

ziprasidone

Core Safety Profile

4.3 Contraindications

- known hypersensitivity to ziprasidone or any of the excipients
- known QT-interval prolongation
- congenital long QT syndrome
- acute myocardial infarction
- uncompensated heart failure
- arrhythmias treated with class IA and III antiarrhythmic medicinal products.
- concomitant treatment with medicinal products that prolong the QT interval, such as:
 - Class IA and III antiarrhythmics
 - arsenic trioxide
 - halofantrine
 - levomethadyl acetate
 - mesoridazine
 - thioridazine
 - pimozide
 - sparfloxacin
 - gatifloxacin
 - moxifloxacin
 - dolasetron mesilate
 - mefloquine

- sertindole
- cisapride (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

ADDITIONAL TEXT FOR Capsules and Oral Suspension ONLY

General: A medical history, including assessment of family history, and physical examination should be undertaken to identify patients for whom ziprasidone treatment is not recommended (see section 4.3).

QT interval: Ziprasidone causes a mild to moderate dose-related prolongation of the QT-interval (see section 4.8 and 5.1). Ziprasidone should not be given together with medicinal products that are known to prolong the QT-interval (see sections 4.3 and 4.5). Caution is advised in patients with significant bradycardia. Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for malignant arrhythmias and should be corrected before treatment with ziprasidone is started. If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.

If cardiac symptoms, such as palpitations, vertigo, syncope or seizures occur, then the possibility of a malignant cardiac arrhythmia should be considered and a cardiac evaluation including an ECG should be performed. If the QTc interval is > 500 msec, then it is recommended that the treatment should be stopped (see section 4.3).

There have been rare post-marketing reports of torsade de pointes in patients with multiple confounding risk factors taking ziprasidone.

ADDITIONAL TEXT FOR Capsules and Oral Suspension ONLY **Children and Adolescents**

Safety and efficacy of ziprasidone in the treatment of schizophrenia in children and adolescents has not been evaluated.

ADDITIONAL TEXT FOR Intramuscular ONLY

Children and adolescents: The safety and efficacy of ziprasidone intramuscular injection has not been evaluated in children and adolescents.

ADDITIONAL TEXT FOR Intramuscular ONLY

Elderly (> 65 years): Elderly patients have not been included in clinical trials in sufficient numbers. Thus, no recommendations as regards dosing could be given and intramuscular treatment in these patients is not recommended.

Neuroleptic malignant syndrome (NMS): NMS is a rare but potentially fatal complex that has been reported in association with antipsychotic medicinal products, including ziprasidone. The management of NMS should include immediate discontinuation of all antipsychotic medicinal products.

ADDITIONAL TEXT FOR Intramuscular ONLY

Cardiovascular disease: Patients with cardiovascular disease have not been included in the clinical trials in sufficient numbers. Thus, the safe use of the intramuscular product has not been established (see section 4.3).

Blood pressure: Dizziness, tachycardia and postural hypotension are not unusual in patients following intramuscular administration of ziprasidone. Single cases of hypertension have also been reported. Caution should be exercised, particularly in ambulatory patients.

ADDITIONAL TEXT FOR Capsules and Oral Suspension ONLY

Tardive dyskinesia: There is a potential for ziprasidone to cause tardive dyskinesia and other tardive extrapyramidal syndromes after long-term treatment. Patients with bipolar disorder are known to be particularly vulnerable to this category of symptoms. This is more frequent with increased duration of treatment and increasing age. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of ziprasidone should be considered.

ADDITIONAL TEXT FOR Intramuscular ONLY

Tardive dyskinesia: 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.

Seizures: Caution is recommended when treating patients with a history of seizures.

Hepatic Impairment: There is a lack of experience in patients with severe hepatic insufficiency and ziprasidone should be used with caution in this group (see sections 4.2 and 5.2).

ADDITIONAL TEXT FOR Capsules ONLY

Medicinal products containing lactose: As the capsule contains the excipient lactose (see section 6.1), patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Increased risk of cerebrovascular accidents in the dementia population: 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. Zeldox should be used with caution in patients with risk factors for stroke.

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 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.

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 undertaken.

ADDITIONAL TEXT FOR Oral Suspension ONLY

Zeldox 10 mg/ml oral suspension contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

Zeldox 10 mg/ml oral suspension contains 4.65 mg sodium per ml dosed and this should be taken into account in patients on a controlled sodium diet. The usual dose is between 4 and 8 ml twice a day so the total daily sodium load is between 37.2 and 74.4 mg.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic and pharmacodynamic studies between ziprasidone and other medicinal products that prolong the QT interval have not been performed. An additive effect of ziprasidone and these medicinal products cannot be excluded, therefore ziprasidone should not be given with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, arsenic trioxide, halofantrine, levomethadyl acetate, mesoridazine, thioridazine, pimozide, sparfloxacin, gatifloxacin,

moxifloxacin, dolasetron mesilate, mefloquine, sertindole or cisapride.
(See section 4.3)

ADDITIONAL TEXT FOR Capsules and Oral Suspension ONLY

No studies on the interaction of ziprasidone with other medicinal products have been performed in children.

CNS medicinal products/alcohol: Given the primary effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting medicinal products and alcohol.

ADDITIONAL TEXT FOR Intramuscular ONLY

Effect of ziprasidone on other medicinal products: All interaction studies have been conducted with oral ziprasidone.

Effect of ziprasidone on other medicinal products: An *in vivo* study with dextromethorphan showed no marked inhibition of CYP2D6 at plasma concentrations 50% lower than those obtained after 40 mg ziprasidone twice daily. *In vitro* data indicated that ziprasidone may be a modest inhibitor of CYP2D6 and CYP3A4. However, it is unlikely that ziprasidone will affect the pharmacokinetics of medicinal products metabolised by these cytochrome P450 isoforms to a clinically relevant extent.

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 had no effect on the pharmacokinetics of lithium.

ADDITIONAL TEXT FOR Capsules and Oral Suspension ONLY

As ziprasidone and lithium are associated with cardiac conduction changes, the combination may pose a risk for pharmacodynamic interactions including arrhythmias.

There are limited data on co-medication with the mood stabilisers carbamazepine and valproate.

Effects of other medicinal products on ziprasidone: The CYP3A4 inhibitor ketoconazole (400 mg/day) increased the serum concentrations of ziprasidone by <40%. The serum concentrations of S-methyl-dihydroziprasidone and ziprasidone sulfoxide, at the expected Tmax of

ziprasidone, were increased by 55% and 8% respectively. No additional QTc prolongation was observed. Changes in pharmacokinetics due to coadministration of potent CYP3A4 inhibitors are unlikely to be of clinical importance, therefore no dosage adjustment is required.

Carbamazepine therapy, 200 mg b.i.d for 21 days, resulted in a decrease of approximately 35% in the exposure to ziprasidone.

ADDITIONAL TEXT FOR Capsules and Oral Suspension ONLY
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There are no data on co-medication with valproate.
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Antacid - multiple doses of aluminium and magnesium containing antacid or cimetidine have no clinically significant effect on the pharmacokinetics of ziprasidone under fed conditions.

Serotonergic medicinal products: In isolated cases, there have been reports of serotonin syndrome temporally associated with the therapeutic use of ziprasidone in combination with other serotonergic medicinal products such as SSRIs (see section 4.8). The features of serotonin syndrome can include confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea.

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.

4.6 Pregnancy and lactation

Reproductive toxicity studies have shown undesirable effects on the reproductive process, at doses associated with maternal toxicity and/or sedation. There was no evidence of teratogenicity (see section 5.3).

Use in pregnancy: 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 unless the expected benefit to the mother outweighs the potential risk to the foetus.

Use in lactation: It is not known whether ziprasidone is excreted in breast milk. Patients should not breast feed an infant if they are taking ziprasidone. If treatment is necessary, breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

Ziprasidone may cause somnolence and may influence the ability to drive and use machines. Patients likely to drive or operate machines should be cautioned appropriately.

4.8 Undesirable effects

ADDITIONAL TEXT FOR Intramuscular ONLY

Ziprasidone intramuscular: The table below contains adverse events with possible, probable or unknown relationship to ziprasidone in phase 2/3 trials. The most common reactions were nausea, sedation, dizziness, injection site pain, headache and somnolence. . Additional reactions reported from the post-marketing experience are included as Frequency 'Not known' in italics in the list below.

All adverse reactions are listed by class and frequency (very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (<1/1000)), not known (cannot be estimated from the available data).

The adverse reactions listed below may also be associated with the underlying disease and/or concomitant medications.

ADDITIONAL TEXT FOR Intramuscular ONLY

System	Adverse drug reactions
Organ	
Class	
Frequency	

Metabolism and nutrition disorders

Uncommon Anorexia

Psychiatric disorders

Uncommon Agitation, antisocial behaviour, psychotic disorder, insomnia, tic

Not known *Insomnia; mania/ hypomania*

Nervous system disorders

Common Akathisia, dizziness, dystonia, headache, sedation, somnolence

Uncommon Cogwheel rigidity, dizziness postural, dysarthria, dyskinesia, dyspraxia, parkinsonism, tremor

Not known *Neuroleptic malignant syndrome; serotonin syndrome (see section 4.5); facial droop*

Cardiac disorders

Uncommon Bradycardia, tachycardia

Not known *Torsade de pointes (see section 4.4)*

Ear and labyrinth disorders

Uncommon Vertigo

Vascular disorders

Common Hypertension

Uncommon Flushing, orthostatic hypotension

ADDITIONAL TEXT FOR Intramuscular ONLY

System	Adverse drug reactions
Organ	
Class	
Frequency	

Not known	<i>Syncope, venous thromboembolism</i>
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Respiratory, thoracic and mediastinal disorders

Uncommon	Laryngospasm
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Gastrointestinal disorders

Common	Nausea, vomiting
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Uncommon	Constipation, diarrhoea, loose stools, dry mouth
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Skin and subcutaneous tissue disorders

Uncommon	Hyperhidrosis
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Not known	<i>Hypersensitivity, angioedema</i>
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Musculoskeletal and connective tissue disorders

Common	Muscle rigidity
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Renal and Urinary disorders

Not known	<i>Enuresis</i>
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Immune system disorders

Not known	<i>Anaphylactic reaction</i>
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Hepatobiliary disorders

Uncommon	Hepatic enzyme increased
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General disorders and administration site conditions

Common	Asthenia, Injection site burning, Injection site pain
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ADDITIONAL TEXT FOR Intramuscular ONLY

System **Adverse drug reactions**
Organ
Class
Frequency

Uncommon Drug withdrawal syndrome, fatigue, influenza like illness,
injection site discomfort, injection site irritation

Investigations

Uncommon Blood pressure decreased, hepatic enzyme increased

ADDITIONAL TEXT FOR Intramuscular ONLY

The most common cardiovascular adverse events reported from fixed dose clinical trials with intramuscular ziprasidone were: dizziness (10 mg - 11%, 20 mg - 12%), tachycardia (10 mg - 4%, 20 mg - 4%) and postural dizziness (10mg - 2%, 20mg - 2%), orthostatic hypotension, 20 mg - 5%) and hypotension (10mg - 2%).

In premarketing fixed dose clinical trials with ziprasidone intramuscular injection, increased blood pressure and hypertension were observed in 2.2% of patients receiving 10 mg and increased blood pressure was observed in 2.8% of patients receiving 20 mg.

Oral ziprasidone has been administered in clinical trials (see section 5.1) to approximately 6500 subjects. The most common adverse reactions in schizophrenia clinical trials were sedation and akathisia. In bipolar mania clinical trials, the most common adverse reactions were sedation, akathisia, extrapyramidal disorder and dizziness.

The table below contains adverse events based on combined short term (4-6 week), fixed dose, schizophrenia studies and short term (3 week), flexible dose, bipolar mania studies with a probable or possible relationship to treatment with ziprasidone and which occur at an incidence greater than placebo. . Additional reactions reported from the post-marketing experience are included as Frequency 'Not known' in italics in the list below.

All adverse reactions are listed by class and frequency (very common ($>1/10$), common ($>1/100$, $<1/10$), uncommon ($>1/1000$, $<1/100$), rare ($<1/1000$)) and not known (cannot be estimated from the available data).

The adverse reactions listed below may also be associated with the underlying disease and/or concomitant medications.

System Organ Class	Adverse drug reactions
Frequency	
Infections and Infestations	
Rare	Rhinitis
Metabolism and nutrition disorders	
Uncommon	Increased appetite
Rare	Hypocalcaemia
Psychiatric disorders	
Common	Restlessness
Uncommon	Agitation, anxiety, throat tightness, nightmare,
Rare	Panic attack, depressive symptom, bradyphrenia, flat affect, anorgasmia
Not known	<i>Insomnia; mania/hypomania</i>
Nervous system disorders	
Common	Dystonia, akathisia, extrapyramidal disorder, parkinsonism, (including cogwheel rigidity, bradykinesia, hypokinesia) tremor, dizziness, sedation, somnolence, headache
Uncommon	Generalised tonic clonic seizures, tardive dyskinesia, dyskinesia, drooling, ataxia, dysarthria, oculogyric crisis, disturbance in attention, hypersomnia, hypoaesthesia, , paraesthesia, lethargy
Rare	Torticollis, paresis, akinesia, hypertonia, restless legs syndrome
Not known	<i>Neuroleptic malignant syndrome; serotonin syndrome (see section 4.5); facial droop</i>
Blood and lymphatic system disorders	
Rare	Lymphopenia, eosinophil count increased

System Organ Class	Adverse drug reactions
Frequency	
Cardiac disorders	
Uncommon	Palpitations, tachycardia
Rare	Electrocardiogram QT corrected interval prolonged
Not known	<i>Torsade de pointes (see section 4.4)</i>
Eye disorders	
Common	Vision blurred
Uncommon	Photophobia.
Rare	Amblyopia, visual disturbance, eye pruritis, dry eyes
Ear and labyrinth disorders	
Uncommon	Vertigo, tinnitus
Rare	Ear pain
Vascular disorders	
Uncommon	Hypertensive crisis, hypertension, orthostatic hypotension, hypotension
Rare	Systolic hypertension, diastolic hypertension, labile blood pressure
Not known	<i>Syncope, venous thrombembolism</i>
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, sore throat
Rare	Hiccups
Gastrointestinal disorders	
Common	Nausea, vomiting, constipation, dyspepsia, dry mouth, salivary hypersecretion
Uncommon	Diarrhoea, dysphagia, gastritis, gastrointestinal

System Organ Class	Adverse drug reactions
Frequency	
Rare	discomfort, swollen tongue, tongue thick, flatulence, Gastro-oesophageal reflux, loose stools
Skin and subcutaneous tissue disorders	
Uncommon	Urticaria, rash, rash maculo-papular, acne
Rare	Psoriasis, dermatitis allergic, alopecia, swelling face, erythema, rash papular, skin irritation
Not known	<i>Hypersensitivity, angioedema</i>
Musculoskeletal and connective tissue disorders	
Common	Musculoskeletal rigidity
Uncommon	Musculoskeletal discomfort, muscle cramp, pain in extremity, joint stiffness
Rare	Trismus
Renal and urinary disorders	
Rare	Urinary incontinence, dysuria
Not known	<i>Enuresis</i>
Reproductive system and breast disorders	
Rare	Erectile dysfunction, erection increased, galactorrhoea, gynaecomastia
Not known	<i>Priapism</i>
Immune system disorders	
Not known	<i>Anaphylactic reaction</i>
Hepatobiliary disorders	
Uncommon	Hepatic enzyme increased

System	Adverse drug reactions
Organ Class	
Frequency	
Rare	Liver function test abnormal
General disorders and administration site conditions	
Common	Asthenia, fatigue
Uncommon	Chest discomfort, gait abnormal, pain, thirst
Rare	Pyrexia, feeling hot
Investigations	
Rare	Blood lactate dehydrogenase increased

In short-term and long-term ziprasidone schizophrenia and bipolar mania clinical trials, the incidence of tonic clonic seizures and hypotension was uncommon, occurring in less than 1% of ziprasidone treated patients.

Ziprasidone causes a mild to moderate dose-related prolongation of the QT interval (see section 5.1). In schizophrenia clinical trials, an increase of 30 to 60 msec was seen in 12.3% (976/7941) of ECG tracings from ziprasidone-treated and 7.5% (73/975) of ECG tracings from placebo-treated patients. A prolongation of >60 msec was seen in 1.6% (128/7941) and 1.2% (12/975) of tracings from ziprasidone and placebo-treated patients, respectively. The incidence of QTc interval 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. Comparable findings were observed in bipolar mania clinical trials.

In long term maintenance treatment in schizophrenia clinical trials, prolactin levels in patients treated with ziprasidone were sometimes elevated, but, in most patients, returned to normal ranges without cessation of treatment. In addition, potential clinical manifestations (e.g. gynaecomastia and breast enlargement) were rare.

ADDITIONAL TEXT FOR Capsules and Oral Suspension ONLY

Children and Adolescents with Bipolar mania

Oral ziprasidone has been administered in clinical trials (see section 5.1) to 267 paediatric subjects with bipolar disorder. In a placebo-controlled study, the most frequent adverse reactions (reported with a frequency >10%) were sedation, somnolence, headache, fatigue and nausea. The frequency, type and severity of adverse reactions in these subjects were generally similar to those in adults with bipolar disorder who are treated with ziprasidone.

Ziprasidone was associated with a similar mild to moderate dose-related prolongation of the QT interval in the paediatric bipolar clinical trial to those seen in the adult population. Tonic clonic seizures and hypotension were not reported in the placebo-controlled paediatric bipolar clinical trials.

4.9 Overdose

Experience with ziprasidone in overdose is limited. The largest confirmed single ingestion of ziprasidone is 12,800 mg. In this case, extrapyramidal symptoms and a QTc interval of 446 msec (with no cardiac sequelae)

were reported. In general, the most commonly reported symptoms following overdose are, extrapyramidal symptoms, somnolence, tremor and anxiety.

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. There is no specific antidote to ziprasidone.