

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZELDOX 10 mg/ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains ziprasidone hydrochloride monohydrate equivalent to 10 mg of ziprasidone.

Excipient(s) with known effects:

Each ml contains 1.36 mg methyl parahydroxybenzoate.

Each ml contains 0.17 mg propyl parahydroxybenzoate.

Each ml contains 4.66 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension

White to slightly yellow opaque cherry flavoured aqueous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ziprasidone is indicated for the treatment of schizophrenia in adults.

Ziprasidone is indicated for the treatment of manic or mixed episodes of moderate severity in bipolar disorder in adults and children and adolescents aged 10-17 years (prevention of episodes of bipolar disorder has not been established - see section 5.1).

4.2 Posology and method of administration

Posology

Adults

The recommended dose, in acute treatment of schizophrenia and 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 a maximum of 80 mg twice daily. If indicated, the maximum recommended dose may be reached as early as day 3 of treatment.

It is of particular importance not to exceed the maximum dose as the safety profile above 160 mg/day has not been confirmed and ziprasidone is associated with dose-related prolongation of the QT interval (see sections 4.3 and 4.4).

In maintenance treatment of schizophrenia patients, ziprasidone should be administered at the lowest effective dose; in many cases, a dose of 20 mg twice daily may be sufficient.

Measure the dose as closely as possible using the oral syringe provided. Ziprasidone oral suspension should be administered directly into the mouth. Although the suspension should

be taken with food, it should not be diluted or mixed into any food or beverages prior to administration.

Elderly

A lower starting dose is not routinely indicated but should be considered for those 65 and over when clinical factors warrant.

Patients with renal impairment

No dose adjustment is required in patients with impaired renal function (see section 5.2).

Patients with hepatic impairment

In patients with hepatic insufficiency, lower doses should be considered (see sections 4.4 and 5.2).

Paediatric Population

Bipolar Mania

The recommended dose, in acute treatment of bipolar mania, in paediatric patients (age 10 to 17 years) is a single dose of 20 mg on day 1, with food. Ziprasidone should subsequently be administered with food in two daily divided doses, and should be titrated over 1-2 weeks to a target range of 120-160 mg/day for patients weighing ≥ 45 kg, or to a target range of 60-80 mg/day for patients weighing < 45 kg. Subsequent dosing should be adjusted on the basis of individual clinical status within the range of 80-160 mg/day for patients weighing ≥ 45 kg, or 40-80 mg/day for patients weighing < 45 kg. Asymmetric dosing, with morning doses 20 mg or 40 mg less than evening doses, was permitted in the clinical trial (see sections 4.4, 5.1 and 5.2).

It is of particular importance not to exceed the weight-based maximum dose as the safety profile above the maximum dose (160 mg/day for children ≥ 45 kg and 80 mg/day for children < 45 kg has not been confirmed and ziprasidone is associated with dose-related prolongation of the QT interval (see sections 4.3 and 4.4).

Schizophrenia

The safety and efficacy of ziprasidone in paediatric patients with schizophrenia have not been established (see sections 4.4 and 5.1).

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1. Known QT-interval prolongation. Congenital long QT syndrome. Recent acute myocardial infarction. Uncompensated heart failure. Arrhythmias treated with class IA and III antiarrhythmic medicinal products.

Concomitant treatment with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, arsenic trioxide, halofantrine, levomethadyl acetate, mesoridazine, thioridazine, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, dolasetron mesilate, mefloquine, sertindole or cisapride (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

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

QT interval

Ziprasidone causes a mild to moderate dose-related prolongation of the QT-interval (see sections 4.8 and 5.1).

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

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

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

Paediatric population

Safety and efficacy of ziprasidone in the treatment of schizophrenia in children and adolescents have not been established (see section 5.1).

Neuroleptic malignant syndrome (NMS)

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

Severe Cutaneous Adverse Reactions

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

Other severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, have been reported with ziprasidone exposure.

Severe cutaneous adverse reactions are sometimes fatal. Discontinue ziprasidone if severe cutaneous adverse reactions occur.

Tardive dyskinesia

There is a potential for ziprasidone to cause tardive dyskinesia and other tardive extrapyramidal syndromes after long-term treatment. Patients with bipolar disorder are known to be particularly vulnerable to this category of symptoms. This is more frequent with

increased duration of treatment and increasing age. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of ziprasidone should be considered.

Falls

Ziprasidone may cause somnolence, dizziness, postural hypotension, gait disturbance, which may lead to falls. Caution should be taken when treating patients at higher risk, and a lower starting dose should be considered (e.g. elderly or debilitated patients) (see section 4.2).

Seizures

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

Hepatic Impairment

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

Increased risk of cerebrovascular accidents in the dementia population

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

Zeldox contains methyl parahydroxybenzoate and propyl parahydroxybenzoate

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

Zeldox contains sodium

Zeldox 10 mg/ml oral suspension contains 4.66 mg sodium per each ml, equivalent to 0.23% of the WHO maximum recommended daily intake (RDI) of 2 g sodium for an adult.

Increased Mortality in Elderly people with Dementia

Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death and/or potentially, cerebrovascular adverse events compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Zeldox is not licensed for the treatment of dementia-related behavioural disturbances.

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.

Priapism

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

Hyperprolactinemia

As with other drugs that antagonize dopamine D₂ receptors, ziprasidone may elevate prolactin levels. Disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic and pharmacodynamic studies between ziprasidone and other medicinal products that prolong the QT interval have not been performed. An additive effect of ziprasidone and these medicinal products cannot be excluded, therefore ziprasidone should not be given with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, arsenic trioxide, halofantrine, levomethadyl acetate, mesoridazine, thioridazine, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, dolasetron mesilate, mefloquine, sertindole or cisapride (see section 4.3).

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

CNS medicinal products /alcohol

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

Effect of ziprasidone on other medicinal products

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

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

Lithium - Co-administration of ziprasidone had no effect on the pharmacokinetics of lithium. As ziprasidone and lithium are associated with cardiac conduction changes, the combination may pose a risk for pharmacodynamic interactions including arrhythmias, however, in controlled clinical trials, the combination of ziprasidone plus lithium has not demonstrated an increased clinical risk, compared to lithium alone.

There are limited data on co-medication with the mood stabiliser carbamazepine.

A pharmacokinetic interaction of ziprasidone with valproate is unlikely due to the lack of common metabolic pathways for the two drugs. In a study in patients, the co-administration of ziprasidone and valproate showed that the mean concentrations of valproate were within the therapeutic range as compared to valproate administered with placebo.

Effects of other medicinal products on ziprasidone

The CYP3A4 inhibitor ketoconazole (400 mg/day), which also inhibits p-gp, increased the serum concentrations of ziprasidone by < 40%. The serum concentrations of S-methyldihydroziprasidone and ziprasidone sulphoxide, at the expected T_{max} of ziprasidone, were increased by 55% and 8% respectively. No additional QTc prolongation was observed.

Changes in pharmacokinetics due to co-administration of potent CYP3A4 inhibitors are unlikely to be of clinical importance, therefore no dosage adjustment is required. *In vitro* and animal data suggest that ziprasidone may be a P-glycoprotein (p-gp) substrate. The *in vivo* relevance for humans remains unknown. Since ziprasidone is a substrate of CYP3A4 and induction of CYP3A4 and P-gp is related, co-administration with inducers of CYP3A4 and p-gp such as carbamazepine, rifampin and St John's Wort could cause decreased concentrations of ziprasidone.

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

Antacid - multiple doses of aluminium and magnesium containing antacid or cimetidine have no clinically significant effect on the pharmacokinetics of ziprasidone under fed conditions.

Serotonergic medicinal products

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

Protein binding

Ziprasidone extensively binds to plasma proteins. The *in vitro* plasma protein binding of ziprasidone was not altered by warfarin or propranolol, two highly protein-bound drugs, nor did ziprasidone alter the binding of these drugs in human plasma. Thus, the potential for drug interactions with ziprasidone due to displacement is unlikely.

4.6 Fertility, pregnancy and lactation

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

Pregnancy

No studies have been conducted in pregnant women. As human experience is limited, administration of ziprasidone is not recommended during pregnancy unless the expected benefit to the mother outweighs the potential risk to the foetus.

Antipsychotic class labelling

Neonates exposed to antipsychotics (including ziprasidone) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. Zeldox should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly.

Breast-feeding

There are no adequate and well-controlled studies in lactating women. A single case report found that ziprasidone was detectable in breast milk. Patients should be advised not to breast-feed if they are receiving ziprasidone. If treatment is necessary, breast-feeding should be discontinued.

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Oral ziprasidone has been administered in clinical trials (see section 5.1) to approximately 6500 adult subjects. The most common adverse drug reactions in schizophrenia clinical trials were insomnia, somnolence, headache and agitation. In bipolar mania clinical trials, the most common adverse drug reactions were sedation, headache and somnolence.

The table below contains adverse drug reactions based on controlled schizophrenia and bipolar mania studies.

All adverse drug reactions are listed by class and frequency: *very common* ($\geq 1/10$); *common* ($\geq 1/100$ to $< 1/10$); *uncommon* ($\geq 1/1,000$ to $< 1/100$), *rare* ($\geq 1/10,000$ to $< 1/1,000$); *very rare* ($< 1/10,000$); *not known* (*cannot be estimated from the available data*).

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

System Organ Class	Very Common $\geq 1/10$	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1,000$ to $< 1/100$	Rare $\geq 1/10,000$ to $< 1/1,000$	Frequency not known (cannot be estimated from available data)
Immune system disorders			Hypersensitivity	Anaphylactic reaction	
Infections and infestations		Rhinitis			
Blood and lymphatic system disorders				Lymphopenia, eosinophil count increased	
Endocrine disorders			Hyperprolactinaemia		
Metabolism and nutrition disorders			Increased appetite	Hypocalcaemia	
Psychiatric disorders	Insomnia	Mania, agitation, anxiety, restlessness	Panic attack, nightmare, nervousness, depressive symptom, libido decreased	Hypomania, bradyphrenia, anorgasmia, flat affect	
Nervous system disorders	Somnolence, headache	Dystonia, extrapyramidal disorder, parkinsonism, tardive dyskinesia, dyskinesia, hypertonia,	Syncope, grand mal convulsion, ataxia, akinesia, restless legs syndrome, gait disturbance, drooling, paraesthesia, hypoaesthesia, dysarthria,	Neuroleptic malignant syndrome, serotonin syndrome, facial droop, paresis,	

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from available data)
		akathisia, tremor, dizziness, sedation	disturbance in attention, hypersomnia, lethargy		
Eye disorders		Vision blurred, visual impairment	Oculogyric crisis, photophobia, dry eye	Amblyopia, eye pruritus	
Ear and labyrinth disorders			Vertigo, tinnitus, ear pain		
Cardiac disorders		Tachycardia	Palpitations	Torsade de pointes	
Vascular disorders		Hypertension	Hypertensive crisis, orthostatic hypotension, hypotension	Systolic hypertension, diastolic hypertension, labile blood pressure	Embolism venous
Respiratory, thoracic and mediastinal disorders			Throat tightness, dyspnoea, oropharyngeal pain	Laryngospasm, hiccups	
Gastrointestinal disorders		Vomiting, diarrhoea, nausea, constipation, salivary hypersecretion, dry mouth, dyspepsia	Dysphagia, gastritis, gastro-oesophageal reflux disease, abdominal discomfort, tongue disorder, flatulence	Loose stools	
Skin and subcutaneous tissue disorders		Rash	Urticaria, rash maculo-papular, acne, alopecia	Drug reaction with eosinophilia and systemic symptoms (DRESS), psoriasis, angioedema, dermatitis allergic, swelling face, erythema, rash papular, skin irritation	
Musculoskeletal and connective tissue disorders		Muscle rigidity	Torticollis, muscle spasms, pain in extremity, musculoskeletal discomfort, joint stiffness	Trismus	
Renal and urinary disorders			Urinary incontinence, dysuria	Urinary retention, enuresis	
Pregnancy, puerperium and perinatal conditions				Drug withdrawal syndrome neonatal	
Reproductive system and breast disorders		Male sexual dysfunction	Galactorrhoea, gynaecomastia, amenorrhea	Priapism, erection increased, Erectile dysfunction	

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from available data)
General disorders and administration site conditions		Pyrexia, pain, asthenia, fatigue	Chest discomfort, thirst	Feeling hot	
Investigations		Weight decreased, weight increased	Electrocardiogram QT prolonged, liver function test abnormal	Blood lactate dehydrogenase increased	

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

Ziprasidone causes a mild to moderate dose-related prolongation of the QT interval (see section 5.1). In schizophrenia clinical trials, an increase of 30 to 60 msec was seen in 12.3% (976/7941) of ECG tracings from ziprasidone-treated and 7.5% (73/975) of ECG tracings from placebo-treated patients. A prolongation of >60 msec was seen in 1.6% (128/7941) and 1.2% (12/975) of tracings from ziprasidone and placebo-treated patients, respectively. The incidence of QTc interval prolongation above 500 msec was 3 in a total of 3266 (0.1%) in ziprasidone treated patients and 1 in a total of 538 (0.2%) in placebo treated patients. Comparable findings were observed in bipolar mania clinical trials.

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

Paediatric population

In placebo-controlled bipolar disorder trials (ages 10-17 years), the most frequent adverse reactions (reported with a frequency >10%) were sedation, somnolence, headache, fatigue, nausea, dizziness, vomiting, decreased appetite and extrapyramidal disorder. In a placebo-controlled schizophrenia trial (ages 13-17 years), the most frequent adverse reactions (reported with a frequency >10%) were somnolence and extrapyramidal disorder. The paediatric safety profile of ziprasidone was generally similar to the adult profile. However high incidence of sedation and somnolence was observed in paediatric studies.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via **the national reporting system listed in Appendix V**.

4.9 Overdose

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

The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. There is no specific antidote to ziprasidone.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotic, indole derivatives, ATC code N05AE04

Ziprasidone has a high affinity for dopamine type 2 (D₂) receptors and substantially higher affinity for serotonin type 2_A (5HT_{2A}) receptors. Receptor blockade, 12 hours after a single dose of 40 mg, was greater than 80% for serotonin type 2_A and greater than 50% for D₂ using positron emission tomography (PET). Ziprasidone also interacts with serotonin 5HT_{2C}, 5HT_{1D} and 5HT_{1A} receptors where its affinities for these sites are equal to or greater than its affinity for the D₂ receptor. Ziprasidone has moderate affinity for neuronal serotonin and norepinephrine transporters. Ziprasidone demonstrates moderate affinity for histamine H(1)- and alpha(1)-receptors. Ziprasidone demonstrates negligible affinity for muscarinic M(1)-receptors.

Ziprasidone has been shown to be an antagonist at both serotonin type 2_A (5HT_{2A}) and dopamine type 2 (D₂) receptors. It is proposed that the therapeutic 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 norepinephrine and serotonin.

Further information on clinical trials

Schizophrenia

In a 52 week study, ziprasidone was effective in maintaining the clinical improvement during continuation therapy in patients who showed an initial treatment response: there was no clear evidence for a dose-response relationship amongst the ziprasidone groups. In this study, which included patients with both positive and negative symptoms, ziprasidone's efficacy was demonstrated in both positive and negative symptoms.

The incidence of body weight gain, reported as an adverse event in short term (4-6 week) schizophrenia studies was low and identical in ziprasidone-treated and placebo-treated patients (both 0.4%). In a one-year placebo-controlled 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.

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

Results of a large post-marketing safety study

A randomised post-approval study of 18,239 schizophrenic patients with observational follow-up for 1 year was conducted to determine whether ziprasidone's effect on the QTc interval is associated with an increased risk of non-suicide mortality. This study, which was conducted in naturalistic clinical practice settings, showed no difference in the rate of over-all non-suicide mortality between ziprasidone and olanzapine treatments (primary end-point). The study also showed no difference in secondary end-points of all-cause mortality, mortality due to suicide, mortality due to sudden death, however, a non-significant numerically higher incidence of cardiovascular mortality was observed in the ziprasidone group. A statistically significantly higher incidence of all-cause hospitalisation, mainly due to differences in the number of psychiatric hospitalisations, was also observed in the ziprasidone group.

Bipolar mania

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

The efficacy of ziprasidone in the treatment of Bipolar I Disorder in paediatric patients (10 to 17 years of age) was evaluated in two four-week placebo-controlled trial (n=237) of inpatients or outpatients who met DSM-IV criteria for Bipolar I Disorder manic or mixed episodes and had a Y-MRS score ≥ 17 at baseline. These double-blind, placebo-controlled trials compared flexibly-dosed oral ziprasidone (80-160 mg/day (40-80 mg BID) in two divided doses for patients weighing ≥ 45 kg; 40-80 mg/day (20-40 mg BID) for patients weighing < 45 kg) to placebo. Ziprasidone was administered as a single dose of 20 mg on the first day, then titrated over 1-2 weeks, in two daily doses, to a target range of 120-160 mg/day for patients weighing ≥ 45 kg, or 60-80 mg/day for patients weighing < 45 kg. Asymmetric dosing, with morning doses 20 mg or 40 mg less than evening doses, was permitted. Ziprasidone was superior to placebo in change from baseline to week 4 on the Y-MRS total score in both studies. In this clinical trial, the mean daily doses administered were 119 mg and 69 mg in the patients weighing ≥ 45 kg and < 45 kg, respectively.

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

Paediatric Studies

Bipolar mania

Ziprasidone has been evaluated for safety in 237 paediatric patients (age 10 to 17 years) who participated in multiple-dose, clinical trials in bipolar mania; a total of 31 paediatric patients with Bipolar I Disorder were dosed with oral ziprasidone for at least 180 days.

In a 4-week trial in paediatric patients (10-17 years) with bipolar mania, there were no differences between ziprasidone and placebo patients in the mean change from baseline in body weight fasting glucose, total cholesterol, LDL cholesterol, or triglyceride levels.

The efficacy of ziprasidone in the treatment of Bipolar I Disorder was evaluated in a post marketing study in paediatric patients (n = 171 [safety population]; n = 168 [ITT population]) who met DSM-5 criteria for Bipolar I Disorder (manic or mixed) at baseline. The study compared flexibly-dosed oral ziprasidone (80-160 mg/day [40-80 mg BID] for patients weighing ≥ 45 kg; 40-80 mg/day [20-40 mg BID] for patients weighing < 45 kg) to placebo over a 4-week period. The study demonstrated that ziprasidone was superior to placebo in change from baseline to week 4 on the Y-MRS total score. The study did not observe any relevant differences between ziprasidone and placebo patients in the mean change from baseline in body weight fasting glucose, total cholesterol, LDL cholesterol, or triglyceride levels.

There are no long-term double-blind clinical studies investigating the efficacy and tolerability of ziprasidone in children and adolescents.

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

Schizophrenia

The paediatric schizophrenia program was a short-term, 6-week, placebo-controlled trial (A1281134), followed by a 26-week open-label extension study (A1281135) that was designed to provide information on the efficacy, safety and tolerability of oral ziprasidone (40-80 mg BID with meals) during its long-term administration in adolescent subjects aged 13 to 17 years (inclusive) with schizophrenia. The Zeldox paediatric study in schizophrenia was terminated by Pfizer due to lack of efficacy (see section 4.2).

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. The absolute bioavailability of a 20 mg dose is 60% in the fed state. Pharmacokinetic studies have demonstrated that the bioavailability of ziprasidone is increased by up to 100% in the presence of food. It is therefore recommended that ziprasidone should be taken with food.

In a multiple dose study ziprasidone oral suspension was shown to be bioequivalent to ziprasidone capsules under steady-state conditions. In a single dose administration study, equivalence was demonstrated with regard to AUC. The mean $C_{\max}$ of the oral suspension was reduced by approximately 10-15% as compared with capsules. For the multiple dose study, the associated 90% confidence interval around this mean ratio was (79.6–101.0%).

Distribution:

The volume of distribution is approximately 1.1 L/kg. Ziprasidone is more than 99% protein bound in serum.

Biotransformation and elimination:

The mean terminal half-life of ziprasidone after oral administration is 6.6 hours. Steady state is reached within 1-3 days. Mean clearance of ziprasidone administered intravenously is 5 ml/min/kg. Approximately 20% of the dose is excreted in urine, and approximately 66% is eliminated in faeces.

Ziprasidone demonstrates linear kinetics over the therapeutic dose range of 40 to 80 mg twice daily in fed subjects.

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

Ziprasidone is primarily metabolised by two pathways: reduction and methylation to generate S-methyldihydroziprasidone which accounts for approximately two-thirds of the metabolism, and oxidative metabolism accounting for the other third. *In vitro* studies using human liver subcellular fractions indicate that S-methyldihydroziprasidone is generated in two steps. These studies indicate that the first step is mediated primarily by chemical reduction by glutathione as well as by enzymatic reduction by aldehyde oxidase. The second step is methylation mediated by thiol methyltransferase. *In vitro* studies indicate that CYP3A4 is the major cytochrome P450 catalysing the oxidative metabolism of ziprasidone with a potential minor contribution of CYP1A2.

Ziprasidone, S-methyldihydroziprasidone, and ziprasidone sulphoxide, when tested *in vitro*, share properties which may predict a QTc-prolonging effect. S-methyldihydroziprasidone is mainly eliminated in faeces by biliary excretion with a minor contribution by CYP3A4 catalysed metabolism. Ziprasidone sulphoxide is eliminated through renal excretion and by secondary metabolism catalysed by CYP3A4.

Special populations

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

No clinically significant age- or gender-differences in the pharmacokinetics of ziprasidone has been observed. The pharmacokinetics of ziprasidone in paediatric patients 10 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Consistent with the fact that renal clearance contributes very little to its overall clearance, no progressive increases in ziprasidone exposure were noted when ziprasidone was administered to subjects with varying degrees of renal function. Exposures in subjects with mild (creatinine clearance 30-60 ml/min), moderate (creatinine clearance 10-29 ml/min) and severe impairment (requiring dialysis) were 146%, 87% and 75% those of healthy subjects (creatinine clearance >70 ml/min) following oral administration of 20 mg BID for seven days. It is unknown whether serum concentrations of the metabolites are increased in these patients.

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 2 hours longer than in normal patients. The effect of liver impairment on the serum concentrations of the metabolites is unknown.

5.3 Preclinical safety data

Preclinical safety data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential. In reproductive studies in rat and rabbit, ziprasidone has shown no evidence of teratogenicity. Undesirable effects on fertility and decreased pup weights were observed at doses causing maternal toxicity such as decreased body weight gain. Increased perinatal mortality and delayed functional development of offspring occurred at maternal plasma concentrations extrapolated to be similar to the maximal concentrations in human given therapeutic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water, purified
Xylitol, E 967
Sodium chloride
Silica, colloidal anhydrous
Cherry flavour
Xanthan gum, E 415
Methyl parahydroxybenzoate, E 218
Sodium citrate, E 331
Citric acid, anhydrous, E 330
Polysorbate 80, E 433
Propyl parahydroxybenzoate, E 216

6.2 Incompatibilities

Zeldox oral suspension should not be diluted or mixed into any food or beverages prior to administration.

6.3 Shelf-life

Shelf life of the medicinal product as packaged for sale: 3 years

Shelf life after first opening the bottle: 2 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and content of container

HDPE bottles (60 ml) with polypropylene child-resistant closures and low density polyethylene or high density polyethylene/polyester liners.

Polypropylene oral syringe (8 ml) and polyethylene press-in bottle adaptor. The 8 ml oral syringe is calibrated in 1.0 ml (10 mg) increments.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2024-04-19

[To be completed nationally]