

1. PRODUCT NAME

Zusdone 20 mg capsules

Zusdone 40 mg capsules

Zusdone 60 mg capsules

Zusdone 80 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Zusdone 20 mg capsule contains ziprasidone hydrochloride 21.72 mg, equivalent to ziprasidone 20 mg.

Each Zusdone 40 mg capsule contains ziprasidone hydrochloride 43.44 mg, equivalent to ziprasidone 40 mg.

Each Zusdone 60 mg capsule contains ziprasidone hydrochloride 65.16 mg, equivalent to ziprasidone 60 mg.

Each Zusdone 80 mg capsule contains ziprasidone hydrochloride 86.88 mg, equivalent to ziprasidone 80 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Zusdone 20 mg capsules – size 4 capsules with a white body and a blue cap

Zusdone 40 mg capsules – size 4 capsules with a blue body and cap

Zusdone 60 mg capsules – size 3 capsules with a white body and cap

Zusdone 80 mg capsules – size 2 capsules with a white body and a blue cap

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Ziprasidone is indicated for the treatment of acute schizophrenia, and maintenance or continuation therapy.

Ziprasidone is also indicated as a monotherapy for the short-term treatment of acute manic or mixed episodes associated with bipolar 1 disorder.

4.2. Dose and method of administration

Dose

Adults

Schizophrenia

The recommended dose in treatment of schizophrenia is 40 mg twice daily to be taken with food (see Section 5.2). Daily dosage may subsequently be adjusted on the basis of individual clinical status up to a maximum of 80 mg twice daily. If indicated, the maximum recommended dose may be reached as early as day 3 of treatment.

Bipolar Mania

The recommended dose in treatment of bipolar mania is 40 mg twice daily to be taken with food (see Section 5.2). Daily dosage may subsequently be adjusted on the basis of individual clinical status up to a maximum of 80 mg twice daily. If indicated, the maximum recommended dose may be reached as early as day 2 of treatment.

Special populations

Paediatric population

Safety and effectiveness in children under 18 years have not been established.

Elderly population

No dosage adjustment is required in elderly patients (65 years and over).

Renal impairment

No dosage adjustment is required in patients with renal impairment (see section 5.2).

Hepatic impairment

In patients with mild to moderate hepatic insufficiency, lower doses should be considered. There is a lack of experience in patients with severe hepatic insufficiency and ziprasidone should be used with caution in this group (see Section 5.2).

Use in Smokers

No dosage adjustment is required in patients who smoke.

Method of Administration

Oral administration

4.3. Contraindications

Known hypersensitivity to any ingredient of the product.

Recent acute myocardial infarction.

Uncompensated heart failure.

Conditions with a potential to increase QT interval:

- QT-interval prolongation or history of QT prolongation
- Congenital long QT syndrome
- Use with other drugs known to increase the QT interval
- Arrhythmias treated with Class IA and III antiarrhythmic drugs (see Section 4.4).

4.4. Special warnings and precautions for use

QT Interval

Ziprasidone causes a mild to moderate prolongation of the QT interval.

In the pre-marketing clinical trials database for the oral formulation, the incidence of QTc prolongation above 500 msec was 3 in a total of 3266 (0.1%) in ziprasidone-treated patients and 1 in a total of 538 (0.2%) in placebo-treated patients.

In placebo-controlled schizophrenia trials, oral ziprasidone increased the QTc interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg.

A study directly comparing the QT/QTc prolonging effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. In the first phase of the trial, ECGs were obtained at the time of maximum plasma concentration when the drug was administered alone. In the second phase of the trial, ECGs were obtained at the time of maximum plasma concentration while the drug was co-administered with the appropriate inhibitor(s) of the CYP450 metabolism specific for each 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 oral 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 oral ziprasidone on QTc length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg twice daily).

Comparable findings were observed in the bipolar mania clinical trials. In the placebo controlled bipolar mania studies, oral ziprasidone increased the QTc interval (QTcF) compared with placebo by 8 msec. No subject in these studies experienced a QTcF >480 msec. The mean daily dose in these studies was 120 mg.

Some drugs, including Class IA and III antiarrhythmics that prolong the QT/QTc interval greater than 500 msec, have been associated with the occurrence of torsade de pointes and with sudden unexplained death (see Section 4.3).

There have been rare post-marketing reports of torsade de pointes in patients with multiple confounding risk factors taking ziprasidone. A causal relationship with ziprasidone has not been established.

As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking oral ziprasidone at recommended doses. Experience with ziprasidone has not revealed an excess risk of mortality for ziprasidone compared to other antipsychotic drugs or placebo.

Ziprasidone should be used with caution in patients with the following risk factors, which can increase the risk for occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval:

- bradycardia;
- electrolyte imbalance (especially hypokalaemia or hypomagnesaemia)
- concomitant use with other drugs that prolong QT

It is recommended that patients being considered for ziprasidone treatment who are at risk for significant electrolyte disturbances, hypokalaemia in particular, have baseline serum potassium and magnesium measurements. Hypokalaemia may result from diuretic therapy, diarrhoea, 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 (see Section 4.3). 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.

Venous Thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible

risk factors for VTE should be identified before and during treatment with ziprasidone and preventive measures taken.

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 in schizophrenia clinical trials.

Ziprasidone should be used with particular caution in patients with known cardiovascular disease, cerebrovascular disease or conditions which would predispose patients to hypotension.

Neuroleptic Malignant Syndrome (NMS)

In pre-marketing clinical trials there were no reported cases of NMS in patients receiving ziprasidone. NMS, a potentially fatal complex, has been reported in association with antipsychotic drugs, including ziprasidone. 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 creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs, including ziprasidone, must be discontinued.

Severe Cutaneous Adverse Reactions

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported with ziprasidone exposure. DRESS consists of a combination of: a) three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy; and b) one or more systemic complications (such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis).

Other severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome, have also been reported with ziprasidone exposure. SCARs are sometimes fatal and ziprasidone should be discontinued if SCARs occur.

Tardive Dyskinesia

As with other antipsychotics, there is a potential for ziprasidone to cause tardive dyskinesia and other tardive extrapyramidal syndromes after long-term treatment. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of ziprasidone should be considered.

Falls

Antipsychotic drugs (which includes ziprasidone) 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, a fall risk assessment should be completed when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Seizures

As with other antipsychotics, caution is recommended when treating patients with a history of seizures.

Akathisia

The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move and either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot, or both. Particular attention should be paid to the monitoring for such symptoms and signs as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse.

Parkinson's Disease

Physicians should weigh the risks versus the benefits when prescribing ziprasidone to patients with Parkinson's disease or dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high-risk patients should accompany 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.

CNS Drugs/Alcohol

Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting agents, including alcohol and drugs acting on the dopaminergic and serotonergic systems.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis have been shown to be at an increased risk of death and/or potentially, cerebrovascular adverse events compared with placebo when treated with some antipsychotic drugs. Study data with ziprasidone in the treatment of elderly patients with dementia are insufficient to conclude whether or not there is an increased risk of death with ziprasidone versus placebo in this patient population. Ziprasidone is not approved for the treatment of elderly patients with dementia-related psychosis.

Cerebrovascular Adverse Events, including Stroke, in Elderly Patients with Dementia

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Ziprasidone should be used with caution in patients with risk factors for stroke.

Hyperglycaemia and Diabetes Mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycaemia or diabetes in patients treated with ziprasidone. Although fewer patients have been treated with ziprasidone, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia related adverse events is not completely understood. However, epidemiological studies, which did not include ziprasidone, suggest an increased risk of treatment emergent hyperglycaemia related adverse events in patients treated with atypical antipsychotics included in these studies. Because ziprasidone was not marketed at the time these studies were performed, it is not known if ziprasidone is associated with this increased risk. Precise risk estimates for hyperglycaemia related adverse events in patients treated with atypical antipsychotics 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 mellitus (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 patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued, however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect medicine.

Rash

In premarketing schizophrenia trials with oral 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 events were reported to

recover completely. Upon appearance of rash for which an alternative aetiology cannot be identified, ziprasidone should be discontinued.

Hyperprolactinaemia

As with other drugs that antagonise 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 section 5.3). 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.

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

Priapism

Cases of priapism have been reported with antipsychotic use, including ziprasidone. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

4.5. Interaction with other medicines and other forms of interaction

Class IA and III Antiarrhythmic Drugs (see Section 4.3 and 4.4).

Concomitant Use with Other Drugs that Prolong QT Interval. As with other antipsychotic agents, there is an increased potential of QTc prolongation in the presence of Type IA and IIIA antiarrhythmics. Coadministration with the potent CYP3A4 inhibitor, ketoconazole, did not affect QTc, when compared to oral ziprasidone alone (see Section 4.4).

CNS Drugs/Alcohol (see Section 4.4).

Effect of Ziprasidone on Other Drugs

Using human liver microsomes, ziprasidone demonstrated no inhibitory effect on CYP1A2, CYP2C9 or CYP2C19. The concentration of ziprasidone required to inhibit CYP2D6 and CYP3A4 *in vitro* was at least 1000-fold higher than the free concentration that can be expected *in vivo*. Ziprasidone is unlikely to cause clinically important drug interactions mediated by these enzymes.

Dextromethorphan

Consistent with *in vitro* results, a study in normal healthy volunteers showed that ziprasidone did not alter the CYP2D6 mediated metabolism of dextromethorphan to its major metabolite, dextrorphan.

Oral Contraceptives

Ziprasidone administration resulted in no significant change to the pharmacokinetics of oestrogen (ethinyl oestradiol, a CYP3A4 substrate) or progesterone components.

Lithium

Co-administration of ziprasidone has no effect on the pharmacokinetics of lithium. As ziprasidone and lithium are associated with cardiac conduction changes, the combination may pose a potential for pharmacodynamic interaction, including arrhythmias. While there have been no reports of clinically significant QTc increases in clinical trials of adjunctive therapy involving ziprasidone and lithium, caution should be exercised in prescribing the two drugs together.

Protein Binding

Ziprasidone extensively binds to plasma proteins. 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 unlikely.

Effects of Other Drugs on Ziprasidone

Ziprasidone is metabolised by aldehyde oxidase and to a lesser extent by CYP3A4. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase.

CYP3A4 Inhibitors

In vitro data indicate that ziprasidone is a P-glycoprotein (P-gp) substrate. The *in vivo* relevance is unknown.

Ketoconazole 400 mg/day, a potent inhibitor of CYP3A4, produced an increase of approximately 35% in ziprasidone exposure (AUC and C_{max}). These changes produced by ketoconazole are unlikely to be clinically relevant.

Cimetidine, a non-specific CYP inhibitor, did not significantly affect ziprasidone pharmacokinetics.

CYP3A4 Inducers

Co-administration with inducers of CYP-3A4 and P-gp such as carbamazepine, rifampin and St John's wort (*Hypericum perforatum*) could cause decreased concentrations of ziprasidone.

Carbamazepine, 200 mg twice daily, an inducer of CYP3A4, produced a decrease of 36% in ziprasidone exposure. These changes produced by carbamazepine are unlikely to be clinically relevant.

CNS Medicines

Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs. As it exhibits *in vitro* dopamine antagonism, ziprasidone may antagonise the effects of direct and indirect dopamine agonists.

Antacid

Multiple doses of aluminium and magnesium-containing antacids did not affect the pharmacokinetics of ziprasidone.

Benztropine, Propranolol and Lorazepam

Pharmacokinetic evaluation of ziprasidone serum concentrations of patients in clinical trials has not revealed any evidence of clinically significant interactions with benzotropine, propranolol or lorazepam.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential receiving ziprasidone should be advised to use an appropriate method of contraception.

Pregnancy

Category C.

No studies have been conducted in pregnant women. Women of child-bearing potential receiving ziprasidone should therefore be advised to use an appropriate method of contraception. As human experience is limited, administration of ziprasidone is not recommended during pregnancy.

Non-teratogenic class effect: Neonates exposed to antipsychotic drugs (including ziprasidone) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-marketing reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required additional medical treatment or monitoring.

Ziprasidone should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low as possible and as short as possible.

Breast-feeding

There are no adequate and well-controlled studies in lactating women. Limited data indicate the ziprasidone and its active metabolites are excreted into breast milk at very low levels. Patients should be advised not to breast feed if they are receiving ziprasidone.

Fertility

There are no adequate and well-controlled studies in women and men exposed to ziprasidone.

Reproductive toxicity studies with oral ziprasidone have not shown adverse effects on the reproductive process, other than those secondary to maternal toxicity resulting from an exaggerated pharmacological effect at doses equal to or greater than 17.5 times the maximum recommended human dose (MRHD). There was no evidence of teratogenicity at any dose level (see Section 5.3).

4.7. Effects on ability to drive and use machines

As with other psychoactive medicines, ziprasidone may cause somnolence. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that ziprasidone does not affect them adversely.

4.8. Undesirable effects

In short-term placebo-controlled clinical trials, the frequency of adverse events associated with the use of ziprasidone across the therapeutic dose range are identified below:

>1/100

Hypotension, QT interval prolongation, respiratory disorder (including coryzal symptoms).

The table below contains treatment-emergent adverse events which occurred at an incidence of $\geq 1\%$ in monotherapy double-blind, placebo-controlled studies in patients with bipolar mania and short term double-blind, placebo-controlled studies in patients with schizophrenia.

Body System/Adverse Event	Percentage of Patients Reporting Event	
	Ziprasidone (N=1159)	Placebo (N=497)
Psychiatric Disorders		
Restlessness	1.6	0.6
Insomnia	1.2	2.4
Nervous System Disorders		
Akathisia	8.7	4.8
Dizziness	6.2	3.2
Dyskinesia	1.2	0.6
Dystonia	4.5	1.2
Extrapyramidal Disorder	5.7	1.8
Headache	5.3	4.8

Parkinsonism	1.2	0.4
Sedation	9.2	2.6
Somnolence	4.7	1.2
Tremor	2.5	1.6
Eye Disorders		
Vision Blurred	1.6	0.8
Gastrointestinal Disorders		
Constipation	2.7	2.0
Dry Mouth	2.5	1.4
Diarrhoea	0.9	1.0
Dyspepsia	1.7	0.6
Gastrointestinal Discomfort	0.77	2.6
Nausea	4.0	3.0
Salivary Hypersecretion	1.0	0.2
Tongue Thick	1.4	0.2
Vomiting	2.2	1.2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal stiffness	1.8	0.4
General Disorders and Administration Site Conditions		
Asthenia	1.3	0.2
Fatigue	1.6	0.4

All adverse reactions are listed by class and frequency: very common (>10%), common (1% to 10%), uncommon (0.1% to 1%) and rare (<0.1%).

Infections and Infestations

Uncommon: Rhinitis.

Blood and Lymphatic System Disorders

Rare: Lymphopenia.

Metabolism and Nutrition Disorders

Uncommon: Increased appetite.

Psychiatric Disorders

Common: Anxiety, agitation.

Uncommon: Nightmare, nervousness, libido decreased.

Rare: Anorgasmia, bradyphrenia, flat affect, panic attack, somnambulism.

Nervous System Disorders

Common: Tardive dyskinesia, hypertonia.

Uncommon: Ataxia, bradykinesia, cogwheel rigidity, disturbance in attention, dizziness postural, drooling, dysarthria, generalised tonic-clonic seizures, hypokinesia, hypersomnia, hypoaesthesia, lethargy, paraesthesia hyperkinesia, speech disorder.

Rare: Akinesia, paresis, restless legs syndrome.

Eye Disorders

Common: Visual impairment.

Uncommon: Photophobia, oculoeryic crisis.

Rare: Amblyopia, eye pruritus.

Ear and Labyrinth Disorders

Uncommon: Tinnitus, vertigo.

Rare: Ear pain, vertigo positional.

Cardiac Disorders

Uncommon: Bundle branch block right, palpitation.

Respiratory, Thoracic and Mediastinal Disorders

Uncommon: Dyspnoea, oropharyngeal pain, throat tightness.

Rare: Hiccups, laryngospasm.

Gastrointestinal Disorders

Uncommon: Dysphagia, flatulence, gastritis.

Rare: Gastro-oesophageal reflux, diarrhoea.

Skin and Subcutaneous Tissue Disorders

Common: Rash.

Uncommon: Acne, rash maculopapular, urticaria.

Rare: Alopecia, dermatitis allergic, erythema, psoriasis, skin irritation, swelling face, rash papular.

Musculoskeletal and Connective Tissue Disorders

Uncommon: Joint stiffness, muscle spasms, pain in extremity, torticollis.

Rare: Arthropathy, musculoskeletal discomfort, trismus.

Renal and Urinary Disorders

Uncommon: Dysuria, urinary incontinence, urinary hesitation.

Rare: Urinary retention.

Reproductive System and Breast Disorders

Common: Male sexual dysfunction.

Uncommon: Galactorrhoea, gynaecomastia, amenorrhoea.

General Disorders and Administration Site Conditions

Uncommon: Gait disturbance, thirst, malaise.

Rare: Chest pain, feeling hot, pyrexia, sluggishness.

Investigations

Uncommon: Hepatic enzyme increased, heart rate increased, electrocardiogram QT interval prolonged.

Rare: Blood lactate dehydrogenase increased, body temperature increased, eosinophil count increased, eosinophil count abnormal, hypocalcaemia, liver function test abnormal, heart rate increased.

Other Findings

Extrapyramidal Symptoms (EPS)

In double-blind active controlled clinical trials in patients with schizophrenia, the Movement Disorder Burden Scale, a composite measure of EPS, was statistically significantly ($p < 0.05$) in favour of ziprasidone versus haloperidol and risperidone. In addition the reported incidence of akathisia and use of anticholinergic drugs was greater in the haloperidol and risperidone groups relative to ziprasidone. The incidence of reported EPS for ziprasidone-treated patients in the short-term, placebo-controlled trials was 5% vs 1% for placebo.

Body Weight

The incidence of body-weight gain, recorded as an adverse event in short-term 4- and 6-week, fixed-dose, placebo-controlled schizophrenia trials, was low and identical in ziprasidone-treated and placebo-treated patients (both 0.4%). There was a small increase in median weight in ziprasidone-treated patients (0.5 kg) but not in placebo-treated patients.

In a one-year placebo-controlled schizophrenia study a median weight loss of 1-3 kg was observed in ziprasidone-treated patients compared to a 3 kg median loss in placebo-treated patients.

QT Interval

In schizophrenia clinical trials, a mean QT interval increase from screening of 3.3 msec was measured. A prolongation of >60 msec was seen in 1.6% and 1.2% of tracings from ziprasidone- and placebo- treated patients, respectively. In the premarketing clinical trials database, the number of cases of clinically significant abnormalities in QTc prolongation (≥ 500 msec) was 3 in a total of 3266 (0.1%) in ziprasidone treated patients and 1 in a total of 538 (0.2%) in placebo treated patients. Comparable findings were observed in bipolar mania clinical trials.

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.

Vital Sign Changes

Ziprasidone is associated with orthostatic hypotension (see section 4.4).

Prolactin Levels

There were only transient prolactin increases seen during chronic dosing with ziprasidone.

Physical and Psychological Dependence

Ziprasidone has not been systemically 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 behaviour, 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 behaviour).

Post-Marketing Experience

The following adverse reactions have been reported during post-marketing experience:

Immune System Disorders: Hypersensitivity.

Investigations: Weight decreased, weight increased.

Endocrine Disorders: Hyperprolactinaemia.

Psychiatric Disorders: Mania/hypomania, somnambulism, sleep-related eating disorder and sleep apnoea.

Nervous System Disorders: Syncope, facial droop, neuroleptic malignant syndrome (see Section 4.4); serotonin syndrome (alone or in combination with serotonergic medicinal products), sedation.

Cardiac Disorders: Tachycardia, torsade de pointes (see Section 4.4).

Vascular Disorders: Orthostatic hypotension, embolism venous (see Section 4.4).

Gastrointestinal Disorders: Dysphagia, tongue oedema.

Skin and Subcutaneous Tissue Disorders: Angioedema, rash, drug reaction with eosinophilia and systemic symptoms (DRESS).

Renal and Urinary Disorders: Enuresis, urinary incontinence.

Reproductive System and Breast Disorders: Galactorrhoea, priapism.

General Disorders and Administration Site Conditions: Fatigue.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. Overdose

Symptoms

Experience with ziprasidone in overdosage is limited. The largest confirmed single ingestion is 12,800 mg. In this case, extrapyramidal symptoms and a QTc interval of 446 msec (with no cardiac sequelae) were reported. In overdose cases in general, the most commonly reported symptoms are extrapyramidal symptoms, somnolence, tremor, and anxiety.

Treatment

In cases of suspected overdose, the possibility of multiple drug involvement should be considered. There is no specific antidote to ziprasidone. In cases of acute overdosage, establish and maintain an airway and ensure adequate ventilation and oxygenation. Gastric lavage, (after intubation, if patient is unconscious) and administration of activated charcoal, together with a laxative, should be considered. The possibility of obtundation, seizures 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. Given the high protein binding of ziprasidone, haemodialysis is unlikely to be beneficial in the treatment of overdose. Close medical monitoring and supervision should continue until the patient recovers.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics, Indole derivatives; ATC code: N05AE04

Mechanism of Action

Receptor Binding Studies

Ziprasidone has a high affinity for dopamine type 2 (D₂) receptors and substantially higher affinity for serotonin type 2_A (5HT_{2A}) receptors. Ziprasidone also interacts with serotonin 5HT_{2C}, 5HT_{1D} and 5HT_{1A} receptors where its affinities for these sites are equal to or greater than its affinity for the D₂ receptor. Ziprasidone has moderate affinity for neuronal serotonin and noradrenaline transporters. Ziprasidone demonstrates moderate affinity for histamine H₁- and alpha₁-receptors. Antagonism at these receptors has been associated with somnolence and

orthostatic hypotension, respectively. Ziprasidone demonstrates negligible affinity for muscarinic M₁-receptors. Antagonism at this receptor has been associated with memory impairment.

Receptor Functional Studies

Additional preclinical studies were carried out to identify agonist or antagonist effects at receptors to which ziprasidone binds with high to moderate affinity. Ziprasidone has been shown to be an antagonist at both serotonin type 2_A (5HT_{2A}) and dopamine type 2 (D₂) receptors. It is proposed that the antipsychotic activity is mediated, in part, through this combination of antagonist activities. As with other drugs having efficacy in bipolar disorder, the mechanism of action of ziprasidone in bipolar disorder is unknown.

Ziprasidone is also a potent antagonist at 5HT_{2C} and 5HT_{1D} receptors, a potent agonist at the 5HT_{1A} receptor and inhibits neuronal reuptake of noradrenaline and serotonin. The serotonergic and neuronal reuptake properties of ziprasidone are associated with antidepressant activity. In addition, 5HT_{1A} agonism has been associated with anxiolytic effects. Potent antagonism at the 5HT_{2C} receptor has been associated with antipsychotic activity.

Human PET Studies

At 12 hours following a 40 mg oral dose of ziprasidone, receptor blockade was greater than 80% for 5HT_{2A} and greater than 50% for D₂ using positron emission tomography (PET).

Clinical Efficacy and Safety

Schizophrenia

The efficacy of ziprasidone in the treatment of the positive and negative symptoms of schizophrenia was established in four- and six-week placebo- and active-controlled clinical trials of hospitalised patients experiencing an acute exacerbation of the illness.

In a 52-week placebo-controlled clinical trial of chronic stable inpatients ziprasidone was significantly effective versus placebo in the prevention of relapse of schizophrenia. Ziprasidone demonstrated continuing improvement in primary negative symptoms and in global (psychological, social and occupational) functioning in this study of inpatient population over a 52-week period.

An analysis of the effect of ziprasidone on patients with clinically significant depressive symptoms, defined as ≥ 14 on the Montgomery-Asberg Depression Rating Scale (MADRS), was conducted in two multicenter placebo-controlled studies in acute schizophrenia. A statistically significant improvement versus placebo ($p < 0.05$) in the MADRS was observed in these two studies in patients receiving 60 mg and 80 mg twice daily.

Results of a Large Post-Marketing Safety Study

A randomised post-approval study of 18,239 schizophrenic patients with observational follow-up for 1 year was conducted to determine whether ziprasidone's known effect on the QTc interval (see section 4.4) is associated with an increased risk of nonsuicide mortality. This study, which was conducted in naturalistic clinical practice settings, showed no difference in its primary endpoint of the rate of non-suicide mortality between ziprasidone and olanzapine treatments.

Bipolar Mania

The efficacy of ziprasidone in bipolar mania was established in two placebo controlled, double blind, 3 week studies which compared ziprasidone with placebo and one double blind, 12 week study which compared ziprasidone to haloperidol and placebo. These studies included approximately 850 patients meeting DSM-IV criteria for bipolar I disorder with an acute or mixed episode, with or without psychotic features. The baseline presence of psychotic features in the studies was 49.7%, 34.7% or 34.9%. Efficacy was assessed using the Mania Rating Scale (MRS). The Clinical Global Impression-Severity (CGI-S) scale was either a coprimary or key secondary efficacy variable in these studies. Ziprasidone treatment (40-80 mg twice daily, mean daily dose 120 mg) resulted in statistically significantly greater improvement in both MRS and CGI-S scores at Last Visit (3 weeks) compared with placebo. In the 12 week study, haloperidol treatment (mean daily dose 16 mg) produced significantly greater reductions in MRS scores compared with ziprasidone (mean daily dose 121 mg). Ziprasidone demonstrated comparable efficacy to haloperidol in terms of the proportion of patients maintaining a response to treatment from week 3 to week 12.

There are no long-term clinical studies investigating the efficacy of ziprasidone in the prevention of recurrence of manic/depressive symptoms.

General

In a double-blind comparative study, metabolic parameters including weight, fasting levels of total cholesterol, triglycerides, insulin and an insulin resistance (IR) index were measured. In patients receiving ziprasidone no significant changes from baseline were observed in any of these metabolic parameters.

5.2. Pharmacokinetic properties

Absorption

Following oral administration of multiple doses of ziprasidone with food, peak serum concentrations typically occur 6 to 8 hours post-dose. Ziprasidone demonstrates linear kinetics over the therapeutic dose range of 40-80 mg twice daily in fed subjects.

The absolute bioavailability of a 20 mg dose is 60% in the fed state. The absorption of ziprasidone is reduced by 50% when ziprasidone is administered under fasting conditions.

Twice daily dosing generally leads to attainment of steady state within 3 days. Systemic exposures at steady state are related to dose.

At steady-state, the mean terminal elimination half-life of ziprasidone is about 6.6 hours following oral dosing. Mean systemic clearance of ziprasidone administered intravenously is 7.5 mL/min/kg and the volume of distribution is approximately 1.5 L/kg.

Distribution

Ziprasidone is extensively bound (>99%) to plasma proteins and its binding appears to be independent of concentration.

Metabolism and Elimination

Ziprasidone is extensively metabolised after oral administration with only a small amount (<1%) excreted in the urine or faeces (<4%) as unchanged drug. Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benisothiazole piperazine (BITP) sulphoxide, BITP sulphone, ziprasidone sulphoxide and S-methyldihydroziprasidone. Approximately 20% of the dose is excreted in the urine, with approximately 66% being eliminated in the faeces. Unchanged ziprasidone represents about 44% of total drug-related concentration in serum.

In vitro studies indicate that CYP3A4 is the major cytochrome P450 catalyzing the oxidative metabolism of ziprasidone. S-methyl-dihydroziprasidone is generated in two steps catalyzed by aldehyde oxidase and thiol methyltransferase.

Ziprasidone, S-methyl-dihydroziprasidone, and ziprasidone sulphoxide, when tested *in vitro*, share properties which may predict a QTc-prolonging effect. S-methyl-dihydroziprasidone is mainly eliminated by faecal excretion and CYP3A4 catalysed metabolism. The sulphoxide is eliminated through renal extraction and by secondary metabolism catalysed by CYP3A4.

In a phase I trial, the CYP3A4 inhibitor ketoconazole (400 mg/day) increased the serum concentrations of ziprasidone by <40%. The serum concentration of S-methyldihydroziprasidone, at the expected T_{max} of ziprasidone, was increased by 55% during ketoconazole treatment. No additional QTc prolongation was observed.

Special Populations

Age and Gender

No clinically significant differences in the pharmacokinetics of ziprasidone in young and elderly male or female subjects were observed following oral administration.

Use in Smokers

Pharmacokinetic evaluation of ziprasidone serum concentrations of patients treated orally has not revealed any significant pharmacokinetic differences between smokers and non-smokers.

Use in Renal Disease

No marked differences in the pharmacokinetics of oral ziprasidone have been observed in patients with moderate to severe impairments in renal function as compared to subjects with normal renal function. It is unknown whether serum concentrations of the metabolites are increased in these patients.

Use in Hepatic Disease

In mild to moderate impairment of liver function (Child-Pugh A or B), the serum concentrations of ziprasidone after oral administration were 30% higher and the terminal half-life was about two hours longer than in normal subjects.

5.3. Preclinical safety data

Preclinical trial data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential. In reproductive studies in rats and rabbits, ziprasidone has shown no evidence of teratogenicity. Adverse effects on fertility and increased number of pups born dead, decreased pup weights and delayed functional development were observed at doses that caused maternal toxicity (e.g. sedation and decreased body weight gain). Increased perinatal mortality and delayed functional development of offspring occurred at maternal plasma concentrations extrapolated to be similar to the maximal concentrations in humans given therapeutic doses.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Capsule content

Magnesium stearate, Silica colloidal anhydrous, Croscarmellose sodium, Pregelatinized maize starch

20 mg capsules

Body: Titanium dioxide (E171), Gelatin

Cap: Indigo carmine (E132), Titanium dioxide (E171), Gelatin

40 mg capsules

Body and cap: Indigo carmine (E132), Titanium dioxide (E171), Gelatin

60 mg capsules

Body and cap: Titanium dioxide (E171), Gelatin

80 mg capsules

Body: Titanium dioxide (E171), Gelatin

Cap: Indigo carmine (E132), Titanium dioxide (E171), Gelatin

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 30°C. Protect from light and moisture.

6.5. Nature and contents of container

Blister packs, Al/OPA/PVC – 30, 60, 90 capsules

HDPE bottle packs with PP child-resistant cap – 100 capsules

Not all strengths or pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd

P O Box 45 027

Auckland 0651

New Zealand

Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

21 August 2014

10. DATE OF REVISION OF THE TEXT

31 May 2019

Summary table of changes

Section Changed	Summary of new information
All	SPC format.
4.1	Update section to remove typographical error
4.4	Additional warning on falls and occurrence of cerebrovascular events
4.6	Update to fertility information for no adequate and well-controlled studies performed and advise for women with childbearing potential to use contraception. Update to breast-feeding information.
4.8	Update section and organised adverse effect according to SOC list. Update to Post-Marketing Experience, subsection "Psychiatric Disorders" "somnambulism, sleep-related eating disorder and sleep apnoea".