AUSTRALIAN PRODUCT INFORMATION

ZELDOX IM®

(ziprasidone mesilate) powder for injection

1 NAME OF THE MEDICINE

Ziprasidone mesilate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZELDOX IM contains ziprasidone (as mesilate). When reconstituted with 1.2 mL Water for Injections, each vial contains 20 mg ziprasidone and 294 mg of the inactive ingredient, sulfobutyl betadex sodium (SBECD) per ml.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

ZELDOX IM is presented as a sterile lyophilised powder in a single dose vial.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Acute treatment and short term management of agitation and disturbed behaviour in patients with schizophrenia and related psychoses when oral therapy is not appropriate.

4.2 DOSE AND METHOD OF ADMINISTRATION

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 up to a maximum of 40 mg/day.

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

If therapy is indicated, oral ziprasidone hydrochloride capsules, up to 80 mg twice daily, should replace the intramuscular administration as soon as possible.

Dosage Adjustment in Renal Impairment

As SBECD is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special Populations, Renal impairment).

Dosage Adjustment in Hepatic Impairment

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

In patients with mild to moderate hepatic insufficiency, lower doses should be considered.

A toxicity study in dogs showed intrahepatic cholestasis and elevation of serum ALT and alkaline phosphatase at oral ziprasidone doses producing exposure (plasma AUC) about twice the maximal clinical exposure.

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 PHARMACOKINETIC PROPERTIES, Special Populations, Hepatic impairment).

Dosage Adjustment in the Elderly

Ziprasidone intramuscular has not been systematically evaluated in elderly patients (65 years and over).

Dosage Adjustment in Patients Who Smoke

No dosage adjustment is required in patients who smoke (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special Populations, Smoking).

Preparation for Administration

ZELDOX IM should only be administered by intramuscular injection. This product is for single use in one patient only. Vials require reconstitution prior to administration, any unused portion should be discarded.

Add 1.2 mL of Sterile Water for Injections to the vial and shake vigorously until all the drug is dissolved. Each mL of reconstituted solution contains 20 mg ziprasidone. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final solution. This medicinal product must not be mixed with other medicinal products or solvents other than Sterile Water for Injections.

To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary, store at 2-8 °C (Refrigerate. Do not freeze) for not more than 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Due to the viscosity of the solution, approximately 0.5 mL of the reconstituted solution remains in the vial following 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 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

QT Prolongation and Pro-arrhythmias

Ziprasidone causes a mild to moderate prolongation of the QT interval. 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. The mean change in QTc

from baseline was calculated 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 trial, ECGs were obtained at the time of maximum plasma concentration while the drug was coadministered with the appropriate inhibitor(s) of the CYP450 metabolism specific for each drug. The effect of oral ziprasidone on QTc length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg twice daily).

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. In schizophrenia clinical trials with ziprasidone, the electrocardiograms of 3/3266 (0.1%) patients who received ziprasidone and 1/538 (0.2%) patients who received placebo revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone.

A study evaluating the QT/QTc prolonging effect of intramuscular ziprasidone, with intramuscular haloperidol as a control, was conducted in patient volunteers. ECGs were obtained at the time of maximum plasma concentration following two injections of ziprasidone (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular ziprasidone is 50% higher than the recommended therapeutic dose. The mean change in QTc from baseline was calculated, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone was 4.6 msec and 12.8 msec, following the first and second injections, -respectively. The mean increase in QTc from baseline for haloperidol was 6.0 msec and 14.7 msec, following the first and second injections, injection respectively. No patients had a QTc interval exceeding 500 msec.

Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. There have been rare post-marketing reports of torsade de pointes in patients with multiple confounding risk factors taking ziprasidone. A causal relationship between torsade de pointes and ziprasidone has not been established.

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

Certain circumstances may increase the risk of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) electrolyte imbalances (especially hypokalaemia or hypomagnesaemia); (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval (see Section 4.3 CONTRAINDICATIONS).

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 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, syncope or seizures, the prescriber should initiate further evaluation, e.g. Holter monitoring, may be useful. The possibility of a malignant cardiac arrhythmia should also be considered and a cardiac evaluation including an ECG should be performed.

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.

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic malignant syndrome, a potentially fatal complex, has been reported in association with antipsychotic drugs, including ziprasidone. The clinical manifestations are hyperthermia, muscle rigidity, altered mental status and signs of autonomic instability such as irregular pulse and blood pressure, tachycardia, cardiac arrhythmias and diaphoresis. Additional features may include elevated creatine phosphokinase, 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, should 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

In fixed-dose, placebo-controlled trials, in patients with schizophrenia, of up to six weeks duration, the incidence of treatment emergent tardive dyskinesia was comparable in patients receiving oral ziprasidone and placebo and lower than patients treated with active comparator (0.4% ziprasidone, 1.2% haloperidol and 0.7% placebo). In a 52-week, placebo-controlled trial in patients with schizophrenia, only one out of 219 patients treated with oral ziprasidone experienced tardive dyskinesia.

As with other antipsychotic agents, the risk of tardive dyskinesia and other tardive extrapyramidal syndromes may increase with long term exposure and therefore if signs or symptoms of tardive dyskinesia appear in a patient on ziprasidone, a dose reduction or drug discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

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.

Cardiovascular Disease

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

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.

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 α1-adrenergic antagonist properties. Syncope was reported in 0.6% of the patients treated with oral 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.

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 the oral preparation of ziprasidone should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

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.

CNS Drugs and 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.

Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

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 oral 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, oral 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 PRECLINICAL SAFETY DATA, 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 at this time.

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.

Seizures

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

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death and/or potentially, cerebrovascular adverse events compared with placebo. Analyses of seventeen oral placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Ziprasidone is not approved for the treatment of elderly patients with dementia-related psychosis.

Sleep apnoea

Sleep apnoea and related disorders have been reported in patients treated with antipsychotics, such as ziprasidone, with or without prior history of sleep apnoea, and with or without concomitant weight-gain. Caution should be taken in patients who have a history of or are at risk for sleep apnoea, or who are concomitantly using central nervous system depressants.

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.

Priapism

Cases of priapism have been reported with antipsychotic use, including ziprasidone.

Use in Hepatic Impairment

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

In patients with mild to moderate hepatic insufficiency, lower doses should be considered.

A toxicity study in dogs showed intrahepatic cholestasis and elevation of serum ALT and alkaline phosphatase at oral ziprasidone doses producing exposure (plasma AUC) about twice the maximal clinical exposure.

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 PHARMACOKINETIC PROPERTIES, Special Populations, Hepatic Impairment).

Use in Renal Impairment

As SBECD is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function (see Section 5.3 PHARMACOKINETIC PROPERTIES, Special Populations, Renal Impairment).

Use in the Elderly

Ziprasidone intramuscular injection has not been systematically evaluated in elderly patients (65 years and over).

Paediatric Use

Ziprasidone intramuscular injection has not been systematically evaluated in subjects under 18 years of age.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

All interaction studies have been conducted with oral ziprasidone.

Effect of Ziprasidone on Other Medicines

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*. Although the clinical relevance of this finding is uncertain, ziprasidone is unlikely to cause clinically important drug interactions mediated by these enzymes.

QTc Prolongation

As with other antipsychotic agents, there is an increased potential of QTc prolongation in the presence of Type IA and IIIA antiarrhythmics. 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.

Coadministration with the potent CYP3A4 inhibitor, ketoconazole, did not affect QTc, when compared to ziprasidone alone (see Section 4.3 CONTRAINDICATIONS).

Dextromethorphan

The pharmacokinetics and metabolism of dextromethorphan, a CYP2D6 substrate were unaffected by ziprasidone.

Oral Contraceptives

Ziprasidone administration at a dose of 20 mg twice daily resulted in no significant change to the pharmacokinetics of estrogen (ethinyl estradiol 0.03 mg, a CYP3A4 substrate) or progesterone components (levonorgestrel 0.15 mg).

Lithium

Co-administration of ziprasidone at a dose of 40 mg twice daily had no effect on the pharmacokinetics of lithium at a dose of 450 mg twice daily for 7 days. In this study, steady state lithium concentrations prior to coadministration of ziprasidone were 0.49 mEq/L.

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 Medicines on Ziprasidone

CYP3A4 Inhibitors

Coadministration of potent CYP3A4 inhibitors has the potential of increasing ziprasidone serum concentrations. The clinical importance of this potential has not been clearly defined.

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

Ketoconazole, a potent CYP3A4 inhibitor (400 mg/day), increased the serum concentrations of ziprasidone by approximately 35% to 40% when compared to ziprasidone alone. The serum concentration of S-methyl-dihydroziprasidone, at the expected Tmax of ziprasidone, was increased by 55% during ketoconazole treatment. No additional QTc prolongation was observed.

Cimetidine, a CYP3A4 inhibitor, at a dose of 800 mg QD for 2 days did not significantly alter the pharmacokinetics of ziprasidone.

CYP3A4 Inducers

Co-administration with inducers of CYP3A4 and P-gp such as carbamazepine, rifampin and St John's wort (*Hypericum perforatum*) could cause decreased concentrations of ziprasidone.

Carbamazepine, a CYP3A4 inducer, produced a decrease in AUC (36%) and Cmax (25%) of ziprasidone.

CNS Drugs

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 antacid did not affect the pharmacokinetics of ziprasidone.

Other

In addition, pharmacokinetic screening of patients in clinical trials has not revealed any evidence of clinically significant interactions with benztropine, propranolol or lorazepam.

Ziprasidone has not been studied for drug interaction with valproate or lamotrigine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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

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

Ziprasidone hydrochloride was shown to increase time to copulation in rats at oral doses of 10 to 160 mg/kg/day (0.5 to 8 times the oral MRHD on a mg/m^2 basis). Fertility was impaired in rats dosed orally with ziprasidone hydrochloride 160 mg/kg/day, with a no-effect dose level of 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The effect appeared to be in the female since the length of the oestrous cycle was increased, a pharmacologic effect of dopamine antagonists in rats. Increased oestrous cycle length was observed in female rats treated intramuscularly with ziprasidone mesilate 2 mg/kg/day or greater (less than the clinical exposure based on AUC). Fertility was not impaired when males were given oral ziprasidone hydrochloride 160 mg/kg/day or intramuscular ziprasidone mesilate 20 mg/kg/day (6 times the clinical exposure based on AUC) and mated with untreated females, and there were no treatment related findings in the testes of male rats given ziprasidone hydrochloride 200 mg/kg/day orally (11 times the MRHD on a mg/m^2 basis).

Use in Pregnancy - Category C

In animal studies ziprasidone hydrochloride crossed the placenta and demonstrated developmental toxicity, including possible teratogenic effects at doses/exposures similar to clinical doses/exposures. When ziprasidone hydrochloride was administered to pregnant rabbits during the period of organogenesis, there was an increased incidence of fetal structural abnormalities (ventricular septal defects and other cardiovascular malformations and kidney alterations) at an oral dose of 30 mg/kg/day (3 times the MRHD on a mg/m^2 basis), and an increased incidence of vertebral arches fused to the pelvis after intramuscular ziprasidone mesilate at 5 mg/kg/day or greater (twice the clinical exposure based on AUC). There was no evidence to suggest that these developmental effects were secondary to maternal toxicity. The developmental no-effect doses were 10 mg/kg/day orally (similar to the MRHD on a mg/m^2 basis) and 1 mg/kg/day intramuscular ziprasidone mesilate (less than clinical exposure based on AUC). Studies in rats have not shown adverse effects on embryo-fetal development, other than those associated with maternal toxicity, when ziprasidone hydrochloride was administered during the period of organogenesis at oral doses up to 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis) or intramuscular ziprasidone mesilate up to 40 mg/kg/day (11-fold the clinical exposure based on AUC).

The incidence of still births was increased when ziprasidone was administered at oral doses of ziprasidone hydrochloride of 10 mg/kg/day or greater to rats throughout gestation or intramuscular doses of ziprasidone mesilate of 2 mg/kg/day or greater. Estimated systemic exposure at the no-effect dose for perinatal mortality (5 mg/kg/day or 2 mg/kg/day for oral and intramuscular administration, respectively) was less than that in humans at the maximum recommended dose. Offspring showed increased postnatal mortality, suppression of growth and delayed development when ziprasidone was administered to rats orally during gestation and lactation at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis) or intramuscularly at 6 mg/kg/day or greater (2 times the clinical exposure based on AUC). The estimated systemic exposure in dams at the no effect dose for offspring (5 mg/kg/day orally or 2 mg/kg/day intramuscularly) was less than that in humans at the MRHD.

There are no adequate and well controlled clinical trials 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 and as short as possible.

Use in Lactation

There are no adequate and well-controlled studies in lactating women. Limited data indicate that ziprasidone and its active metabolites are excreted into breast milk at very low levels. Offspring showed increased postnatal mortality, suppression of growth and delayed development when ziprasidone was administered to rats orally during gestation and lactation at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis) or intramuscularly at 6mg/kg/day or greater (2 times the clinical exposure based on AUC). The estimated systemic exposure in dams at the no effect dose for offspring (5 mg/kg/day orally or 2 mg/kg/day intramuscularly) was less than that in humans at the MRHD. Patients should be advised not to breast feed if they are taking ziprasidone.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with other psychoactive medicines, ziprasidone may cause somnolence. Patients likely to drive or operate other machines should therefore be cautioned appropriately.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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.

All adverse reactions are listed by class and frequency (very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100) and rare (<1/1000).

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

Body System	Adverse Drug Reactions
Metabolism and Nutrition Disorders	
Uncommon	Decreased appetite.
Psychiatric Disorders	
Common	Agitation, insomnia.
Uncommon	Antisocial behaviour, psychotic disorder, tic, anxiety.
Nervous System Disorders	
Common	Extrapyramidal disorder, akathisia, tremor, dizziness, dystonia, headache, sedation, somnolence.
Uncommon	Cogwheel rigidity, dizziness postural, dysarthria, dyskinesia, dyspraxia, parkinsonism.

Body System	Adverse Drug Reactions
Cardiac Disorders	
Common	Tachycardia.
Uncommon	Bradycardia.
Ear and Labyrinth Disorders	
Uncommon	Vertigo.
Vascular Disorders	
Common	Hypertension.
Uncommon	Flushing, orthostatic hypotension.
Rare	Hot flush.
Respiratory, Thoracic and Mediastinal Disorders	
Uncommon	Laryngospasm.
Gastrointestinal Disorders	
Common	Nausea, vomiting, constipation, dry mouth.
Uncommon	Diarrhoea.
Skin and Subcutaneous Tissue Disorders	
Uncommon	Hyperhidrosis.
Renal and Urinary Disorders	
Rare	Dysuria.
Musculoskeletal and Connective Tissue Disorders	
Common	Muscle rigidity.
General Disorders and Administration Site Conditions	
Common	Asthenia, injection site burning, injection site pain.
Uncommon	Drug withdrawal syndrome, fatigue, influenza-like illness, injection site discomfort, injection site irritation.
Investigations	
Uncommon	Blood pressure decreased, hepatic enzyme increased.

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%), postural dizziness (10 mg – 2%, 20 mg – 2%), orthostatic hypotension, 20 mg – 5%) and hypotension (10 mg – 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.

The table below contains treatment-emergent, all causality adverse events with an incidence of ≥1% for ziprasidone IM and haloperidol IM from two clinical studies.

Body System / Adverse Event	Percentage of Patients Reporting Events	
	Ziprasidone IM N=559	Haloperidol IM N=260
Body as a Whole		
Appl. / inj. / incision / insertion site pain	6 (1.07)	0 (0.00)
Asthenia	20 (3.58)	1 (0.38)
Headache	11 (1.97)	4 (1.54)
Digestive		
Constipation	2 (0.36)	3 (1.15)
Increased salivation	2 (0.36)	4 (1.54)
Nausea	15 (2.68)	3 (1.15)
Vomiting	13 (2.33)	2 (0.77)
Nervous		
Agitation	3 (0.54)	7 (2.69)
Akathisia	8 (1.43)	19 (7.31)
Anxiety	11 (1.97)	9 (3.46)
Dizziness	32 (5.72)	6 (2.31)
Dyskinesia	1 (0.18)	3 (1.15)
Dystonia	6 (1.07)	15 (5.77)
Extrapyramidal syndrome	10 (1.79)	42 (16.15)
Hypertonia	7 (1.25)	13 (5.00)
Insomnia	31 (5.55)	14 (5.38)
Somnolence	26 (4.65)	9 (3.46)
Tremor	4 (0.72)	3 (1.15)
Respiratory		
Respiratory tract infection	1 (0.18)	3 (1.15)

Body System / Adverse Event	Percentage of Patients Reporting Events	
	Ziprasidone IM	Haloperidol IM
	N=559	N=260
Special Senses		
Abnormal vision	1 (0.18)	3 (1.15)

Ziprasidone Oral

The table below contains treatment-emergent adverse events that occurred at an incidence of greater than or equal to 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 Events	
	Ziprasidone	Placebo
	N=1159	N=497
General Disorders and Administration Site Conditions		
Asthenia	1.3	0.2
Fatigue	1.6	0.4
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
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
Psychiatric Disorders		
Restlessness	1.6	0.6
Insomnia	1.2	2.4

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%).

General Disorders and Administration Site Conditions

Uncommon: Gait disturbance, thirst, malaise.

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

Cardiac Disorders

Uncommon: Bundle branch block right, palpitation.

Gastrointestinal Disorders

Uncommon: Dysphagia, flatulence, gastritis.

Rare: Gastro-oesophageal reflux, diarrhoea.

Blood and Lymphatic System Disorders

Rare: Lymphopenia.

Ear and Labyrinth Disorders

Uncommon: Tinnitus, vertigo.

Rare: Ear pain, vertigo positional.

Eye Disorders

Common: Visual impairment.

Uncommon: Photophobia, oculogyric crisis.

Rare: Amblyopia, eye pruritus.

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.

Infections and Infestations

Uncommon: Rhinitis.

Metabolism and Nutrition Disorders

Uncommon: Increased appetite.

Musculoskeletal and Connective Tissue Disorders

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

Rare: Arthropathy, musculoskeletal discomfort, trismus.

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.

Psychiatric Disorders

Common: Anxiety, agitation.

Uncommon: Nightmare, nervousness, libido decreased.

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

Respiratory, Thoracic and Mediastinal Disorders

Uncommon: Dyspnoea, oropharyngeal pain, throat tightness.

Rare: Hiccups, laryngospasm.

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, amenorrhea.

Skin and Subcutaneous Tissue Disorders

Common: Rash.

Uncommon: Acne, rash maculopapular, urticaria.

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

Other Findings for Ziprasidone Oral

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 with oral ziprasidone, an increase of 30 to 60 msec was seen in 12.3% (976/7941) of ECG tracings from ziprasidone-treated and 7.5% (83/975) 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.

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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Prolactin Levels

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

In phase 2/3 clinical trials, prolactin levels in patients treated with ziprasidone were sometimes elevated (12%) compared with the placebo group (3%), but potential clinical manifestation (e.g. gynaecomastia 0.1%) were rare. In most patients, levels returned to normal ranges without cessation of treatment. In the clinical studies the degree and incidence of prolactin elevation was lower in ziprasidone patients than in patients treated with haloperidol (29%) or risperidone (60%).

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 events have been reported with the oral and/or intramuscular formulation during post-marketing experience.

Immune System Disorders: Hypersensitivity.

Investigations: Weight decreased, weight increased.

Endocrine Disorders: Hyperprolactinaemia.

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

Respiratory, Thoracic and Mediastinal Disorders: Sleep apnoea.

Nervous System Disorders: Syncope, facial droop, neuroleptic malignant syndrome (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE); serotonin syndrome (alone or in combination with serotonergic medicinal products), tardive dyskinesia, dystonia, sedation.

Cardiac Disorders: Tachycardia, torsade de pointes (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Vascular Disorders: Orthostatic hypotension, hypotension, embolism venous (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Gastrointestinal Disorders: Dysphagia, tongue oedema, vomiting.

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 Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs and Symptoms

Experience with oral ziprasidone in overdosage is limited. In overdose cases in general, the most commonly reported symptoms are extrapyramidal symptoms, somnolence, tremor and anxiety. Hypertension, hypotension, diarrhoea, tachycardia and prolongation of the QTc and QRS intervals have also been reported. Respiratory depression may occur following massive overdoses due to CNS depression. 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.

Treatment of Overdosage

In cases of suspected overdose, the possibility of multiple drug involvement should be considered. There is no specific antidote to ziprasidone. In case of acute overdose, establish and maintain an airway and ensure adequate ventilation and oxygenation. Monitor respiratory function, vital signs and blood pressure.

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

Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. If sympathomimetic agents are used for vascular support, adrenaline (epinephrine) and dopamine should not be used, since beta stimulation combined with α1 antagonism associated with ziprasidone may worsen hypotension. Monitor for CNS depression, seizures and extrapyramidal reactions. In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Monitor liver function tests as increased serum liver enzymes may result following overdose.

The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis, therefore emesis is not recommended. Administration of activated charcoal should be considered and is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Receptor Binding Studies

Ziprasidone exhibited high *in vitro* binding affinity for the dopamine D_2 and D_3, the serotonin $5HT_{2A}$, $5HT_{2C}$, $5HT_{1A}$ and $5HT_{1D}$ and α_1 adrenergic receptors (Kis of 4.8, 7.2, 0.4, 1.3, 3.4, 2, and 10 nM, respectively) and moderate affinity for the histamine H1 receptor (Ki=47 nM). Ziprasidone functioned as an antagonist at the D_2, $5HT_{2A}$, and $5HT_{1D}$ receptors, and as an agonist at the $5HT_{1A}$ receptor. Ziprasidone inhibited synaptic reuptake of serotonin and noradrenaline. No appreciable affinity was exhibited for the other receptor/binding sites tested, including the cholinergic muscarinic receptor (IC50>1μM).

The mechanism of action of ziprasidone in the acute control of the agitated psychotic patient is unknown. The mechanism of action of ziprasidone in schizophrenia, as with other drugs having efficacy in schizophrenia, is also unknown, however, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism.

Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of ziprasidone. Ziprasidone's antagonism of histamine H1 receptors may explain the somnolence observed with this drug. Ziprasidone's antagonism of adrenergic α1 receptors may explain the orthostatic hypotension observed with this drug.

Receptor Functional Studies

Ziprasidone has been shown to be an antagonist at both serotonin type 2A ($5HT_{2A}$) and dopamine type 2 (D_2) 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 $5HT_{2C}$ and $5HT_{1D}$ receptors, a potent agonist at the $5HT_{1A}$ receptor and inhibits neuronal reuptake of noradrenaline and serotonin.

Positron Emission Tomography Studies

Receptor blockade, 12 hours after a single oral dose of 40 mg, was greater than 80% for $5HT_{2A}$ and greater than 50% for D_2 using positron emission tomography (PET).

Clinical Trials

Two pivotal, single-blinded, active comparator trials were conducted to compare the effects of ziprasidone IM to IM haloperidol in patients with acute exacerbation of schizophrenia or schizoaffective disorder.

A multi-centre, parallel group study (1) compared ziprasidone IM (N=429) and IM haloperidol (N=138) administered for 1-3 days, followed by oral ziprasidone and haloperidol for another 6 weeks. The IM dosing was 10 mg or 20 mg ziprasidone or 2.5 mg or 5 mg haloperidol, administered at least twice. During the subsequent oral administration, the total daily ziprasidone dose was 80-160 mg and the daily haloperidol dose was 5-20 mg/day.

The other multi-centre, parallel group study (2) compared IM ziprasidone (N=130) and IM haloperidol (N=122) administered for 1-3 days, followed by oral ziprasidone and haloperidol for another 6 weeks. The IM and oral dosing regimens for ziprasidone and haloperidol are the same as the regimens in the other study.

In both studies, male and female subjects aged 18-70 years at the time of randomisation were eligible for inclusion in this study. Subjects had to meet Diagnostic and Statistical Manual (of Mental Disorders) (DSM)-IV criteria for schizophrenia or schizoaffective disorder. Subjects entering hospital (or in patients transferring to a higher dependency unit) within the previous seven days because of acute exacerbation of psychotic symptoms were included. Subjects had to have a minimum score of 40 on the Brief Psychiatric Rating Scale (BPRS) scale (1-7) and agree to receive intramuscular medication for 1-3 days (at least two administrations). Subjects were excluded if they were receiving concurrent treatment with antipsychotic agents at randomisation (within 12 hours prior to randomisation); for depot agents a period of two weeks or one cycle, whichever was the longer, had to occur between last administration and randomisation.

The results for the BPRS from these two studies are presented in the table below; responders were those patients with a Clinical Global Impression - Improvement (CGI-I) score of 1, 2 or 3 (equates to very much improved to improved).

	Study 1		**Study 2**	
	End IM Phase	**End IM/Oral Phase**	**End IM Phase**	**End IM/Oral Phase**
Change from baseline – total BPRS score (ziprasidone vs. haloperidol)	-6.15 vs. -4.13 p=0.0018	-	-7.73 vs. -5.86 p=0.0664	-
95% CI treatment difference – total BPRS score	-3.27, -0.76	-1.86, 3.47 p=0.55	-3.86, 0.13	-3.43, 2.43 p=0.7385
Responder rates	56% ziprasidone 51% haloperidol p=0.4866	74% ziprasidone 75% haloperidol p=0.4840	62% ziprasidone 58% haloperidol p=0.5353	78% ziprasidone 76% haloperidol p=0.5948

Ziprasidone was superior to haloperidol (LOCF on the ITT Analysis Set) in the change from baseline in the total BPRS score at the end of the IM phase in the first study and comparable to haloperidol in the second

study. Ziprasidone was also comparable to haloperidol with respect to responder rates at both the end of the IM and the end of the IM/oral phase in both studies.

Results of a Large Post-Marketing Safety Study (Zodiac Study)

A randomised post approval study of 18,239 patients with observational follow-up for 1 year was conducted to determine whether ziprasidone is associated with an increased risk of non-suicide mortality in patients with schizophrenia, compared to olanzapine. This study, which was conducted in naturalistic clinical practice settings, showed no significant difference in its primary endpoint of the rate of non-suicide mortality between ziprasidone and olanzapine treatments (risk ratio 1.02; 95%CI 0.76-1.39. All cause mortality also did not differ between the two treatment groups (risk ratio 1.01; 95%CI 0.77-1.33).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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. Exposure increases in a dose-related manner and following three days of intramuscular dosing, little accumulation is observed.

Distribution

Ziprasidone is greater than 99% protein bound, binding primarily to albumin and α_1-acid glycoprotein. Twice daily dosing generally leads to attainment of steady state within one to three days. Systemic exposures at steady state are related to dose. Ziprasidone has a volume of distribution of approximately 1.1 L/kg when administered intravenously.

Metabolism

Ziprasidone is extensively metabolised after oral administration with only a small amount excreted in the urine (<1%) 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 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 catalysing the oxidative metabolism of ziprasidone with some potential contribution from CYP1A2. S-methyl-dihydroziprasidone is generated in two steps catalysed 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 biliary excretion and CYP3A4 catalysed metabolism. The sulphoxide is eliminated through renal excretion and by secondary metabolism catalysed by CYP3A4 (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

After ziprasidone is administered intramuscularly, approximately 20% of the dose is excreted in urine and approximately 66% is eliminated in faeces.

Excretion

The mean terminal phase half-life after multiple oral dosing in normal volunteers and schizophrenic patients is between 6 and 10 hours, with a range of individual values from 3 to 18 hours.

The mean terminal half-life on the third day of dosing ranged from 8 to 10 hours. The mean terminal half-life of ziprasidone after intravenous administration is 3 hours. Mean clearance of ziprasidone administered intravenously is 5 mL/min/kg.

The mean terminal half-life of ziprasidone after intramuscular administration of single doses ranges from 2 to 5 hours.

Special Populations

Age and Gender

No clinically significant age- or gender-differences in the pharmacokinetics were observed following oral administration.

Race

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

Smoking

Pharmacokinetic screening of patients treated orally has not revealed any significant pharmacokinetic differences between smokers and non-smokers.

Renal Impairment

Because ziprasidone is highly metabolised, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a major impact on the pharmacokinetics of ziprasidone. The pharmacokinetics of oral ziprasidone following 8 days of 20 mg twice daily dosing were similar among subjects with varying degrees of renal impairment (n=27), and subjects with normal renal function, indicating that dosage adjustment based upon the degree of renal impairment is not required. Ziprasidone is not removed by haemodialysis.

No marked differences in the pharmacokinetics of oral ziprasidone have been observed in patients with decreased kidney function (creatinine clearance >10mL/min). It is unknown whether serum concentrations of the metabolites are increased in these patients.

As SBECD is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function.

Hepatic Impairment

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ziprasidone hydrochloride was tested for genotoxic potential in assays for gene mutation and chromosomal damage. There was a reproducible response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Equivocal results were obtained in both the *in vitro* mammalian cell gene mutation assay and the *in vitro* chromosomal aberration assay in human lymphocytes. Ziprasidone hydrochloride was negative in the *in vivo* chromosomal aberration assay in mouse bone marrow.

Carcinogenicity

Lifetime carcinogenicity studies were conducted with ziprasidone hydrochloride administered in the diet to rats and mice. In rats, there was no evidence of increased tumour incidences at doses up to 12 mg/kg/day, corresponding to systemic exposure (plasma $AUC_{0\text{-}24h}$) similar to that in humans at the maximum recommended dose. In male mice, there was no increase in tumour incidences at doses up to 200 mg/kg/day, corresponding to systemic exposure about 2.5 times that in humans. In female mice, dose-related increases in the incidence of hyperplasia and neoplasia in the pituitary (shown immunohistochemically to be prolactin

producing) and mammary gland were seen at 50 to 200 mg/kg/day, corresponding to systemic exposure about 1 to 4 times greater than that in humans; a no-effect dose level for these effects was not established. Proliferative changes in the pituitary and mammary glands of rodents have been observed following chronic administration of other antipsychotic agents and are associated with increased prolactin concentrations. Although clinical and epidemiological studies have not shown an association between chronic administration of this class of drugs and tumourigenesis in humans, the use of ziprasidone in patients with familial history or previously detected breast cancer should be avoided. Caution should be exercised when considering ziprasidone treatment in patients with pituitary tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sulfobutyl betadex sodium (SBECD),

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products or solvents other than Sterile Water for Injections.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary, store at 2-8 °C (Refrigerate. Do not freeze) for not more than 24 hours.

Store below 30 °C in dry form. Protect from Light.

Keep vial in the original pack until ready to use.

6.5 NATURE AND CONTENTS OF CONTAINER

ZELDOX IM is presented in a single dose vial.

Container type: Clear Type I glass vial.

Pack size: 1 x vial.

Australian Register of Therapeutic Goods (ARTG)

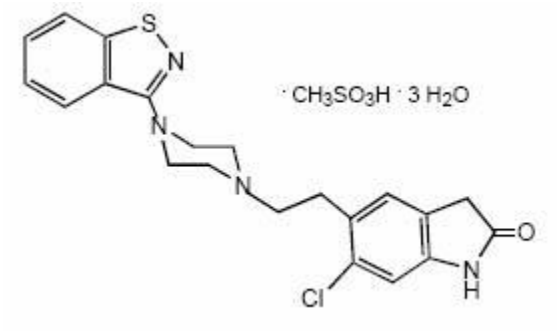
AUST R 408532 – ZELDOX IM ziprasidone (as mesilate) 20 mg powder for injection vial

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Ziprasidone is an antipsychotic agent chemically unrelated to phenothiazine or butyrophenone antipsychotic agents.

The chemical name for ziprasidone mesilate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, methanesulfonate, trihydrate.

Australian Approved Names: Ziprasidone ($C_{21}H_{21}ClN_4OS$) and Ziprasidone mesilate ($C_{21}H_{21}ClN_4OS.CH_3SO_3H.3H_2O$).

The molecular formula of ziprasidone mesilate is $C_{21}H_{21}CIN_4OS.CH_3SO_3H.3H_2O$. Ziprasidone mesilate has a molecular weight of 563.09 and the free base has a molecular weight of 412.94.

Ziprasidone is a white to off-white powder. Ziprasidone mesilate is slightly soluble in methanol (5.0 mg/mL) and water (1.1 mg/mL) and practically insoluble in tetrahydrofuran (0.09 mg/mL). The solubility of ziprasidone mesilate in 30% (w/v) sulfobutyl betadex sodium (SBECD) was determined to be 45 mg/mL.

CAS Number

The CAS Registry Numbers are 146939-27-7 (ziprasidone) and 185021-64-1 (ziprasidone mesilate).

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8 SPONSOR

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Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

9/11/2009

10 DATE OF REVISION

24/08/2023

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
2, 6.1	Removal of Water for Injections
6.5	Addition of the container type, pack size and AUST R number

ZELDOX IM® is a Viatris company trade mark

ZELDOX IM_pi\Aug23/00