ZELDOX
(Ziprasidone Hydrochloride)

1. NAME OF THE MEDICINAL PRODUCT

ZELDOX

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules containing ziprasidone hydrochloride monohydrate equivalent to 40 and 60 mg ziprasidone.

3. PHARMACEUTICAL FORM

ZELDOX is available as capsules for oral administration:
40 mg – No. 4 blue capsules, marked "Pfizer" and ZDX 40
60 mg – No. 3 white capsules, marked "Pfizer" and ZDX 60

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Schizophrenia

ZELDOX is indicated for the management of schizophrenia and other psychotic disorders, and for maintenance of clinical improvement and prevention of relapse during continuation therapy.[1]

Bipolar Mania

ZELDOX is indicated for the treatment of manic or mixed episodes associated with bipolar disorder, in adults and pediatric patients ages 10 to 17 years[64,65] and as an adjunct to lithium or valproate for the maintenance treatment of bipolar disorder.[88]

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Use of Ziprasidone Capsules

For oral use. Capsules should be taken with food and swallowed whole without chewing, crushing or opening beforehand.[100]

Use in Adults

Schizophrenia and Bipolar Mania

The recommended initial dose is 40 mg twice daily, to be taken with food (See section **5.2 - Pharmacokinetic properties**). 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.[3]

Maintenance Treatment (as an adjunct to lithium or valproate)

Continue treatment at the same dose on which the patient was initially stabilized, within the range of 40-80 mg twice daily with food. Patients should be periodically reassessed to determine the need for maintenance treatment.[88]

Use in Children

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 - Special warnings and precautions for use**, **5.1. Pharmacodynamic properties** and **5.2 - Pharmacokinetic properties**).

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** – **Contraindications** and **4.4 - Special warnings and precautions for use**).

Use in the Elderly

Generally, no dosage adjustment is required in elderly patients (65 years and over).[4]

Use in Renal Impairment

No dosage adjustment is required in patients with renal impairment.[5]

Use in Hepatic Impairment

In patients with mild to moderate hepatic insufficiency, lower doses should be considered. There is a lack of experience in patients with severe hepatic insufficiency and ziprasidone should be used with caution in this group[6] (see section **5.2 - Pharmacokinetic properties**).

Use in Smokers

No dosage adjustment is required in patients who smoke.[7,8]

4.3. CONTRAINDICATIONS

ZELDOX is contraindicated in patients with:

- Known hypersensitivity to ziprasidone or any of the excipients;
- Known QT interval prolongation including congenital long QT Syndrome;[9]

- Recent myocardial infarction;[9]
- Uncompensated heart failure;[9]
- Cardiac arrhythmias requiring treatment with Class IA and III antiarrhythmic drugs[9] (see section **4.4 - Special warnings and precautions for use**).

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

QT Interval

Ziprasidone causes a mild to moderate prolongation of the QT interval.[10]

In the pre-marketing clinical trials database, the incidence of QTc prolongation above 500 msec was 3 in a total of 3266 (0.1%) in ziprasidone-treated patients and 1 in a total of 538 (0.2%) in placebo-treated patients.[11,56]

Some drugs including Class IA and III antiarrhythmics that prolong the QT interval greater than 500 msec have been associated with the rare occurrence of *torsade de pointes*, a life-threatening arrhythmia (See section **4.3 - Contraindications**).

There have been rare post-marketing reports of *torsade de pointes* in patients with multiple confounding risk factors taking ziprasidone. A causal relationship with ziprasidone has not been established.[71]

Ziprasidone should be used with caution in patients with the following risk factors, which can increase the risk for occurrence of this arrhythmia:

- bradycardia;
- electrolyte imbalance;
- concomitant use with other drugs that prolong QT.[12]

If cardiac symptoms suggestive of arrhythmias are observed or reported during treatment, then appropriate cardiac diagnostics should be performed. If the QTc interval is greater than 500 msec, it is recommended that treatment 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.[93]

Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), a potentially fatal complex, has been reported in association with antipsychotic drugs, including ziprasidone.[67,72] 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 must 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 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.[94,95]

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.[94]

Tardive Dyskinesia

There is a potential for ziprasidone to cause tardive dyskinesia and other tardive extrapyramidal syndromes after long-term treatment. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of ziprasidone should be considered.[14]

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.[98]

Seizures

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

CNS Drugs/Alcohol

Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting agents, including alcohol and drugs acting on the dopaminergic and serotonergic systems.[15]

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis have been shown to be at an increased risk of death and/or potentially, cerebrovascular adverse events compared with placebo when treated with some antipsychotic drugs.[86,87,98] Study data with ziprasidone in the treatment of elderly patients with dementia are insufficient to conclude whether or not there is an increased risk of death with ziprasidone versus placebo in this patient population. Ziprasidone is not approved for the treatment of elderly patients with dementia-related psychosis.[75]

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.[90]

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 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.[90]

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Class IA and III Antiarrhythmic Drugs (See sections **4.3 - Contraindications** and **4.4 - Special warnings and precautions for use** – QT Interval)

Concomitant use with other drugs that prolong QT Interval (See section **4.4 - Special warnings and precautions for use** – QT Interval)

CNS Drugs/Alcohol (See section **4.4 - Special warnings and precautions for use** - CNS Drugs/Alcohol)

Effect of Ziprasidone on Other Drugs

Using human liver microsomes, ziprasidone demonstrated no inhibitory effect on CYP1A2, CYP2C9 or CYP2C19.[81] 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*.[82,83,84]

Dextromethorphan – Consistent with *in vitro* results, a study in normal healthy volunteers showed that ziprasidone did not alter the CYP2D6 mediated metabolism of dextromethorphan to its major metabolite, dextrorphan.[16]

Oral Contraceptives – Ziprasidone administration results in no significant change to the pharmacokinetics of estrogen (ethinyl estradiol, a CYP3A4 substrate) or progesterone components.[17]

Lithium – Co-administration of ziprasidone has no effect on the pharmacokinetics of lithium.[18]

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.[19]

Effects of Other Drugs on Ziprasidone

In vitro and animal data suggest that ziprasidone may be a P-glycoprotein (P-gp) substrate. The *in vivo* relevance for humans remains unknown.

Ketoconazole (400 mg/day), a potent inhibitor of CYP3A4, which also inhibits P-gp, produced an increase of approximately 35% in ziprasidone exposure (AUC and C_{max}).[21] Since ziprasidone is a substrate of CYP3A4 and induction of CYP3A4 and P-gp is related, co-administration with inducers of CYP-3A4 and P-gp such as carbamazepine, rifampin and St. John's Wort could cause decreased concentrations of ziprasidone.[93,96] Carbamazepine 200 mg twice daily, an inducer of CYP3A4, produced a decrease of 36% in ziprasidone exposure.[22]

Cimetidine, a nonspecific CYP inhibitor, did not significantly affect ziprasidone pharmacokinetics.[23]

Antacid − Multiple doses of aluminium and magnesium-containing antacids did not affect the pharmacokinetics of ziprasidone.[24]

4.6. FERTILITY, PREGNANCY AND LACTATION

Use in Pregnancy

No studies have been conducted in pregnant women. Women of childbearing potential receiving ziprasidone should therefore be advised to use an appropriate method of contraception. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. Ziprasidone should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus[90] (See section **5.3 - Preclinical safety data**).

Use in Lactation

There are no adequate and well-controlled studies in lactating women. Limited data indicate that ziprasidone is excreted into breast milk at very low levels. Patients should be advised not to breastfeed if they are receiving ziprasidone.[29,99]

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.[98]

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Ziprasidone may cause somnolence. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that ziprasidone does not affect them adversely.

4.8. UNDESIRABLE EFFECTS

Adverse drug reactions reported from clinical trials and post - marketing experience include:

Adverse Drug Reaction Table[97]

System Organ Class	Adverse Drug Reactions
Immune system disorders	Hypersensitivity*†
Endocrine disorders	Hyperprolactinaemia*
Psychiatric disorders	Mania[76]*α; Agitation*; Nervousness; Insomnia[59]; Anxiety; Libido decreased
Nervous system disorders	Neuroleptic malignant syndrome[67]*; Serotonin syndrome (alone or in combination with serotonergic medicinal products)[77]*; Syncope[78]*; Grand mal convulsion; Dystonia[D]; Extrapyramidal disorder*†; Tardive dyskinesia[85]*; Dyskinesia; Ataxia; Hypertonia; Hyperkinesia; Akathisia; Tremor; Somnolence; Speech disorder; Headache; Dizziness; Sedation*; Facial droop[85]*
Eye disorders	Oculogyric crisis[D]; Visual impairment†
Cardiac disorders	*Torsade de pointes*[71]*; Tachycardia[58]*
Vascular disorders	Venous thromboembolism (VTE)[93]*‡; Orthostatic hypotension*†
Respiratory, thoracic and mediastinal disorders	Laryngospasm[D]
Gastrointestinal disorders	Dysphagia[85]*; Vomiting; Constipation; Tongue oedema[85]*†; Nausea; Tongue disorder[D]; Salivary hypersecretion†; Dry mouth; Dyspepsia
Skin and subcutaneous tissue disorders	Drug reaction with eosinophilia and systemic symptoms (DRESS)[94]*; Angioedema[79]*; Rash[60]*
Musculoskeletal and connective tissue disorders	Torticollis[D]; Muscle rigidity
Renal and urinary disorders	Urinary retention; Urinary incontinence[85]*; Urinary hesitation; Enuresis[85]*
Reproductive system and breast disorders	Priapism[80]*; Male sexual dysfunction; Galactorrhoea[67,72]*; Gynaecomastia; Amenorrhea
General disorders and administration site conditions	Asthenia; Malaise; Fatigue*
Investigations	Electrocardiogram QT prolonged[92]*†; Weight decreased*†; Weight increased*†

* ADR identified post-marketing
† MedDRA updated
α hypomania included; frequency not known
D Acute dystonic reactions
‡ Antipsychotic medication class effect

Pediatric Population

In the placebo-controlled clinical trials in bipolar disorder (ages 10-17 years), the most frequent adverse reactions (reported with a frequency >10%) were sedation, somnolence, headache, fatigue, dizziness, nausea, vomiting, and decreased appetite and extrapyramidal disorders. 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 pediatric safety profile of ziprasidone was similar to the adult profile, except for an increased incidence of sedation and somnolence in pediatric patients.[92,101] Ziprasidone was associated with a mild to moderate dose-related prolongation of the QT interval in pediatric clinical trials similar to that seen in the adult population.[92,101]

4.9. OVERDOSE

Experience with ziprasidone overdosage is limited. The largest confirmed single ingestion is 12,800 mg. In this case, extrapyramidal symptoms and a QTc interval of 446 msec (with no cardiac sequelae) were reported.[73] In overdose cases in general, the most commonly reported symptoms are extrapyramidal symptoms, somnolence, tremor, and anxiety.[74]

There is no specific antidote to ziprasidone. In cases of acute overdosage, establish and maintain an airway and ensure adequate ventilation and oxygenation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal, together with a laxative, should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Given the high protein binding of ziprasidone, hemodialysis is unlikely to be beneficial in the treatment of overdose. Close medical monitoring and supervision should continue until the patient recovers.[38]

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Receptor Binding Studies

Ziprasidone has a high affinity for dopamine type 2 (D_2) receptors and substantially higher affinity for serotonin type 2_A ($5HT_{2A}$) receptors. 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 D_2 receptor. Ziprasidone has moderate affinity for neuronal serotonin and norepinephrine transporters. Ziprasidone demonstrates moderate affinity for histamine H_1- and $alpha_1$-receptors. Antagonism at these receptors has been associated with somnolence and orthostatic hypotension, respectively. Ziprasidone demonstrates negligible affinity for muscarinic M_1-receptors. Antagonism at this receptor has been associated with memory impairment.[39]

Receptor Functional Studies

Ziprasidone has been shown to be an antagonist at both serotonin type 2_A ($5HT_{2A}$) and dopamine type 2 (D_2) receptors. It is proposed that the antipsychotic activity is mediated, in part, through this combination of antagonist activities.

Ziprasidone is also a potent antagonist at $5HT_{2C}$ and $5HT_{1D}$ receptors, a potent agonist at the $5HT_{1A}$ receptor and inhibits neuronal reuptake of norepinephrine and serotonin.[40]

Human PET Studies

At 12 hours following a 40 mg oral dose of ziprasidone, receptor blockade was greater than 80% for $5HT_{2A}$ and greater than 50% for D_2 using positron emission tomography (PET).[41]

Further Information from Clinical Trials

In a double-blind comparative study, metabolic parameters including weight, fasting levels of total cholesterol, triglycerides, insulin 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.[61]

Results of a Large Post-Marketing Safety Study

A randomized post-approval study of 18,239 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 in patients with schizophrenia. This study, which was conducted in naturalistic clinical practice settings, showed no difference in the rate of non-suicide mortality between ziprasidone and olanzapine treatments.[89]

Pediatric Studies in Bipolar Disorder

The efficacy of ziprasidone in pediatric patients (10 to 17 years of age) with bipolar disorder was established in two multiple dose, 4-week, placebo-controlled clinical trials in a total of 408 patients, of which 235 patients received ziprasidone and 173 patients received placebo. Ziprasidone was superior to placebo in change from baseline to week 4 on the Y-MRS total score in both studies.[101]

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.

Pediatric Studies in Schizophrenia

Ziprasidone was evaluated in pediatric schizophrenia but the studies were terminated due to lack of efficacy[101].

5.2. PHARMACOKINETIC PROPERTIES

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.[42]

The absolute bioavailability of a 20 mg dose is 60% in the fed state. The absorption of ziprasidone is reduced by up to 50% when ziprasidone is administered under fasting conditions.[43] 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, bioequivalence was demonstrated with regard to AUC. A slightly lower C_{max} was achieved with oral suspension than with capsules.[68]

Twice daily dosing generally leads to attainment of steady - state within three days. Systemic exposures at steady - state are related to dose.[44]

At steady - state, the mean terminal elimination half-life of ziprasidone is about 6.6 hours following oral dosing.[45] Mean systemic clearance of ziprasidone administered intravenously is 7.5 mL/min/kg and the volume of distribution is approximately 1.5 L/kg. Ziprasidone is extensively bound (>99%) to plasma proteins and its binding appears to be independent of concentration.[46]

Ziprasidone is extensively metabolized after oral administration with only a small amount (<1%) excreted in urine or feces (<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-methyldihydroziprasidone.[47] Approximately 20% of the dose is excreted in urine, with approximately 66% being eliminated in feces. Unchanged ziprasidone represents about 44% of total drug-related material in serum.[48]

Ziprasidone is primarily metabolized 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 catalyzing the oxidative metabolism of ziprasidone.[49,91]

Ziprasidone, S-methyldihydroziprasidone, and ziprasidone sulphoxide, when tested *in vitro*, share properties which may predict a QTc-prolonging effect. S-methyldihydroziprasidone is mainly eliminated by fecal excretion and CYP3A4 catalyzed metabolism. The sulphoxide is eliminated through renal extraction and by secondary metabolism catalyzed by CYP3A4.[49]

In a phase I trial, the CYP3A4 inhibitor ketoconazole (400 mg/day) increased the serum concentrations of ziprasidone by <40%. The serum concentration of S-methyldihydroziprasidone, at the expected T_{max} of ziprasidone, was increased by 55% during ketoconazole treatment. No additional QTc prolongation was observed.[50]

No clinically significant differences in the pharmacokinetics of ziprasidone in young and elderly male or female subjects were observed following oral administration.[51]

Pharmacokinetic screening of patients treated orally has not revealed any significant pharmacokinetic differences between smokers and non-smokers.[52,53]

No clinically significant age- or gender-differences in the pharmacokinetics of ziprasidone has been observed. The pharmacokinetics of ziprasidone in pediatric patients 10 to 17 years of age were similar to those in adults after correcting for the differences in body weights.[101]

No marked differences in the pharmacokinetics of oral ziprasidone have been observed in patients with moderate to severe impairments in renal function as compared to subjects with normal renal function.[54] It is unclear whether serum concentrations of the metabolites are increased in these patients.

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

5.3. PRECLINICAL SAFETY DATA

Preclinical safety data on ziprasidone revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential. In reproductive studies in rats and rabbits, ziprasidone has shown no evidence of teratogenicity. Adverse effects on fertility and increased numbers of pups born dead, decreased pup weights and delayed functional development were observed at doses that caused adverse effects suggestive of maternal toxicity (e.g., sedation, decreased body weight gain). Increased perinatal mortality and delayed functional development of offspring occurred at maternal plasma concentrations extrapolated to be similar to the maximal concentrations in humans given therapeutic doses.[55]

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Lactose monohydrate, pregelatinized maize starch, magnesium stearate, gelatin, titanium dioxide, indigotin

6.2. INCOMPATIBILITIES

None known

6.3. SHELF LIFE

48 months

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Storage and Handling

Ziprasidone capsules should be stored at controlled room temperature, 15°C - 30°C (59°F - 86°F).

6.5. HOW SUPPLIED

Blister Strips

ZELDOX (Ziprasidone HCl) is available as 40 mg and 60 mg capsules in aluminum foil/foil blister strips in cartons containing 14 capsules.

6.6. INSTRUCTION FOR USE AND HANDLING

Capsules should be swallowed whole.

Caution:

To be sold on the prescription of a registered medicinal practitioner only.

Avoid exposure to heat and sunlight.

Dosage:

Use as directed by the physician.

Keep all medicines out of the reach of children.

ZELDOX CAP/LPD-PK-08
According to CDS V 19.0 dated 16-April-2021; Supersedes CDS V 18.0 dated 01-October-2020

Marketed by:
Pfizer Pakistan Limited

*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*

7. REFERENCES

1. Clinical Expert Report (CER) (June 1998), Section 4.1.1, p. 11.

2. Paragraph deleted from section 4.1 (Therapeutic indications) per ziprasidone team when IPI was retired (22Sep06): The efficacy of ziprasidone in the treatment of the positive and negative symptoms of schizophrenia was established in four- and six-week placebo- and active-controlled clinical trials of hospitalized patients experiencing an acute exacerbation of the illness. – CER, Section 4.1.1, p. 11 and Section 4.6, p. 26.

3. CER, Section 6.2, p. 56.

4. CER, Section 3.3.4, p.8.

5. CER, Section 3.3.4, p.8.

6. CER, Section 3.3.4, p.8.

7. CER, Section 3.3.6, p. 10.

8. Appendix Z (Population Pharmacokinetics), figs. 10, 24.

9. Cardiovascular MRP-1 Assessment Report Appendix III, p. 13.

10. Cardiovascular MRP-1 Assessment Report Appendix III, pp. 7-13.

11. FDA Psychopharmacological Drugs Advisory Committee, 19 July 2000, Briefing Document for Zeldox® Capsules, pp. 65-69.

12. CPMP/986/96 Points to Consider: The Assessment of The Potential for QT Interval Prolongation by Non-Cardiovascular Medicinal Products, p.2.

13. Statement deleted from section 4.4 (Special warnings and precautions for use) (28 Feb 05): In pre-marketing clinical trials there were no reported cases of NMS in patients receiving ziprasidone. – CER Section 5.6.8, p. 51.

14. CER Section 5.6.1, pp. 41-42.

15. CER Section 3.3.6, p. 10; CER Section 6.1, p. 55.

16. CER Section 3.3.6, p. 10.

17. CER Section 3.3.6, p. 10.

18. CER Section 3.3.6, p. 10.

19. CER Section 3.3.6, p. 10.

20. Paragraph deleted from section 4.5 (Interactions with other medicinal products and other forms of interaction) per ziprasidone team when IPI was retired (22Sep06): Ziprasidone is metabolized by aldehyde oxidase and to a lesser extent by CYP3A4. There are no known clinically relevant

inhibitors or inducers of aldehyde oxidase. – Response to MPA Pharmacokinetic Assessor's Request 07Jul2000, p. 2.

21. CER Sections 3.3.6, pp. 9-10.

22. CER Sections 3.3.6, p. 10.

23. CER Section 3.3.6, p. 9.

24. CER Section 3.3.6, p. 9.

25. Paragraph deleted from section 4.5 (Interactions with other medicinal products and other forms of interaction) per ziprasidone team when IPI was retired (22Sep06): Benztropine, Propranolol, Lorazepam – Pharmacokinetic evaluation of ziprasidone serum concentrations of patients in clinical trials has not revealed any evidence of clinically significant interactions with benztropine, propranolol or lorazepam. – CER Section 3.3.6, p. 10.

26. Paragraph deleted from section 4.5 (Interactions with other medicinal products and other forms of interaction) per ziprasidone team when IPI was retired (22Sep06): Benztropine, Propranolol, Lorazepam – Pharmacokinetic evaluation of ziprasidone serum concentrations of patients in clinical trials has not revealed any evidence of clinically significant interactions with benztropine, propranolol or lorazepam. – Appendix Z, figs. 13, 14, 15, 25.

27. Paragraph deleted from section 4.6 (Pregnancy and lactation) per ziprasidone team when IPI was retired (22Sep06): Reproductive toxicity studies with oral ziprasidone have not shown adverse effects on the reproductive process, other than those secondary to maternal toxicity resulting from an exaggerated pharmacological effect at doses equal to or greater than 17.5 times the maximum recommended human dose (MRHD). – Pharmatoxicological Expert Report (PER) (May 1997) Section 4.7, p. 24.

28. Statement deleted from section 4.6 (Pregnancy and lactation) per ziprasidone team when IPI was retired (22Sep06): There was no evidence of teratogenicity at any dose level (See section 5.3 Preclinical Safety Data). – CER Section 5.6.12, p. 52.

29. CER Section 5.6.12, p.52.

30. Table 5.3.6.2bR Incidence and Severity of Treatment-Emergent Adverse Events (Treatment Related). Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies. Date of Table Generation: 10Jan97.

31. CER Section 5.6.1, p. 41.

32. Geodon NDA Integrated Summary of Safety Data, Section H.5.G, pp. 64-66.

33. Study 128-303, Table 8.1.

34. CER Section 5.4, p. 37.

35. CER Section 5.2, p. 31.

36. Statement deleted from section 4.9 (Overdose) (28Feb05): In the largest overdose reported during pre-marketing clinical trials, a patient experienced sedation, slurred speech and transitory hypertension (200/95 mmHg) following ingestion of a confirmed 3240 mg of oral ziprasidone. – American Journal of Psychiatry 157:5 May 2000, p. 835.

37. Statement deleted from section 4.9 (Overdose) (28Feb05): The maximum observed QTc interval was 478 msec, six hours post-ingestion. No clinically significant changes in cardiac rhythm or function were observed and the patient was discharged following overnight observation in the emergency room. – AEM report #9907409.

38. Written Summary Section 5.9, p. 83.

39. PER Section 2, pp. 1-8.

40. PER Section 2, pp. 1-8.

41. CER Section 3.2.1, p. 5.

42. CER Section 3.3.1, pp. 6-7.

43. Pharmacokinetic MRP-1 Assessment Report, Section 3.1, pp. 3-4.

44. CER Section 3.3.2, p. 7.

45. CER Section 3.3.3, p. 7.

46. CER Section 3.3.2, p. 7.

47. Response to MPA Pharmacokinetic Assessor's Request 07July2000, pp. 1-2.

48. CER Section 3.3.3, p. 7.

49. Response to MPA Pharmacokinetic Assessor's Request 07July2000, pp. 1-2.

50. Pharmacokinetic MRP-1 Assessment Report Amendment II, pp. 32-33.

51. CER Section 3.3.4, p. 8.

52. CER Section 3.3.6, p. 10.

53. Appendix Z (Population Pharmacokinetics), figs. 10, 24.

54. CER Section 3.3.4, p.8.

55. PER Section 4, pp. 16-29.

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