

DATA SHEET

## ZELDOX IM®

### Generic Name

Ziprasidone mesilate

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## COMPOSITION

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Powder for solution for intramuscular injection.

Ziprasidone mesilate, equivalent to 20 mg of ziprasidone per mL, following reconstitution.

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## CLINICAL PARTICULARS

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### Indications

ZELDOX IM is indicated for the acute control and short-term management of the agitated psychotic patient. If indicated, the patient may continue with oral ziprasidone.

In two one-week open-label, active-controlled trials, ziprasidone was administered by intramuscular injection for up to three days with patients subsequently continuing on oral ziprasidone. Maintenance of efficacy, safety and tolerability were demonstrated for the transition from intramuscular to oral administration of ziprasidone.

A dose-related reduction in agitated behaviour was observed with onset of significant improvement noted at 15 minutes and then from 1 hour post injection until endpoint (2 hours) with the 10 mg dose and from 30 minutes post injection until endpoint (4 hours) with the 20 mg dose.

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## DOSAGE AND ADMINISTRATION

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### *Use in Adults*

Ziprasidone IM is for intramuscular use only. Do not administer intravenously.

The recommended dose is 10 to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every 2 hours, doses of 20 mg may be administered every 4 hours.

Intramuscular administration of ziprasidone for more than 3 consecutive days has not been studied.

If continuation therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as soon as clinically appropriate.

### ***Use in Children***

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

### ***Use in the Elderly***

Safety and effectiveness in the elderly (65 years and over) have not been established.

### ***Use in Renal Impairment***

Since the cyclodextrin excipient is excreted exclusively by the kidney, ziprasidone intramuscular injection should be administered with caution in patients with impaired renal function (see **Pharmacokinetic Properties**).

### ***Use in Hepatic Impairment***

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

### ***Use in Smokers***

No dosage adjustment is required in patients who smoke.

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## **CONTRAINDICATIONS**

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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 **Warnings and Precautions**).

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## WARNINGS AND PRECAUTIONS

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### *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. One in 541 (0.18%) patients receiving intramuscular ziprasidone had QTc prolongation ( $\geq 500$  msec).

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  $\geq 480$  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 **Contraindications**).

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;
- 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 **Contraindications**). 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)***

In pre-marketing clinical trials there were no reported cases of NMS in patients receiving ziprasidone either orally or by intramuscular injection. 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.

### ***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.

### ***Cardiovascular Disease***

Safety and effectiveness in patients with cardiovascular disease have not been established.

### ***Blood Pressure***

Dizziness, tachycardia and postural hypotension are not unusual in patients following intramuscular administration of ziprasidone. Hypertension has also been reported. Caution should be exercised, particularly in ambulatory patients.

Oral ziprasidone may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its  $\alpha_1$ -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.

### ***Seizures***

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

### ***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 Patient 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.

### ***\*Post-marketing Reports of Mortality***

As with other IM antipsychotics, fatalities with the use of ziprasidone IM, generally in patients with multiple confounding risk factors, have been reported. Although a causal relationship has not been established, ziprasidone IM should be used with caution.

### ***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 etiology cannot be identified, ziprasidone should be discontinued.

### ***Hyperprolactinaemia***

As with other drugs that antagonise dopamine D<sub>2</sub> 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 **Carcinogenicity**). 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.\*

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## **INTERACTIONS**

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### **Class IA and III Antiarrhythmic Drugs (see **Contraindications** and **Warnings and Precautions – QT Interval**)**

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 **Warnings and Precautions – QT Interval**)

### **CNS Drugs/Alcohol (see **Warnings and Precautions – CNS Drugs/Alcohol**)**

All interaction studies have been conducted with oral ziprasidone.

### ***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* is 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, dextorphan.

### ***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 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.

### ***Ketoconazole***

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

### ***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.

### ***Cimetidine***

A non-specific CYP<sub>450</sub> inhibitor, did not significantly affect ziprasidone pharmacokinetics.

### ***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.

### ***Pregnancy and Lactation***

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 **Preclinical Data**).

### ***Use in 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-market 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 and as short as possible.\*

### ***Use in Lactation***

It is not known whether ziprasidone is excreted in breast milk. Patients should be advised not to breast feed an infant if they are receiving ziprasidone.

### ***Effects on Ability to Drive and Use of Machines***

As with other psychoactive drugs, 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.

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## **ADVERSE EFFECTS**

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In controlled clinical trials, treatment-related adverse events associated with the use of ziprasidone IM (n=286) occurring at a frequency of  $\geq 1\%$  are identified below:

- **Body as a Whole:** asthenia (1.1%), headache (1.8%), injection site pain (5.2%)
- **Cardiovascular:** hypertension (1.4%), postural hypotension (1.1%)
- **Digestive:** diarrhoea (1.1%), nausea (4.2%)

- **Nervous System:** akathisia (1.1%), dizziness (3.5%), somnolence (6.6%)

Additional treatment-related adverse events occurring at a frequency of  $\geq 1\%$  in three post-approval open-label controlled clinical trials included extrapyramidal disorder, insomnia, vomiting and fatigue.\*

The following adverse reactions have been reported with the oral and/or intramuscular\* formulation during post-marketing experience:

- **Immune System Disorders:** allergic reaction
- **Psychiatric Disorders:** insomnia, mania/hypomania
- **Nervous System Disorders:** dystonia, facial droop, neuroleptic malignant syndrome; serotonin syndrome (alone or in combination with serotonergic medicinal products); tardive dyskinesia
- **Cardiac Disorders:** tachycardia, torsade de pointes (see **Warnings and Precautions**)
- **Vascular Disorders:** postural hypotension, hypotension\*, syncope
- **Gastrointestinal Disorders:** dysphagia, swollen tongue, vomiting
- **Skin and Subcutaneous Tissue Disorders:** angioedema, rash
- **Renal and Urinary Disorders:** enuresis, urinary incontinence
- **Reproductive System and Breast Disorders:** galactorrhea, priapism

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## OVERDOSE

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There is no experience of overdosage with ziprasidone intramuscular injection.

Experience with ziprasidone capsules 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.

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 overdose, 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.

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## PHARMACOLOGICAL PROPERTIES

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### Pharmacodynamic Properties

#### *Receptor Binding Studies*

Ziprasidone has a high affinity for dopamine type 2 (D<sub>2</sub>) receptors and substantially higher affinity for serotonin type 2<sub>A</sub> (5HT<sub>2A</sub>) receptors. Ziprasidone also interacts with serotonin 5HT<sub>2C</sub>, 5HT<sub>1D</sub> and 5HT<sub>1A</sub> receptors where its affinities for these sites are equal to or greater than its affinity for the D<sub>2</sub> receptor. Ziprasidone has moderate affinity for neuronal serotonin and norepinephrine transporters. Ziprasidone demonstrates moderate affinity for histamine H<sub>1</sub>- and alpha<sub>1</sub>-receptors. Antagonism at these receptors has been associated with somnolence and orthostatic hypotension, respectively. Ziprasidone demonstrates negligible affinity for muscarinic M<sub>1</sub>-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<sub>A</sub> (5HT<sub>2A</sub>) and dopamine type 2 (D<sub>2</sub>) receptors. It is proposed that the antipsychotic activity is mediated, in part, through this combination of antagonist activities.

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

#### *Human PET Studies*

At 12 hours following a 40 mg oral dose of ziprasidone, receptor blockade was greater than 80% for 5HT<sub>2A</sub> and greater than 50% for D<sub>2</sub> using positron emission tomography (PET).

### Further Information from Clinical Trials\*

#### *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 **Warnings and Precautions**) is associated with an increased risk of non-suicide 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.

### Pharmacokinetic Properties

The bioavailability of ziprasidone administered intramuscularly is 100%. After intramuscular administration of single doses, peak serum concentrations typically occur at approximately

60 minutes post-dose or earlier and the mean half-life ( $t_{1/2}$ ) ranges from approximately two to five hours. Exposure increases in a dose-related manner and following three days of intramuscular dosing, little accumulation is observed.

Mean systemic clearance of ziprasidone administered intravenously is 7.5 mL/min/kg and the volume of distribution is approximately 1.5 L/kg.

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

The metabolism and elimination of ziprasidone mesilate has not been systematically evaluated after intramuscular administration. The metabolic excretory pattern of ziprasidone following intramuscular administration should not differ from that observed after oral administration because non-metabolic clearance is low.

Ziprasidone is extensively metabolised after oral administration, with only a small amount (<1%) excreted in urine or faeces (<4%) as unchanged drug. Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benzisothiazole piperazine (BITP) sulphoxide, BITP sulphone, ziprasidone sulphoxide and S-methyl-dihydroziprasidone. Approximately 20% of the dose is excreted in urine, with approximately 66% being eliminated in faeces. Unchanged ziprasidone represents about 44% of total drug-related material 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 catalyzed 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-methyl-dihydroziprasidone, at the expected T<sub>max</sub> of ziprasidone, was increased by 55% during ketoconazole treatment. No additional QTc prolongation was observed.

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

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

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

As the cyclodextrin excipient in ziprasidone intramuscular injection is cleared by renal filtration, ziprasidone should be administered with caution to patients with impaired renal function.

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

### **Preclinical Data**

Preclinical trial data on ziprasidone administered orally 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 numbers of pups born dead, decreased pup weights and delayed functional development were observed at doses that caused maternal toxicity (e.g. sedation, 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.

In parenteral studies of ziprasidone there were no adverse findings relevant to the clinical use of the product.

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## **PHARMACEUTICAL PARTICULARS**

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### ***Presentation***

ZELDOX IM for intramuscular injection is presented as a sterile lyophilised powder in a single dose vial as ziprasidone mesilate containing the equivalent of 30 mg ziprasidone. When reconstituted, each mL contains 20 mg of ziprasidone and 294 mg of the inactive ingredient, sulfobutyl betadex sodium.

An ampoule containing 1.2mL of Sterile Water for Injections Ph. Eur. is also supplied for reconstitution purposes.

### ***Storage and Handling***

Store below 30 °C in dry form. Do not freeze.

Keep vials in the original pack until ready to use.

Chemical and physical in-use stability of the reconstituted product has been demonstrated for 24 hours at ambient temperature (<30°C) and for seven days at 2°C to 8°C. However, from a microbiological point of view, immediate use after reconstitution or after 24 hours at 2°C to 8°C is recommended.

### ***Instructions for Use and Handling***

The contents of the vial should be reconstituted by introduction of 1.2 mL of the supplied Water for Injections affording a concentration of 20mg ziprasidone per mL, and shaken until complete dissolution has occurred. Only clear solutions, free of visible particles, should be used.

Only one dose should be withdrawn from each vial and the remainder should be discarded.

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## **MEDICINE CLASSIFICATION**

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Prescription Medicine.

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## **NAME AND ADDRESS**

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## **DATE OF PREPARATION**

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27 January 2012

\* Please note changes in Data Sheet