>Borderline to High (≥100 mg/dL and &lt;126 mg/dL to ≥126 mg/dL)</td>
<td>Ziprasidone</td>
<td>159</td>
<td>54 (34.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>66</td>
<td>22 (33.3%)</td>
</tr>
</tbody>
</table>

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

In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline in random glucose for ziprasidone 20-40 mg BID was +0.8 mg/dL (N=14); for ziprasidone 60-80 mg BID was +2.8 mg/dL (N=10); and for placebo was -2.9 mg/dL (N=9).

Table 3: 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>Fasting Glucose</td>
<td>Normal to High (&lt;100 mg/dL to ≥126 mg/dL)</td>
<td>Ziprasidone</td>
<td>272</td>
<td>5 (1.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>210</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td></td>
<td>Borderline to High (≥100 mg/dL and &lt;126 mg/dL to ≥126 mg/dL)</td>
<td>Ziprasidone</td>
<td>19</td>
<td>12 (65.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>71</td>
<td>7 (9.9%)</td>
</tr>
</tbody>
</table>

Fasting
dyslipidemia

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>Ziprasidone High Dose: 60-80 mg BID</td>
<td>232</td>
<td>17 (7.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo Low Dose: 20-40 mg BID</td>
<td>210</td>
<td>2 (1.0%)</td>
<td></td>
</tr>
</tbody>
</table>

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

Table 5: Lipid Mean Change from Baseline (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>Ziprasidone</td>
<td>681</td>
<td>232 (34.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>260</td>
<td>32 (20.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Borderline to High (≥150 mg/dL and &lt;200 mg/dL to ≥200 mg/dL)</td>
<td>Ziprasidone</td>
<td>92</td>
<td>43 (46.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>41</td>
<td>12 (29.3%)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Ziprasidone</td>
<td>682</td>
<td>76 (11.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>261</td>
<td>26 (10.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Borderline to High (≥200 mg/dL and &lt;240 mg/dL to ≥240 mg/dL)</td>
<td>Ziprasidone</td>
<td>207</td>
<td>56 (27.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>82</td>
<td>22 (26.8%)</td>
</tr>
</tbody>
</table>

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

In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline in random triglycerides for ziprasidone 20-40 mg BID was +0.3 mg/dL (N=12); for ziprasidone 60-80 mg BID was -9.7 mg/dL (N=10); and for placebo was -12.8 mg/dL (N=9).

Table 6: 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>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>Ziprasidone</td>
<td>371</td>
<td>66 (17.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>286</td>
<td>62 (21.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Borderline to High (≥150 mg/dL and &lt;200 mg/dL to ≥200 mg/dL)</td>
<td>Ziprasidone</td>
<td>58</td>
<td>16 (27.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>47</td>
<td>14 (29.8%)</td>
</tr>
</tbody>
</table>

Fasting
dyslipidemia

Table 7: Lipid Mean Change from Baseline (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>Ziprasidone</td>
<td>359</td>
<td>39 (10.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>270</td>
<td>17 (6.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Borderline to High (≥100 mg/dL and &lt;160 mg/dL to ≥160 mg/dL)</td>
<td>Ziprasidone</td>
<td>174</td>
<td>18 (9.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>141</td>
<td>14 (9.9%)</td>
</tr>
</tbody>
</table>

Fasting
weight gain

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>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>Ziprasidone</td>
<td>371</td>
<td>66 (17.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>286</td>
<td>62 (21.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Borderline to High (≥150 mg/dL and &lt;200 mg/dL to ≥200 mg/dL)</td>
<td>Ziprasidone</td>
<td>58</td>
<td>16 (27.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>47</td>
<td>14 (29.8%)</td>
</tr>
</tbody>
</table>

Fasting
weight gain

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>Category Change (at least once) from Baseline</th>
<th>Treatment Arm</th>
<th>N</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>Ziprasidone</td>
<td>681</td>
<td>232 (34.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>260</td>
<td>32 (20.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Borderline to High (≥150 mg/dL and &lt;200 mg/dL to ≥200 mg/dL)</td>
<td>Ziprasidone</td>
<td>92</td>
<td>43 (46.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>41</td>
<td>12 (29.3%)</td>
</tr>
<tr>
<td></td>
<td>Borderline to High (≥200 mg/dL and &lt;240 mg/dL to ≥240 mg/dL)</td>
<td>Ziprasidone</td>
<td>207</td>
<td>56 (27.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>82</td>
<td>22 (26.8%)</td>
</tr>
</tbody>
</table>

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

In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline in random triglycerides for ziprasidone 20-40 mg BID was +0.3 mg/dL (N=12); for ziprasidone 60-80 mg BID was -9.7 mg/dL (N=10); and for placebo was -12.8 mg/dL (N=9).

In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline in random total cholesterol for ziprasidone 20-40 mg BID was +2.5 mg/dL (N=14); for ziprasidone 60-80 mg BID was -19.7 mg/dL (N=10); and for placebo was -28.0 mg/dL (N=9).
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>Drug</th>
<th>Low Dose (20-40 mg)</th>
<th>High Dose*: (60-80 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Weight (kg) Changes from Baseline (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+0.4 (N=295)</td>
<td>+0.4 (N=388)</td>
</tr>
<tr>
<td></td>
<td>+0.1 (N=451)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.4% (N=295)</td>
<td>4.4% (N=388)</td>
</tr>
<tr>
<td></td>
<td>1.8% (N=451)</td>
<td></td>
</tr>
</tbody>
</table>

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

Schizophrenia - The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 4- and 6-week placebo-controlled schizophrenia clinical trials, revealing a statistically significantly greater incidence of weight gain for ziprasidone (10%) compared to placebo (4%). A median weight gain of 0.5 kg was observed in ziprasidone patients compared to no median change in weight in placebo patients. In this set of clinical trials, weight gain was reported as an adverse reaction in 0.4% and 0.4% of ziprasidone and placebo patients, respectively. During long-term treatment with ziprasidone, a categorization of patients at baseline based on the basis of body mass index (BMI) revealed the greatest mean weight gain and highest incidence of clinically significant weight gain (≥7% of body weight) in patients with low BMI (~23) compared to normal (23-27) or overweight patients (~27). In some patients, the mean increases were 4 kg for patients with a “low” BMI baseline, 0 mg change for patients with a “normal” BMI, and a 1.3 kg mean weight loss for patients who entered the program with a “high” BMI.

Bipolar Disorder – During a 6-month placebo-controlled bipolar maintenance study in adults with ziprasidone as an adjunct to lithium or valproate, the incidence of clinically significant weight gain (≥7% of body weight) during the double-blind period was 5.6% for both ziprasidone and placebo treatment groups who completed the 6 months of observation for relapse. Interpretation of these findings should be made in 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.

5.7 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.

5.8 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).

5.9 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.

5.10 Leukopenia, Neutropenia, and Agranulocytosis
In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents. Agranulocytosis (including fatal cases) has also been reported. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC), absolute neutrophil count <1000/mm³, increased frequency of infections or ischemic heart disease, heart failure, or conduction abnormalities, cerebrovascular disease, or conditions which would predispose patients to neutropenia (dehydration, hypovolemia, and treatment with antihypertensive medications).

5.11 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.

5.12 Dystonia
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].

5.13 Hypertroplactinemia
As with other drugs that antagonize dopamine D₂ receptors, ziprasidone elevates prolactin levels in humans. Increased prolactin levels were also observed in animal studies with this compound, and were associated with an increase in mammary gland neoplasia in mice; a similar effect was not observed in rats (see Nonclinical Toxicology (13.11)). 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 libido.

5.14 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, and motor skills, patients should be advised about 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.

5.15 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.

5.16 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.

5.17 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.

5.18 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 (5.2), (5.8)].

5.19 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 levels. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec [see Warnings and Precautions (5.2)].

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Clinical trials for oral ziprasidone included approximately 5700 patients and/or normal subjects exposed to one or more doses of ziprasidone. Of these 5700, over 4800 were patients who participated in multiple-dose effectiveness trials, and their experience corresponded to approximately 1831 patient-years. These patients include: (1) 4331 patients who participated in multiple-dose trials, predominantly in schizophrenia, representing approximately 1698 patient-years of exposure as of February 5, 2000; and (2) 472 patients who participated in bipolar mania trials representing approximately 153 patient-years of exposure. An additional 127 patients with bipolar disorder participated in maintenance treatment studies 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 are reported based on the frequency of collection of the adverse events and may not reflect the frequency of their occurrence in practice. Adverse reactions are not listed in order of decreasing frequency of occurrence. Adverse reactions are grouped together by system organ class and listed in order of decreasing frequency within each system organ class. Within each adverse reaction listed, adverse reactions are further grouped together according to suspected mechanism or anatomical site if this information is available.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with Oral Ziprasidone
The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and 2-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which ziprasidone was administered in doses ranging from 10 to 200 mg/day.

Commonly Observed Adverse Reactions in Short-Term Placebo-Controlled Trials
The following adverse reactions were the most commonly observed adverse reactions associated with ziprasidone treatment (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (ziprasidone-placebo incidence at least twice that for placebo):

- Somnolence (see Table 11)
- Respiratory Tract Infection

Schizophrenia trials (see Table 11)
Dystonia generally show a difference between ziprasidone and placebo. In 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, paralysis and twitching. None of these adverse reactions occurred individually at an incidence greater than 10% in bipolar mania trials. Dizziness which includes the adverse reaction terms dizziness and lightheadedness. Akathisia, Abnormal Vision, Asthenia, Vomiting.

**SCHIZOPHRENIA**

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

Approximately 4.1% (29/702) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 2.2% (6/273) on placebo. The most common reaction associated with dropout was rash, including 7 dropouts for rash among ziprasidone patients (1%) compared to no placebo patients [see Warnings and Precautions (5.7)].

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

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

**Table 11: Treatment-Emergent Adverse Reaction Incidence in Short-Term Oral Placebo-Controlled Trials – Schizophrenia**

<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>Nervous</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
</tr>
<tr>
<td>Constipation</td>
<td>9</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>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>

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

**Respiratory**

- Respiratory Tract Infection
- Rhinitis
- Cough Increased

Skin and Appendages

- Rash
- Fungal Dermatitis

Special Senses

- Abnormal Vision

**Cardiovascular**

- Nausea
- Constipation
- Diarrhea
- Dry Mouth

**Digestive**

- Nausea
- Constipation
- Diarrhea
- Dry Mouth

**Nervous**

- Nausea
- Constipation
- Diarrhea
- Dry Mouth

**Skin and Appendages**

- Rash
- Fungal Dermatitis

**Special Senses**

- Abnormal Vision

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

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

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

**Dystonia** - Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

**Vital Sign Changes** - Ziprasidone is associated with orthostatic hypotension [see Warnings and Precautions (5.8)]

**ECG Changes** - Ziprasidone is associated with an increase in the QTc interval [see Warnings and Precautions (5.8)]. In the schizophrenia trials, ziprasidone was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients.

**Other Adverse Reactions Observed During the Premarketing Evaluation of Oral Ziprasidone**

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

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

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

**Body as a Whole**

- Abdominal pain, flu syndrome, fever, accidental fall, face edema, chillis, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident

**Cardiovascular System**

- Hypothyroidism, hyperthyroidism, thyroiditis

**Hemic and Lymphatic System**

- Thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphopenia, polycythemia, thrombocytopenia

**Metabolic and Nutritional Disorders**

- BUN increased, creatinine increased, hyperlipemia, hypercholesterolemia, hyperkalemia, hypochromia, hypoglycemia, hypernatremia, hypoproteinemia, glucose tolerance decreased, gout, hypercholesteremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypogammaglobinemia, ketosis, respiratory alkalosis

**Musculoskeletal System**

- Myalgia

**Respiratory System**

- Mucolipidosis, nystagmus, torticollis, circumsoral paresis, opisthotonus, reflexes increased, trismus

**Skin and Appendages**

- Pneumonia, epistaxis

**Special Senses**

- Conjunctivitis, dry eyes, tinnitus, phlebitis, cataract, photophobia

- Eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis
**Urogenital System**

*Infrequent* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria

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

**BIPOLAR DISORDER**

Acute Treatment of Manic or Mixed Episodes

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

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

Adverse Reactions Occurring at an Incidence of 2% or More Among Ziprasidone-Treated Patients

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

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

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

* Extrapyramidal Symptoms includes the following adverse reaction terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse reactions occurred individually at an incidence greater than 1% in bipolar mania trials.

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

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

<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>Headache</td>
<td>3</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>9</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>0</td>
</tr>
<tr>
<td>Flu Syndrome</td>
<td>1</td>
</tr>
<tr>
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6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of GEODON. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Adverse reaction reports not listed above that have been received since market introduction include rare occurrences of the following: Cardiac Disorders: Tachycardia, torsade de pointes (in the presence of multiple confounding factors), (see Warnings and Precautions (5.2)); Digestive System Disorders: Swollen Tongue; Reproductive System and Breast Disorders: Galactorrhea, priapism; Nervous System Disorders: Facial Droop, neuroleptic malignant syndrome, serotonin syndrome (alone or in combination with serotonergic medicinal products); tardive dyskinesia; Psychiatric Disorders: Insomnia, mania/hypomania; Skin and Subcutaneous Tissue Disorders: Allergic reaction (such as allergic dermatitis, angioedema, pruritic edema, urticaria), rash; Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); Urogenital System Disorders: Emuresis, 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 alcohol dehydrogenase. There are no known clinically relevant inhibitors or inducers of aldehyde dehydrogenase. 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 if it is taken in combination with other centrally acting drugs. Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents. Ziprasidone may antagonize the effects of levodopa and dopamine agonists.

7.4 Pharmacokinetic Interactions

Carbamazepine

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

Ketoconazole

Ketoconazole, a potent inhibitor of CYP3A4, at a dose of 400 mg QD for 5 days, increased the AUC and Cmax of ziprasidone by about 35-40%. Other inhibitors of CYP3A4 would be expected to have similar effects.

Cilnidipine

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

Ampicillin

Ampicillin and pharmacokinetic effects of concomitantly administered oral contraceptives, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg).

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 doses with 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 progestogen-containing 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 substrate, to its major metabolite, dextrophan. There was no statistically significant change in the urinary dextromethorphan/dextrophan 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 doses adjusted, at last 10 mg/kg/day, to saturated valproate in a maintenance trial of bipolar patients did not affect pharmacokinetic 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 benzotropine, propranolol, or lorazepam.

7.10 Food Interaction

The absolute bioavailability of a 20 mg dose under fed conditions is approximately 68%. 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 MRHD of 200 mg/day on a mg/m² basis). There was no evidence to suggest that these developmental effects were secondary to maternal toxicity. The developmental no-effect dose was 10 mg/kg/day (equivalent to the MRHD on a mg/m² basis). In rats, embryofetal toxicity (decreased fetal weights, delayed skeletal ossification) was observed following administration of 10 to 160 mg/kg/day (0.5 to 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. A no-effect level was not established for these effects.

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

Non-Teratogenic Effects

Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; 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 years old 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 to ziprasidone in the elderly with those in younger adults.

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 no evidence of renal impairment were not different. However, baseline creatinine clearance was not available in any of these subjects, and other reported clinical experience has not identified differences in the pharmacokinetics of ziprasidone.

8.7 Hepatic Impairment

As ziprasidone is cleared substantially by the liver, the presence of hepatic impairment would be expected to increase the AUC of ziprasidone; a multiple-dose study at 20 mg twice daily for 5 days in subjects (n=13) with clinically significant (Childs-Pugh Class A and B) cirrhosis revealed an increase in AUC of 1.9-fold (p=0.03) 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; therefore, smoking should 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 non-smokers.

9 DRUG ABUSE AND DEPENDENCE

9.1 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 from such limited experience the extent to which ziprasidone will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ziprasidone misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

In premarketing trials involving more than 5400 patients and/or normal subjects, accidental or intentional overdosage was reported (see Overdosage (7.2)). All oral tablets were misused, diverted, and/or abused once marketed. In the patient taking the largest confirmed dose, 3,240 mg, the only adverse effects reported were minimal sedation, slurring of speech, and transitory hypertension (200/95). Adverse reactions reported with ziprasidone overdose included extrapyramidal symptoms, somnolence, tremor, and anxiety. [see Adverse Reactions (6.2)]

10.2 Management of Overdosage

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

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring (for evaluation of QT prolongation). Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. If sympathomimetic agents are used for vascular support, epinephrine and dopamine
should not be used, since beta stimulation combined with α1 antagonism associated with ziprasidone may worsen hypotension. Similarly, it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of ziprasidone, resulting in problematic hypotension. With several extrapyramidal symptoms, anticholinergic medication should be administered. There is no specific antidote to ziprasidone, and it is not dialyzable. The possibility of multiple drug involvement should be considered. Close medical supervision and monitoring should continue until the patient recovers.

11 DESCRIPTION

GEODON is available as capsules (ziprasidone hydrochloride) for oral administration and as an injection (zipraside mesylate) for intramuscular use only. Ziprasidone is a psychotropic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. It has a molecular weight of 412.94 (free base), with the following chemical name: 5-[2-[(1S,2R)-1-benzothiazol-3-yl]-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one. The empirical formula of \( C_{23}H_{24}N_{13}OS_{1} \) (free base of ziprasidone) represents the following structural formula:

GEODON Capsules contain a monohydrochloride, monohydrate salt of ziprasidone. Chemically, ziprasidone hydrochloride monohydrate is 5-[2-[(1S,2R)-1-benzothiazol-3-yl]-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, monohydrochloride, monohydrate. The empirical formula is \( C_{23}H_{24}N_{13}OS\cdot HCl\cdot H_2O \) and its molecular weight is 467.42. Ziprasidone hydrochloride monohydrate is a white to slightly pink powdery material.

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

GEODON for Injection contains a lyophilized form of zipraside mesylate (20 mg zipraside/mL when reconstituted according to label instructions) [see Dosage and Administration (2.3)]. Each mL of zipraside mesylate for injection (when reconstituted) contains 20 mg of zipraside and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether \( \beta \)-cyclodextrin sodium (SBECD).

GEODON for Injection is available in a single-dose vial as zipraside mesylate (20 mg zipraside/mL after reconstitution) [see Dosage and Administration (2.3)]. The effect on fertility appeared to be in the female since fertility was not impaired when males given 160 mg/kg/day (8 times the MRHD 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/m\(^2\) 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 for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown [see Warnings and Precautions (5.13)].

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 (D\(_2\)) 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 D\(_2\), D\(_3\), and D\(_4\) receptors; the serotonin 5HT\(_2A\), 5HT\(_1A\), and 5HT\(_1D\) receptors; and \( \alpha_1 \)-adrenergic receptors (K\(_i\) of 4.8, 7.2, 0.4, 1.3, 3.2, 4, and 10 nM, respectively). Ziprasidone functions as an antagonist at the D\(_2\), 5HT\(_1A\), and 5HT\(_1D\) receptors, and as an agonist at the 5HT\(_2A\) receptor. Ziprasidone inhibited synaptic reuptake of serotonin and norepinephrine. No appreciable affinity was exhibited for other receptor/binding sites tested, including the cholinergic muscarinic receptor (IC\(_50\) >1 \( \mu \)M). Antagonism at receptors other than dopamine and 5HT3, with similar receptor affinities may explain some of the other psychotomimetic and side effects of ziprasidone. Ziprasidone's antagonism of histamine H\(_1\) receptors may explain the somnolence observed with this drug. Ziprasidone's antagonism of \( \alpha_1 \)-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 primarily hepatic metabolism with a mean terminal half-life of 7.5 mL/min/kg. Ziprasidone is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

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

Distribution: Ziprasidone has a mean apparent volume of distribution of 1.5 L/kg. It is greater than 99% bound to plasma proteins, binding primarily to α1 acid glycoprotein. The in vitro plasma protein binding of ziprasidone was not altered by warfarin or propranolol, two highly protein-bound drugs, nor did ziprasidone alter the binding of these drugs in human plasma. Thus, the potential for drug interactions with ziprasidone due to displacement is minimal.

Metabolism and Elimination: Ziprasidone is extensively metabolized after oral administration with only a small amount excreted in the urine (less than 1%) or feces (less than 4%) as unchanged drug. Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benzothiazole (BITP) sulphonyl, BITP-sulphone, ziprasidone sulphoxide, and S-methylhydroxyziprasidone. Approximately 20% of the dose is excreted in the urine, with approximately 66% being eliminated in the feces. Unchanged ziprasidone represents about 44% of total drug-related material in serum. In vitro studies using human liver subcellular fractions indicate that S-methyldihydroziprasidone is generated in two steps. These studies indicate that the reduction reaction is mediated primarily by chemical reduction by glutathione as well as by enzymatic reduction by aldehyde oxidase and the subsequent methylation is mediated by thiol methyltransferase. In vitro studies using human liver microsomes and recombinant enzymes indicate that CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone. CYPIA2 may contribute to a much lesser extent. Based on
A study was conducted in stable chronic or subchronic (CGI-S ≤ 5) schizophrenia 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 for relapse. Patients were observed for “impending psychotic relapse,” defined as CGI-improvement score of ≤ 5 (much worse or very much worse) and/or scores ≥ (moderately severe) on the hostility or uncooperativeness items of the PANSS. Patients were significantly superior to placebo in time to relapse, with no significant difference between the different dose groups. There were insufficient data to examine population subsets based on age and race. 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 mono-

therapy 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 affect, need for sleep, excessive energy, excessive activity, grandiosity), the Behavior and Ideation subscale (irritability, motor hyperactivity, accelerated speech, racing thoughts, poor judgment) and impaired insight; and (2) the Clinical Global Impression-Severity of Illness Scale (CGI-S), which was used to assess the clinical significance of treatment response.

The results of the oral ziprasidone trials in adult bipolar I disorder, manic/mixed episode follow: in a 3-week placebo-controlled trial (n=210), the dose of ziprasidone was 40 mg twice daily on Day 1 and 80 mg twice daily on Day 2. Titration within the range of 40-80 mg twice daily (in 20 mg twice daily increments) was permitted for the duration of the study. Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score. The mean daily dose of ziprasidone in this study was 132 mg. In a second 3-week placebo-controlled trial (n=205), the dose of ziprasidone (administered twice daily) was increased to 40 mg twice daily (in 20 mg twice daily increments) was permitted for the duration of the 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 both bipolar I disorder and met criteria for mixed/manic episodes. Patients whose most recent episode was manic or mixed, with or without psychotic features. In the open-label phase, patients were required to be stabilized on ziprasidone plus lithium or valproic acid for at least 8 weeks in order to be randomized. In the double-blind randomized phase, patients continued treatment with lithium or valproic acid and were randomized to receive 240 mg/day of ziprasidone mesylate. In this 4-week placebo-controlled trial, patients were treated with 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. They are supplied in the following strengths and package configurations:

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</table>

of GEODON Capsules

16. HOW SUPPLIED/STORAGE AND HANDLING

GEODON Capsules are differentiated by capsule color/size and are imprinted in black ink with “Pfizer” and ZDX [dosage 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/white) capsules. They are supplied in the following strengths and package configurations:

<table>
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<th>Package Configuration</th>
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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 294 mg of sulfobutylether β-cyclodextrin sodium (SBEDC).

GEODON Capsules

17. PATIENT COUNSELING INFORMATION

See FDA Approved Patient Labeling 17.4.

Please refer to the patient package insert. To assure safe and effective use of GEODON, the information and instructions provided in the patient information should be discussed with patients.

17.1 Administration with Food

Patients should be instructed 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 (7.8) and Clinical Pharmacology (12.3)].

17.2 QTc Prolongation

Patients should be advised 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 (5.1) and Warnings and Precautions (5.2)].

Patients should be instructed 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, patients should be instructed to report symptoms such as dizziness, palpitations, or syncope to the prescriber [see Warnings and Precautions (5.2)].

17.3 Severe Cutaneous Adverse Reactions

Patients should be instructed 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 (5.4)].

17.4 FDA Approved Patient Labeling

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 294 mg of sulfobutylether β-cyclodextrin sodium (SBEDC).
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 psychotropics, 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 la and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, melofloxine, 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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