Ziprasidone (Geodon) is an antipsychotic in the family of second-generation antipsychotics (SGAs), or atypical antipsychotics. The SGAs came after earlier antipsychotics known as first-generation antipsychotics (FGAs) or conventional or typical antipsychotics, such as chlorpromazine (Thorazine) and haloperidol (Haldol), and they have largely replaced the typical antipsychotics in clinical medicine. The SGAs are considered atypical because they have a wider spectrum of activity with improved efficacy over the FGAs in treating negative symptoms (e.g., flat affect, poverty of speech, lack of motivation and interest, poor grooming and hygiene) of schizophrenia. The SGAs are also less likely to induce side effects associated with movement disorders, such as extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), than the FGAs.

SGAs are not limited to their antipsychotic action; they may also be used in the treatment of bipolar disorder, depression, and anxiety disorders and possibly other neuropsychiatric disorders as well. The efficacy of the SGAs may be mediated primarily by the combination of dopamine and serotonin antagonism, two important neurotransmitters in the brain. Dysfunctions in areas of the brain that involve dopamine and serotonin neurotransmission have been implicated in neuropsychiatric disorders such as schizophrenia and depressive disorders. It is this wider range of action of the SGAs that also accounts for their characterization as atypical.

Ziprasidone was approved by the U.S. Food and Drug Administration (FDA) for the treatment of schizophrenia and acute mania or mixed episodes in bipolar disorder; for maintenance treatment of bipolar disorder in combination with lithium or valproate (e.g., Depakote). The use of a medication for its FDA-approved indications is called its labeled use. In clinical practice, however, practitioners may prescribe medications for unapproved indications (off-label uses) when published clinical studies indicate the efficacy, and the standards of medical practice support the safety, of those treatments. Practitioners may use ziprasidone off-label to treat other neuropsychiatric disorders, including schizoaffective disorder, psychotic depression, and psychosis/agitation associated with Alzheimer’s disease and other dementias.
**Dosing Information**

The recommended starting dosage for treatment of schizophrenia is 20–40 mg twice a day of ziprasidone. Dosages in the range of 60–80 mg twice a day (120–160 mg/day) were generally found to be effective, but dosages higher than 160 mg/day may be needed for patients with treatment-resistant illness. For treatment of bipolar disorder, the recommended starting dosage is 40 mg twice daily, increased to 40–80 mg twice daily. Ziprasidone should be taken with food to enhance absorption of the medication from the stomach into the bloodstream.

Ziprasidone is available in an injectable form, ziprasidone mesylate. For acute agitation, it is administered intramuscularly in doses of 10 mg every 2 hours or 20 mg every 4 hours, as needed, up to maximum dosage of 40 mg/day.

**Common Side Effects**

Common side effects with ziprasidone are drowsiness, dizziness, indigestion, and constipation. Ziprasidone is not associated with any significant weight gain and is notable among the SGAs for its low propensity to affect weight.

There is a very low incidence of EPS from ziprasidone. These are neurological disturbances caused by antipsychotics (or a neurological disorder) in the area of the brain that controls motor coordination. When disruption occurs in a particular area of the brain, it can produce symptoms that mimic Parkinson’s disease (*parkinsonism*), including muscle stiffness, rigidity, tremor, drooling, and a “masklike” facial expression. However, unlike Parkinson’s disease, which is a progressive neurological disease, *parkinsonism* from treatment with an antipsychotic is reversible. Some patients experience *akathisia*, which is a subjective sense of restlessness accompanied by fidgeting and inability to sit or stand still. EPS may be managed by decreasing the antipsychotic dosage or adding an anticholinergic medication (e.g., Cogentin) to counteract the side effect. A beta-blocker, such as propranolol, is usually more effective for akathisia than anticholinergic agents.

Ziprasidone may cause sedation and drowsiness and impair physical coordination and mental alertness. Patients should avoid potentially dangerous activities, such as driving a car or operating machinery, until they are sure that these side effects will not affect their ability to perform these tasks. Avoid alcohol while taking ziprasidone because alcohol can intensify these side effects.

**Adverse Reactions and Precautions**

Patients taking ziprasidone may experience dizziness upon standing from a recumbent position, which may lead to *syncope*, the loss of consciousness resulting from insufficient blood flow to the brain. This is due to the opposing effect of ziprasidone on blood vessels that normally compensate for postural change, resulting in a momentary drop in blood pressure. Dizziness ensues when insufficient blood is supplied to the brain. This reaction is known as *orthostatic hypotension* and is occasionally seen with ziprasidone. Patients generally develop tolerance to orthostatic hypotension, but they should be cautious when rising too quickly, especially when starting therapy or when increasing dosages. Elderly patients and patients taking medications for high blood pressure may be more prone to orthostatic hypotension and are susceptible to syncope (fainting) and falling. Using compression or support stockings may help with blood circulation (i.e., venous return) and offset hypotension. As a precaution, patients should be aware of positional shifts and not rise to their feet suddenly. When lying down, they should get up gradually to a sitting position before standing. If feeling light-headed or dizzy, they should sit and wait for a minute or two before standing up to allow the blood pressure to adjust.

*Tardive dyskinesia* is a potential adverse reaction to antipsychotic medications. It is characterized by late-onset abnormal involuntary movements. This is a potentially irreversible condition that commonly manifests idiosyncratic symptoms such as “pill-rolling” movements of the fingers, darting and writhing.
movements of the tongue, lip puckering, facial grimacing, and other irregular movements. The risk of TD is very small with ziprasidone and other SGAs, even with long-term use. The FGAs, on the other hand, are associated with a higher risk of TD, especially in older patients and with duration of exposure to the medication.

Neuroleptic malignant syndrome (NMS) is a rare, toxic reaction to antipsychotics. The symptoms are severe muscle stiffness, rigidity, elevated body temperature, increased heart rate and blood pressure, irregular pulse, and profuse sweating. NMS may lead to delirium and coma. It can be fatal if medical intervention is not immediately provided. There are no tests to predict whether an individual is susceptible to developing NMS when exposed to an antipsychotic. Thus NMS must be recognized early because it is a medical emergency that requires immediate discontinuation of the antipsychotic, hospitalization, and intensive medical treatment.

Antipsychotics, including ziprasidone, can interfere with the patient’s ability to reduce core body temperature when it becomes elevated under conditions of strenuous exercise or exposure to extreme heat. This can result in heatstroke, and fatal heatstrokes have been reported in patients taking antipsychotics. Taking concomitant anticholinergic medications (e.g., Cogentin) or being dehydrated under those conditions may increase the risk of heatstroke. Patients taking antipsychotic medications should avoid prolonged exposure to extreme heat, and drink adequate amounts of fluids to stay hydrated on hot days or with strenuous exercise.

Ziprasidone may slow electrical conduction in heart tissues (myocardium). This irregular conduction causes a prolongation of the QT interval on electrocardiogram, known as QT prolongation. Some drugs that prolong the QT interval have been associated with arrhythmias and sudden death. This was the concern with ziprasidone when it was first released. The risk may be greater in patients with history of cardiovascular disease and arrhythmia. Since its release (2001), ziprasidone has not revealed an excess risk of death from QT prolongation compared with other antipsychotics. Nevertheless, ziprasidone is not recommended in patients with history of cardiovascular diseases (e.g., heart failure, cardiac arrhythmia) or coadministration with drugs that prolong the QT interval.

Ziprasidone and other SGAs are associated with abnormalities in glucose regulation. Ziprasidone may elevate blood glucose levels (hyperglycemia) and in some cases cause diabetes mellitus. While glucose abnormalities and diabetes are sometimes related to weight gain, these conditions may occur in patients without significant weight gain. Patients who gain excessive weight are more susceptible to ziprasidone’s negative impact on blood sugar and lipids (fats). The FDA requires warning of hyperglycemia and diabetes mellitus and elevated lipids associated with the SGAs, including ziprasidone. Patients taking ziprasidone, especially those with a family history or an established diagnosis of diabetes, should be aware of this adverse reaction and should routinely monitor glucose levels and lipids.

Elderly patients treated with antipsychotics for dementia-related psychosis were found to have an increased risk of death associated with antipsychotic medications. Although this correlation is not clear, most of the deaths in this group were associated with cardiovascular (e.g., heart failure) or infectious (e.g., pneumonia) causes. The FDA has stated that antipsychotic medications are not safe for treating elderly patients with dementia-related psychosis and requires that all manufacturers of antipsychotics issue warnings to this effect.

**Risk During Pregnancy and Breast-Feeding**

Experience with women taking ziprasidone during pregnancy is limited. Ziprasidone has not been studied in human pregnancy to determine its safety, and its effect on the fetus is unknown. It is not known if ziprasidone crosses the human placenta. In animal reproductive studies, it was shown that ziprasidone had toxic effects on the developing fetus, and it may be associated with birth defects in animals at dosages similar to human therapeutic dosages. Animal studies, however, are not always predictive of effects in humans. Ziprasidone should not be used during pregnancy unless the potential benefits outweigh the potential risk to the fetus. Women of childbearing age should be cautioned of the potential hazards to the fetus if they become pregnant while taking this drug.
Nursing mothers should not take ziprasidone because small amounts may pass into breast milk and be ingested by the baby. If stopping the drug is not an alternative, breast-feeding should not be started or should be discontinued.

For more information on pregnancy exposure to atypical antipsychotics, contact the National Pregnancy Registry for Atypical Antipsychotics at 1–866–961–2388 or visit https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/atypicalantipsychotic/.

**Potential Drug Interactions**

Ziprasidone is metabolized extensively in the liver. Drugs that interfere with this metabolism may increase the levels of ziprasidone and therefore the risk of adverse reactions. Drugs that may inhibit ziprasidone’s metabolism include fluoxetine, paroxetine, bupropion, duloxetine, cimetidine, amiodarone, and quinidine. However, enzyme inhibition affecting ziprasidone metabolism is generally minor. More importantly, drugs that are known to affect cardiac conduction and increase QT prolongation pose greater risk by their additive effect and therefore are not recommended with ziprasidone. Co-administration of ziprasidone with drugs observed to prolong the QT interval, for example, include antiarrhythmic agents (e.g., amiodarone, disopyramide, procainamide, quinidine, sotalol), antipsychotics (e.g., pimozide, thioridazine), and certain antibiotics (e.g., levofloxacin, moxifloxacin).

**Overdose**

In cases of ziprasidone overdose, including one pediatric patient, there were no fatalities reported. The symptoms of ziprasidone overdose include sedation, diarrhea, low blood pressure, rapid heart rate, QT prolongation, and acute mental disturbance. The course of an overdose, of course, depends on the amount ingested and whether multiple drugs were ingested.

Any suspected overdose should be treated as an emergency. The person should be taken to the emergency department for observation and treatment. The prescription bottle of medication (and any other medication suspected in the overdose) should be brought along as well because the information on the prescription label can be helpful to the treating practitioner in determining the number of pills ingested.

The American Association of Poison Control Centers (www.aapcc.org) can also be contacted via their helpline at 1-800-222-1222, and they can provide the location of the local poison center.

**Treatment Summary**

- Do not discontinue ziprasidone without consulting your practitioner.
- If you miss a dose, take it as soon as possible. If it is close to the next scheduled dose, skip the missed dose and continue on your regular dosing schedule. Do not take double doses.
- Take ziprasidone with meals; this significantly improves absorption of the medication.
- Avoid prolonged exposure to extreme heat, and drink adequate amounts of fluids to stay hydrated on hot days or with strenuous exercise.
- Ziprasidone may cause sedation and drowsiness, especially during initiation of therapy, and impair your alertness. Use caution when driving or performing tasks that require alertness.
- Be aware that ziprasidone can induce dizziness and light-headedness upon standing from a recumbent position, which may lead to orthostatic hypotension. This reaction is more prone to occur when starting the medication and in elderly patients. Rise slowly and allow your body to adjust to the change in position.
- If you experience rapid heart rate or irregular heartbeat, profuse sweating, stiffness or rigidity, spasms of the neck muscles, breathing difficulty, protrusion of the tongue, or tightness of the throat, seek immediate medical attention.
• Talk to your practitioner if you gain weight after starting ziprasidone. If you experience any signs of hyperglycemia or diabetes, such as excessive thirst or frequent urination, alert your practitioner as soon as possible.
• Store the medication in its originally labeled, light-resistant container, away from heat and moisture. Heat and moisture may precipitate breakdown of your medication, and the medication may lose its therapeutic effects.
• Keep your medication out of the reach of children.

*If you have any questions about your medication, consult your medical practitioner or pharmacist.*