AUSTRALIAN PRODUCT INFORMATION

ZELDOX®

(ziprasidone (as hydrochloride monohydrate)) capsule

1 NAME OF THE MEDICINE

Ziprasidone hydrochloride monohydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20 mg, 40 mg, 60 mg or 80 mg of ziprasidone (as hydrochloride monohydrate) as the active ingredient.

Excipients with known effect: sugars as lactose

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

3 PHARMACEUTICAL FORM

ZELDOX 20 mg capsules: No. 4 blue/white hard gelatin capsule, imprinted in black with "VTRS" and "ZDX 20".

ZELDOX 40 mg capsules: No. 4 blue hard gelatin capsule, imprinted in black with "VTRS" and "ZDX 40".

ZELDOX 60 mg capsules: No. 3 white hard gelatin capsule, imprinted in black with "VTRS" and "ZDX 60".

ZELDOX 80 mg capsules: No. 2 blue/white hard gelatin capsule, imprinted in black with "VTRS" and "ZDX 80".

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ZELDOX (ziprasidone) is indicated:

- for the treatment of schizophrenia, related psychoses, prevention of relapse and for maintenance of clinical improvement during continuation therapy;
- as monotherapy for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder.

4.2 DOSE AND METHOD OF ADMINISTRATION

Use of ZELDOX Capsules

For oral use. ZELDOX capsules should be taken with food and swallowed whole without chewing, crushing or opening beforehand.

Schizophrenia

The recommended dose in treatment of schizophrenia is 40 mg twice daily taken with food. Daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg twice daily. Dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days. The maximum recommended dose of 80 mg twice daily may be reached as early as Day 3 of treatment.

Ziprasidone is effective in the treatment of acutely exacerbated patients and in maintaining the clinical improvement during continuation therapy, in patients who have shown an initial treatment response. In maintenance treatment patients should be administered the lowest effective dose. In many cases, a dose of 20 mg twice daily may be sufficient.

Long-term treatment with ziprasidone is effective in the prevention of recurrent exacerbation of the illness, and is associated with an improvement of negative symptoms.

Bipolar Mania

The recommended dose in treatment of acute bipolar mania is 40 mg twice daily taken with food. Daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg twice daily. The maximum recommended dose of 80 mg twice daily may be reached as early as Day 2 of treatment.

Children and Adolescents

Ziprasidone is not approved for use in paediatric patients and should not be used in children and adolescents younger than 18 years of age (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Paediatric Population).

Dosage Adjustment in Renal Impairment

No dosage adjustment is required in patients with impaired renal function (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special Populations, Renal Impairment).

Dosage Adjustment in Hepatic Impairment

In patients with mild to moderate impairment of liver function (Child Pugh A or B) caused by cirrhosis, lower doses should be considered. The serum concentrations after oral administration were 30% higher and the terminal half-life was about 2 hours longer than in normal patients.

A toxicity study in dogs showed intrahepatic cholestasis and elevation of serum ALT and alkaline phosphatase at oral doses producing exposure (plasma AUC) about twice the maximal clinical exposure. There is a lack of experience in patients with severe hepatic insufficiency and therefore, ziprasidone should be used with caution in this group.

Dosage Adjustment in Patients Who Smoke

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

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 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, 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.

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

Some drugs that prolong the QT/QTc interval greater than 500 msec have been associated with the occurrence of torsade de pointes and with sudden unexplained death (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). 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 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. If the QTc interval is >500 msec, then it is recommended that the treatment should be stopped (see Section 4.3 CONTRAINDICATIONS).

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.

Increased Mortality in Elderly Patient 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 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.

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.

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 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 ziprasidone experienced tardive dyskinesia. However, 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.

Rash

In premarketing schizophrenia trials with ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to dose of ziprasidone, although the finding might also be explained by the longer exposure time in the higher dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g. elevated WBCs. Most patients improved promptly with adjunctive treatment with antihistamines or steroids and/or upon discontinuation of ziprasidone, and all patients experiencing these events were reported to recover completely. Upon appearance of rash for which an alternative aetiology cannot be identified, ziprasidone should be discontinued.

Orthostatic Hypotension

Ziprasidone may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of the patients treated with ziprasidone in schizophrenia clinical trials.

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

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 ZELDOX 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/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.

Seizures

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

Hyperprolactinaemia

As with other drugs that antagonise dopamine D2 receptors, ziprasidone elevates prolactin levels in humans. Increased prolactin levels were also observed in animal studies with this compound, and were associated with an increase in mammary gland neoplasia in mice; a similar effect was not observed in rats (see Section 5.3 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.

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.

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.

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 cirrhosis, the serum concentrations after oral administration were 30% higher and the terminal half-life was about 2 hours longer than in normal patients.

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

Therefore, ziprasidone should be used with caution in patients with hepatic impairment.

Use in Renal Impairment

No dosage adjustment is required in patients with impaired renal function (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special Populations, Renal Impairment).

Use in the Elderly

No dosage adjustment is required in elderly patients (65 years and over) for the treatment of schizophrenia.

Ziprasidone has not been systematically evaluated in subjects 65 years and older for the treatment of bipolar mania.

Paediatric Use

Ziprasidone is not approved for use in paediatric patients and should not be used in children and adolescents younger than 18 years of age (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Paediatric Population).

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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. Coadministration with the potent CYP3A4 inhibitor, ketoconazole, did not affect QTc, when compared to ziprasidone alone (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 oestrogen (ethinyl oestradiol 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

Co-administration 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%. The serum concentration of S-methyl-dihydroziprasidone, at the expected T_{max} 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 C_{max} (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 was shown to increase time to copulation in rats at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 160 mg/kg/day on a mg/m^2 basis). Fertility was impaired in rats dosed orally at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis), 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 in rats of dopamine antagonists. Fertility was not impaired when males given 160 mg/kg/day were mated with untreated females, and there were no treatment related findings in the testes of male rats given 200 mg/kg/day (11 times the MRHD on a mg/m^2 basis).

Use in Pregnancy - Category C

In animal studies ziprasidone crosses the placenta in rats and rabbits and demonstrated developmental toxicity, including possible teratogenic effects at doses similar to human therapeutic doses. When ziprasidone was administered to pregnant rabbits during the period of organogenesis, an increased incidence of fetal structural abnormalities (ventricular septal defects and other cardiovascular malformations and kidney alterations) was observed at a dose of 30 mg/kg/day (3 times the MRHD of 160 mg/day on a mg/m^2 basis). There was no evidence to suggest that these developmental effects were secondary to maternal toxicity. The developmental no-effect dose was 10 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis). Studies in rats have not shown adverse effects on embryo-fetal development, other than those associated with maternal toxicity, when ziprasidone was administered during the period of organogenesis at oral doses up to 160 mg/kg/day, respectively (8 times the MRHD of 160 mg/day on a mg/m^2 basis). The incidence of still births was increased when ziprasidone was administered at oral doses of 10 mg/kg/day or greater to rats throughout gestation (0.5 times the MRHD on a mg/m^2 basis); estimated systemic exposure at the no-effect dose for perinatal mortality (5 mg/kg/day) was less than that in humans at the maximum recommended dose. Offspring showed increased postnatal mortality, suppression of growth and delayed development when ziprasidone 40 mg/kg/day was administered to rats orally during gestation and lactation (2 times the MRHD on a mg/m^2 basis). The estimated systemic exposure in dams at the no-effect dose for offspring (5 mg/kg/day) was less than that in humans at the maximum recommended dose.

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 40 mg/kg/day was administered orally to rats during gestation and lactation (2 times the MRHD on a mg/m^2 basis). The estimated systemic exposure in dams at the no-effect dose for offspring (5 mg/kg/day) was less than that in humans at the maximum recommended dose. Patients should not 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)

The table below contains treatment-emergent adverse events which 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**	
	ZELDOX N=1159	**Placebo 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

Extrapyramidal Symptoms (EPS)

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

Body Weight

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

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

QT Interval

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

Dose Dependency of Adverse Events in Short-term, Placebo-Controlled Trials

An analysis for dose response in this 4-study pool revealed an apparent relation of adverse event to dose for the following events: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision.

Vital Sign Changes

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

Paediatric Population

In placebo-controlled clinical trials in bipolar disorder (aged 10-17 years) and schizophrenia (aged 13-17 years), the paediatric safety profile of ziprasidone was similar to the adult profile, except for an increased incidence of sedation and somnolence in paediatric patients.

Ziprasidone is not approved for use in paediatric patients and should not be used in children and adolescents younger than 18 years of age.

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, 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), 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 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 and dopamine should not be used, since beta stimulation combined with α_1 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

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 (K_is of 4.8, 7.2, 0.4, 1.3, 3.4, 2, and 10 nM, respectively) and moderate affinity for the histamine H_1 receptor (K_i=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 (IC_{50}>1µM).

The mechanism of action of ziprasidone, as with other drugs having efficacy in schizophrenia, is 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. As with other drugs having efficacy in bipolar disorder, the mechanism of action of ziprasidone in bipolar disorder isunknown.

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 H_1 receptors may explain the somnolence observed with this drug. Ziprasidone's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Positron Emission Tomography Studies

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

Clinical Trials

Schizophrenia

The efficacy of ziprasidone in the management of the manifestations of psychotic disorders was established in three short-term (4- and 6-week) and one long-term (52 week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia or schizoaffective disorder. Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS), both multi-item inventories of psychopathology traditionally used to evaluate the effects of drug treatment in psychosis.

Another traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for the Assessment of Negative Symptoms (SANS) and the Montgomery-Asberg Depression Rating Scale (MADRS) were employed in some clinical trials.

In the 52-week, placebo-controlled maintenance trial (N=294), ziprasidone doses of 20, 40 and 80 mg twice daily were statistically superior to placebo in the prevention of recurrent exacerbation of the illness, as well as in the BPRS total and psychosis cluster, the CGI, the PANSS total and negative subscale, and Global Assessment of Functioning. Discontinuations due to adverse events were 7-10% in the ziprasidone groups and 15% in the placebo group.

An analysis of the effect of ziprasidone on patients with clinically significant depressive symptoms (MADRS) ≥14 was conducted in two multicentre placebo-controlled studies in acute schizophrenia. A statistically significant improvement versus placebo($p<0.05$) in the MADRS was observed in patients receiving ziprasidone 60 mg twice daily in one study and 80 mg twice daily in another study.

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).

Bipolar Mania

The efficacy of ziprasidone in mania was established in two placebo-controlled, double- blind, 3-week studies which compared ziprasidone with placebo and one double-blind, 12-week study, which compared ziprasidone to haloperidol and placebo. These studies included 850 patients meeting DSM-IV criteria for Bipolar I Disorder with an acute manic or mixed episode with or without psychotic features. Primary rating

instruments used for assessing manic symptoms in these trials were: (1) the Mania Rating Scale (MRS), which is derived from the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-CB) with items grouped as the Manic Syndrome subscale (elevated mood, less need for sleep, excessive energy, excessive activity, grandiosity), the Behaviour and Ideation subscale (irritability, motor hyperactivity, accelerated speech, racing thoughts, poor judgment) and impaired insight; and (2) the Clinical Global Impression – Severity of Illness Scale (CGI-S), which was used to assess the clinical significance of treatment response.

In a 3-week placebo-controlled, double-blind trial (n=210), the dose of ziprasidone was 40 mg twice daily on Day 1 and 80 mg twice daily on Day 2. Titration within the range of 40-80 mg twice daily (in 20 mg twice daily increments) was permitted for the duration of the study. Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score ($p \leq 0.01$).

In a second 3-week placebo-controlled, double blind trial (n=205), the dose of ziprasidone was 40 mg twice daily on Day 1. Titration within the range of 40-80 mg twice daily (in 20 mg twice daily increments) was permitted for the duration of study (beginning on Day 2). Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score ($p \leq 0.01$ and $p \leq 0.001$ respectively).

In the 12-week placebo-controlled, double-blind, double-dummy trial (n=437), patients were randomised to ziprasidone, haloperidol, or placebo in a ratio of 2:2:1. Patients randomised to ziprasidone or haloperidol took their assigned drug for the 12-week study period. Patients randomised to placebo took placebo for the first 3 weeks of treatment and were then switched to ziprasidone for the remaining 9 weeks of the study. During the first 3 weeks of randomised study medication, the dose of ziprasidone was within the range of 40-80 mg twice daily and the dose of haloperidol was within the range of 4-15 mg twice daily. During the last 9 weeks of treatment, drug dosages could be reduced to as low as 20 mg twice daily for ziprasidone and 2 mg twice daily for haloperidol. Ziprasidone was significantly more effective than placebo in reduction of the MRS total score ($p<0.001$) and CGI-S score ($p=0.002$) at Week 3. In ziprasidone treated patients, significant treatment differences were shown in MRS total score at Day 2 ($p=0.001$) and maintained at Day 7 ($p=0.016$) and Day 14 ($p=0.001$) and in CGI-S scores starting at Day 14 ($p<0.001$). Haloperidol was also significantly more effective than placebo in reduction of the MRS total score ($p \leq 0.01$) and CGI-S score ($p \leq 0.01$) at Week 3.

Mean and LS Mean Change in MRS (LOCF): Monotherapy Studies

	Study 1 (3 week)		**Study 2 (3 week)**		**Study 3 (12 week)**		
	ZELDOX N=131	**Placebo N=66**	**ZELDOX N=137**	**Placebo N=65**	**ZELDOX N=176**	**Haloperidol N=170**	**Placebo N=88**
Baseline							
Mean (SD)	27.48 (7.78)	26.67 (6.99)	26.19 (7.19)	26.42 (7.54)	29.57 (8.01)	30.72 (7.36)	31.32 (7.65)
LS Mean	26.74	26.88	27.09	27.22	28.93	30.12	30.67
Change at Last Visit[a]							
Mean (SD)	-12.4 (12.00)	-7.77 (12.91)	-11.12 (11.46)	-5.62 (9.64)	-10.41 (11.07)	-15.93 (10.61)	-6.10 (9.94)
LS Mean	-12.27	-6.66	-11.16	-5.78	-11.35	-16.55	-6.39
LS Mean Diff (95% CI)	-5.61 (-9.26, -1.96)		-5.38 (-8.46, -2.30)		Zip vs Pbo: -4.96 (-7.58, -2.35) Hal vs Pbo: -10.16 (-12.76, -7.55)		
P value	**0.003**		**0.001**		**Zip vs Pbo: <0.001 Hal vs Pbo: <0.01**		

Note: p-values for pairwise comparisons against placebo based on ANCOVA model for post-baseline time points
Key: SD = standard deviation; LOCF = last observation carried forward
[a] Day 21/Week 3 (or early discontinuation)

Mean Change (SD) in CGI-S (LOCF): Monotherapy Studies

	Study 1 (3 week)		Study 2 (3 week)		Study 3 (12 week)		
	ZELDOX	**Placebo**	**ZELDOX**	**Placebo**	**ZELDOX**	**Haloperidol**	**Placebo**
CGI-S							
Baseline	4.89	4.92	4.54	4.60	4.77	4.83	4.97
	(0.87)	(0.73)	(0.64)	(0.79)	(0.79)	(0.75)	(0.79)
Last Visit[a]	-1.29	-0.88	-1.09	-0.43	-0.89	-1.32	-0.51
	(1.51)	(1.61)	(1.29)	(1.40)	(1.16)	(1.15)	(1.06)
P value	**0.008**		**<0.001**		**0.002**	**<0.001**	**-**

Note: p-values for pairwise comparisons against placebo based on ANCOVA model for post-baseline time points
Key: SD = standard deviation; LOCF = last observation carried forward
[a] Day 21/Week 3 (or early discontinuation)

Maintenance of effect over the 12-week period was observed for both ziprasidone and haloperidol treated groups. 92.5% of the subjects who responded (subjects with at least a 50% decrease from baseline in the MRS at any given visit) in the ziprasidone treated group at the end of Week 3 were still in response by Week 12. Subjects in ziprasidone and haloperidol treatment groups had similar percents of responders at each visit through Week 12.

Based on the MADRS derived scores through Week 4-12, more subjects in the haloperidol treatment group (5.0%) switched to depression than subjects in the ziprasidone treatment group.

An additional randomised, placebo-controlled study (n=205) compared the efficacy, tolerability and safety of ziprasidone and placebo in the presence of adjunctive lithium. All patients were either already receiving lithium or initiated treatment with lithium on Day 1. Patients were randomised to either ziprasidone or placebo in a ratio of 1:1. The dose of ziprasidone was 40 mg twice daily on Day 1 and 80 mg twice daily on Day 2, and adjusted within the range 40-80 mg twice daily thereafter. Lithium treatment in patients not already receiving lithium was initiated at 900 mg daily on Day 1. Lithium was dosed as needed thereafter to maintain a serum level of 0.8 to 1.2 mEq/L, but serum levels were not mandatory during the study. Treatment with ziprasidone plus lithium was not more efficacious than placebo plus lithium, based upon the lack of a statistically significant difference in the rate of change in MRS or CGI-S from Baseline to Day 14

The efficacy of ziprasidone when used in combination with mood stabilisers such as lithium, carbamazepine, sodium valproate or lamotrigine has not been established in the treatment of acute mania.

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

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration of multiple doses of ziprasidone with food, peak serum concentrations typically occur 6 to 8 hours post-dose. Ziprasidone demonstrates linear kinetics over the therapeutic dose range of 40-80 mg twice daily in fed subjects. The absolute bioavailability of a 20 mg dose is 60% in the fed state.

Pharmacokinetic studies have demonstrated that the bioavailability of ziprasidone is significantly increased by up to 100% in the presence of food. It is therefore recommended that ziprasidone should be taken with food.

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).

Excretion

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

Mean systemic clearance of ziprasidone administered intravenously is approximately 5 mL/min/kg.

Special Populations

Elderly (>65 years)

There are no clinically significant differences in the pharmacokinetics of ziprasidone in young adults and elderly.

In a multiple-dose (8 days of treatment) study involving 32 subjects, there was no difference in the pharmacokinetics of ziprasidone between elderly (>65 years) and young (18 to 45 years) adult subjects. Additionally, population pharmacokinetic evaluation of patients in controlled trials has revealed no evidence of clinically significant age-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for age are, therefore, not recommended.

Children and Adolescents

Ziprasidone is not approved for use in paediatric patients and should not be used in children and adolescents younger than 18 years of age.

Gender

In a multiple-dose (8 days of treatment) study involving 32 subjects, there was no difference in the pharmacokinetics of ziprasidone between men and women. Additionally, population pharmacokinetic evaluation of patients in controlled trials has revealed no evidence of clinically significant gender-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for gender are, therefore, not recommended.

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 ziprasidone. Dosage modifications for race are, therefore, not recommended.

Smoking

Based on *in vitro* studies utilising human liver enzymes, ziprasidone is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of ziprasidone. Consistent with these *in vitro* results, population pharmacokinetic evaluation 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 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 ziprasidone have been observed in patients with decreased kidney function (creatinine clearance >10 mL/min).

Hepatic Impairment

As ziprasidone is cleared substantially by the liver, the presence of hepatic impairment would be expected to increase the AUC of ziprasidone; a multiple-dose study at 20 mg twice daily for 5 days in subjects (n=13) with clinically significant (Child Pugh Class A and B) cirrhosis revealed an increase in AUC_{0-12} of 13% and 34% in Child Pugh Class A and B, respectively, compared to a matched control group (n=14). A half-life of 7.1 hours was observed in subjects with cirrhosis compared to 4.8 hours in the control group.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ziprasidone 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 was negative in the *in vivo* chromosomal aberration assay in mouse bone marrow.

Carcinogenicity

Lifetime carcinogenicity studies were conducted with ziprasidone 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 $AUC_{0-24\,h}$) 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

Lactose monohydrate, pregelatinised maize starch, magnesium stearate, gelatin, titanium dioxide, TekPrint SW-9008 Black Ink (ID 2328), indigo carmine CI73015 (20 mg, 40 mg and 80 mg capsules only).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

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

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Al/Al blister packs

Pack size: 20 and 60 capsules of individual pack of each strength

6 capsules (2 x 40 mg, 2 x 60 mg, 2 x 80mg) for the composition pack

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 65526 – ZELDOX ziprasidone (as hydrochloride monohydrate) 20mg capsule blister pack

AUST R 65527 – ZELDOX ziprasidone (as hydrochloride monohydrate) 40mg capsule blister pack

AUST R 65528 – ZELDOX ziprasidone (as hydrochloride monohydrate) 60mg capsule blister pack

AUST R 65529 – ZELDOX ziprasidone (as hydrochloride monohydrate) 80mg capsule blister pack

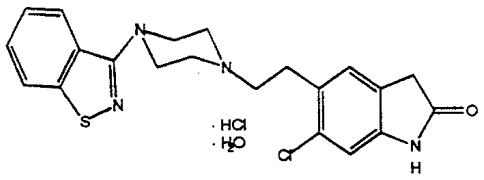
AUST R 134150 – ZELDOX ziprasidone (as hydrochloride monohydrate) 40mg & 60mg & 80mg capsule blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Ziprasidone is an antipsychotic agent for oral administration. It is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents.

Ziprasidone is a white to slightly pink powder.

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

Australian Approved Names: Ziprasidone ($C_{21}H_{21}ClN_4OS$) and Ziprasidone hydrochloride monohydrate ($C_{21}H_{21}ClN_4OS.HCl.H_2O$).

The molecular formula of ziprasidone hydrochloride monohydrate is $C_{21}H_{21}ClN_4OS.HCl.H_2O$. Ziprasidone hydrochloride monohydrate has a molecular weight of 467.42 and the free base has a molecular weight of 412.94.

The measured solubility of ziprasidone hydrochloride is 0.0075% w/v in water at 37°C and 0.0041% w/v in a pH 3.0 buffer at 25°C.

CAS Number

146939-27-7 (ziprasidone) and 138982-67-9 (ziprasidone hydrochloride)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Viatris Pty Ltd

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

29/10/2001

10 DATE OF REVISION

28/04/2025

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes.
3	Updates to product description.
6.5	Updates to pack size and addition of ARTG.

ZELDOX_pi\Apr25/00