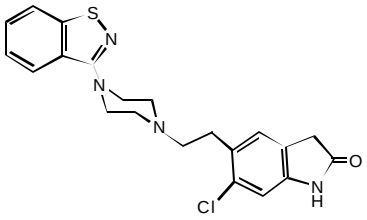
69-5770-00-2

GEODON ™
(ziprasidone HCl)

DESCRIPTION

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



GEODON Capsules contain a monohydrochloride, monohydrate salt of ziprasidone. Chemically, ziprasidone hydrochloride monohydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, monohydrochloride, monohydrate. The empirical formula is $C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$ 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/white) capsules. GEODON Capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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

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 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic 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 α_1-adrenergic receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

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

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

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

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

Special Populations

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.

Race - No specific pharmacokinetic study was conducted to investigate the effects of race. Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for race are, therefore, not recommended.

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.

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 BID 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.

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 BID for 5 days in subjects (n=13) with clinically significant (Childs-Pugh Class A and B) cirrhosis revealed an increase in AUC_{0-12} of 13% and 34% in Childs-Pugh Class A and B, respectively, compared to a matched control group (n=14). A half-life of 7.1 hours was observed in subjects with cirrhosis compared to 4.8 hours in the control group.

Drug-Drug Interactions

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. *In vivo* studies have revealed no effect of ziprasidone on the pharmacokinetics of dextromethorphan, estrogen, progesterone, or lithium (see **Drug Interactions** under **PRECAUTIONS**).

In vivo studies have revealed an approximately 35% decrease in ziprasidone AUC by concomitantly administered carbamazepine, an approximately 35-40% increase in ziprasidone AUC by concomitantly administered ketoconazole, but no effect on ziprasidone's pharmacokinetics by cimetidine or antacid (see **Drug Interactions** under **PRECAUTIONS**).

Clinical Trials

The efficacy of ziprasidone in the treatment of schizophrenia was evaluated in 5 placebo-controlled studies, 4 short-term (4- and 6-week) trials and one long-term (52-week) trial. All trials were in 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 one of the three short-term trials, this single study was inadequate to provide a reliable and valid comparison of ziprasidone and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms 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 effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second 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 trials follow:
(1) In a 4-week, placebo-controlled trial (n=139) comparing 2 fixed doses of ziprasidone (20 and 60 mg BID) with placebo, only the 60 mg BID 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.

(2) In a 6-week, placebo-controlled trial (n=302) comparing 2 fixed doses of ziprasidone (40 and 80 mg BID) with placebo, both dose groups were 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 BID had a numerically greater effect than 40 mg BID, the difference was not statistically significant.

(3) In a 6-week, placebo-controlled trial (n=419) comparing 3 fixed doses of ziprasidone (20, 60, and 100 mg BID) 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 BID 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 BID to 100 mg BID dose range.

(4) In a 4-week, placebo-controlled trial (n=200) comparing 3 fixed doses of ziprasidone (5, 20 and 40 mg BID), none of the dose groups was statistically superior to placebo on any outcome of interest.

(5) A study was conducted in chronic, symptomatically stable schizophrenic inpatients (n=294) randomized to 3 fixed doses of ziprasidone (20, 40, or 80 mg BID) or placebo and followed for 52 weeks. Patients were observed for "impending psychotic relapse", defined as CGI-improvement score of $\geq$6 (much worse or very much worse) and/or scores $\geq$6 (moderately severe) on the hostility or uncooperativeness items of the PANSS on two consecutive days. Ziprasidone was significantly superior to placebo in both time to relapse and rate of 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.

INDICATIONS AND USAGE

Ziprasidone is indicated for the treatment of schizophrenia. When deciding among the alternative treatments

available for this condition, 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**). 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**).

The efficacy of ziprasidone was established in short-term (4- and 6-week) controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY**).

In a placebo-controlled trial involving the follow-up for up to 52 weeks of stable schizophrenic inpatients, GEODON was demonstrated to delay the time to and rate of relapse. The physician who elects to use GEODON for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

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), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**).

Pharmacokinetic/pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus. Ziprasidone is also contraindicated with 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**).

Hypersensitivity

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

WARNINGS

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, and see Drug Interactions under PRECAUTIONS). 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).

A study directly comparing the QT/QTc prolonging effect of 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 coadministered 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 BID).

In placebo-controlled trials, 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 ziprasidone, the electrocardiograms of 2/2988 (0.06%) patients who received GEODON and 1/440 (0.23%) patients who received placebo revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone. One patient had a history of prolonged QTc and a screening measurement of 489 msec; QTc was 503 msec during ziprasidone treatment. The other patient had a QTc of 391 msec at the end of treatment with ziprasidone and upon switching to thioridazine experienced QTc measurements of 518 and 593 msec.

Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QTc prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of ziprasidone at recommended doses in premarketing studies, experience is too limited to rule out an increased risk.

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

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including

(1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

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

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

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

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

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

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

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

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

Given these considerations, ziprasidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

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

PRECAUTIONS

General
Rash - In premarketing trials with ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treament 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 events were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, ziprasidone should be discontinued.

Orthostatic Hypotension - Ziprasidone may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of the patients treated with

ziprasidone.

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

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.

Hyperprolactinemia - As with other drugs that antagonize dopamine D_2 receptors, ziprasidone elevates prolactin levels in humans. Increased prolactin levels were also observed in animal studies with this compound, and were associated with an increase in mammary gland neoplasia in mice; a similar effect was not observed in rats (see **Carcinogenesis**). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment - Somnolence was a commonly reported adverse event 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.

Priapism - One case of priapism was reported in the premarketing database. While the relationship of the event 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.

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.

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.

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

Use in Patients with Concomitant Illness - Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses (see **Renal Impairment** and **Hepatic Impairment** under **CLINICAL PHARMACOLOGY**, **Special Populations**) is limited.

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 **QTc Prolongation** under **WARNINGS** and **Orthostatic Hypotension** under **PRECAUTIONS**).

Information for Patients

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.

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 repleted 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).**

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. Based upon the pharmacodynamic and pharmacokinetic profile of ziprasidone, possible interactions could be anticipated:

Pharmacodynamic Interactions

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

Pharmacokinetic Interactions

The Effect of Other Drugs on Ziprasidone

Carbamazepine - Carbamazepine is an inducer of CYP3A4; administration of 200 mg BID 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.

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

Antacid - The coadministration of 30 mL of MAALOX with ziprasidone did not affect the pharmacokinetics of ziprasidone.

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

Effect of Ziprasidone on Other Drugs

In vitro studies revealed little potential for ziprasidone to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with ziprasidone due to displacement (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**).

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

Oral Contraceptives - Ziprasidone at a dose of 20 mg BID did not affect the pharmacokinetics of concomitantly administered oral contraceptives, ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg).

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis - Lifetime carcinogenicity studies were conducted with ziprasidone in Long Evans rats and CD-1 mice. Ziprasidone was administered for 24 months in the diet at doses of 2, 6, or 12 mg/kg/day to rats, and 50, 100, or 200 mg/kg/day to mice (0.1 to 0.6 and 1 to 5 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m^2 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/m^2 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/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 **Hyperprolactinemia** under **PRECAUTIONS**, **General**).

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

Impairment of Fertility - Ziprasidone was shown to increase time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The effect on fertility appeared to be in the female since fertility was not impaired when males given 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis) were mated with untreated females. In a 6-month study in male rats given 200 mg/kg/day (10 times the MRHD on a mg/m^2 basis) there were no treatment-related findings observed in the testes.

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/m^2 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/m^2 basis). In rats, embryofetal toxicity (decreased fetal weights, delayed skeletal ossification) was observed following administration of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD on a mg/m^2 basis) during organogenesis or throughout gestation, but there was no evidence of teratogenicity. Doses of 40 and 160 mg/kg/day (2 and 8 times the MRHD on a mg/m^2 basis) were associated with maternal toxicity. The developmental no-effect dose was 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 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/m^2 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/m^2 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.

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

Nursing Mothers - It is not known whether, and if so in what amount, ziprasidone or its metabolites are excreted in human milk. It is recommended that women receiving ziprasidone should not breast feed.

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

Geriatric Use - Of the approximately 4500 patients treated with ziprasidone in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability of ziprasidone or for reduced clearance of ziprasidone in the elderly compared to younger adults. 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.

ADVERSE REACTIONS

The premarketing development program for ziprasidone included over 5400 patients and/or normal subjects exposed to one or more doses of ziprasidone. Of these 5400 subjects, over 4500 were patients who participated in multiple-dose effectiveness trials, and their experience corresponded to approximately 1733 patient years. 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.

Adverse events 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. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the table and tabulations that follow, standard COSTART dictionary terminology has been used to classify reported adverse events.

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

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials

The following findings are based on a pool of two 6-week, and two 4-week placebo-controlled trials in which ziprasidone was administered in doses ranging from 10 to 200 mg/day.

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

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

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

Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) in predominantly schizophrenic patients, including only those events that occurred in 1% 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.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

In these studies, the most commonly observed adverse events associated with the use of ziprasidone (incidence of 5% or greater) and observed at a rate on ziprasidone at least twice that of placebo were somnolence (14%), extrapyramidal syndrome (5%), and respiratory disorder (8%).

Table 1. Treatment-Emergent Adverse Event Incidence In Short-Term Placebo-Controlled Trials

	Percentage of Patients Reporting Event	
Body System/Adverse Event	Ziprasidone (N=702)	Placebo (N=273)
Body as a Whole		
Asthenia	5	3
Accidental Injury	4	2
Cardiovascular		
Tachycardia	2	1
Postural Hypotension	1	0
Digestive		
Nausea	10	7
Constipation	9	8
Dyspepsia	8	7
Diarrhea	5	4
Dry Mouth	4	2
Anorexia	2	1
Musculoskeletal		
Myalgia	1	0
Nervous		
Somnolence	14	7
Akathisia	8	7
Dizziness	8	6
Extrapyramidal Syndrome	5	1
Dystonia	4	2
Hypertonia	3	2
Respiratory		
Respiratory Disorder*	8	3
Rhinitis	4	2
Cough Increased	3	1
Skin and Appendages		
Rash	4	3
Fungal Dermatitis	2	1
Special Senses		
Abnormal Vision	3	2

*Cold symptoms and upper respiratory infection account for >90% of investigator terms pointing to "respiratory disorder".

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

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials
An analysis for dose response in this 4-study pool revealed an apparent relation of adverse event to dose for the following events: 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 for ziprasidone-treated patients in the short-term, placebo-controlled trials was 5% vs. 1% 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.

Vital Sign Changes - Ziprasidone is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain - 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 clinical trials, revealing a statistically significantly greater incidence of weight gain for ziprasidone (10%) compared to placebo (4%). A median weight gain of 0.5 kg was observed in ziprasidone patients compared to no median weight change in placebo patients. In this set of clinical trials, weight gain was reported as an adverse event in 0.4% and 0.4% of ziprasidone and placebo patients, respectively. During long-term therapy with ziprasidone, a categorization of patients at baseline on the basis of body mass index (BMI) revealed the greatest mean weight gain and highest incidence of clinically significant weight gain (>7% of body weight) in patients with low BMI (<23) compared to normal (23-27) or overweight patients (>27). There was a mean weight gain of 1.4 kg for those patients with a "low" baseline BMI, no mean change for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients who entered the program with a "high" BMI.

ECG Changes - Ziprasidone is associated with an increase in the QTc interval (see **WARNINGS**). 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 Events Observed During the Premarketing Evaluation of Ziprasidone
Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with ziprasidone at multiple doses >4 mg/day within the database of 3834 patients. All reported events are included except those already listed in Table 1 or elsewhere in labeling, those event terms that were so general as to be uninformative, events reported only once and that did not have a substantial probability of being acutely life-threatening, events that are part of the illness being treated or are otherwise common as background events, and events considered unlikely to be drug-related. It is important to emphasize that, although the events reported occurred during treatment with ziprasidone, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not

already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

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:* hypertension; *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:* vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena.

Endocrine: *Rare:* hypothyroidism, hyperthyroidism, thyroiditis.

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

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

Musculoskeletal System: *Infrequent:* tenosynovitis; *Rare:* myopathy.

Nervous System: *Frequent:* agitation, tremor, dyskinesia, hostility, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus.

Respiratory System: *Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus.

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

Special Senses: *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis.

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class - Ziprasidone is not a controlled substance.

Physical and Psychological 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).

OVERDOSAGE

Human Experience - In premarketing trials involving more than 5400 patients and/or normal subjects, accidental or intentional overdosage of ziprasidone was documented in 10 patients. All of these patients survived without sequelae. In the patient taking the largest confirmed amount,
3240 mg, the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (200/95).

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

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects that might be additive to those of ziprasidone.

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

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

DOSAGE AND ADMINISTRATION

When deciding among the alternative treatments available for schizophrenia, 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**).

Initial Treatment

GEODON Capsules should be administered at an initial daily dose of 20 mg BID with food. In some patients, daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg BID. 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, ordinarily patients should be observed for improvement for several weeks before upward dosage adjustment.

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

Dosing in Special Populations

Dosage adjustments are generally not required on the basis of age, gender, race, or renal or hepatic impairment.

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, systematic evaluation of ziprasidone has shown that its efficacy in schizophrenia is maintained for periods of up to 52 weeks at a dose of 20 to 80 mg BID (see **CLINICAL PHARMACOLOGY**). No additional benefit was demonstrated for doses above 20 mg BID. Patients should be periodically reassessed to determine the need for maintenance treatment.

HOW SUPPLIED

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Bottles of 60	60	NDC-0049-3980-60	398
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Unit dose/80	20	NDC-0049-3960-41	396
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Unit dose/80	60	NDC-0049-3980-41	398
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