Pfizer **ZELDOX®**

1. NAME OF THE MEDICINAL PRODUCT

ZELDOX 20mg capsules, hard
ZELDOX 40mg capsules, hard
ZELDOX 60mg capsules, hard
ZELDOX 80mg capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard
20 mg - No. 4, blue/white capsules, marked "Pfizer" and ZDX 20
40 mg - No. 4 blue capsules, marked "Pfizer" and ZDX 40
60 mg - No. 3 white capsules, marked "Pfizer" and ZDX 60
80 mg - No. 2 blue/white capsules, marked "Pfizer" and ZDX 80

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Ziprasidone is indicated for the treatment of schizophrenia.

Prescribers should consider the potential of ziprasidone to prolong the QT interval (see Section 4.3 Contraindications and 4.4 Special warnings and precautions for use).

4.2 Posology and method of administration

Adults

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

Elderly

No dosage adjustment is required in elderly patients (65 years and over).

Use in renal impairment

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

Use in hepatic impairment

In patients with hepatic insufficiency, lower doses should be considered. (See Section 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

4.3 Contraindications

Known hypersensitivity to ziprasidone or any of the excipients. Known QTinterval prolongation. Congenital long QT syndrome. Recent acute myocardial infarction. Uncompensated heart failure. Arrhythmias treated with class IA and III antiarrhythmic drugs.

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 mesylate, mefloquine, sertindole or cisapride.

(See Section 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicinal products and other forms of interaction)

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, Contraindications)

QT interval

Ziprasidone causes a mild to moderate dose-related prolongation of the QTinterval (see section 4.8). Ziprasidone should therefore not be given together with medicinal products that are known to prolong the QT-interval (see Section 4.3 Contraindications and 4.5 Interactions with other medicinal products and other forms of interaction). 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 Contraindications).

Children and Adolescents

Safety and efficacy of ziprasidone in children and adolescents has not been evaluated.

Neuroleptic malignant syndrome

In clinical trials there were no reported cases of NMS in patients receiving ziprasidone. Since NMS, a rare but potentially fatal complex, has been reported in association with other antipsychotic drugs, a potential risk of this adverse event during use of ziprasidone cannot be excluded. The management of NMS should include immediate discontinuation of all antipsychotic drugs.

Tardive dyskinesia

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

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 Section 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties).

4.5 Interactions with other medicinal products and other forms of interaction

Pharmacokinetic and pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and these drugs 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 mesylate, mefloquine, sertindole or cisapride. (See Section 4.3 Contraindications)

CNS drugs/alcohol

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

Effect of ziprasidone on other drugs

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 drugs 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.

Effects of other drugs on ziprasidone

The CYP3A4 inhibitor ketoconazole (400mg/day) increased the serum concentrations of ziprasidone by <40%. The serum concentrations of S-methyl-dihydroziprasidone and ziprasidone sulphoxide, at the expected Tmax of ziprasidone, were increased by 55% and 8% respectively. No additional QTc prolongation was observed. Changes in pharmacokinetics due to coadministration of potent CYP3A4 inhibitors are unlikely to be of clinical importance, therefore no dosage adjustment is required.

Carbamazepine therapy, 200mg 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.

4.8 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, Preclinical safety data).

Use in pregnancy

No studies have been conducted in pregnant women. Women of child bearing potential receiving ziprasidone should therefore be advised to use an appropriate method of contraception. As human experience is limited, administration of ziprasidone is not recommended during pregnancy unless the expected benefit to the mother outweighs the potential risk to the foetus.

Use in lactation

It is not known whether ziprasidone is excreted in breast milk. Patients should not breast feed an infant if they are taking ziprasidone. If treatment is necessary, breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Zeldox capsules have been administered in clinical trials to over 5500 subjects. The most common adverse reaction was somnolence. The table below contains adverse events with possible, probable or unknown relationship to ziprasidone which occur at an incidence greater than placebo in short term (4-6 week) fixed dose studies.

Organ system	Very common (>1/10)	Common (>1/100, <1/10)	Uncommon (>1/1000, <1/100)	Rare (>1/10000, <1/1000)
Body as a whole		Asthenia, headache	Pain	Allergic reaction, fever
Cardiovascular			Postural hypotension, tachycardia	Migraine
Digestive		Constipation, dry mouth, dyspepsia increased salivation, nausea, vomiting	Flatulence	Tongue oedema

Organ system	Very common (>1/10)	Common (>1/100, <1/10)	Uncommon (>1/1000, <1/100)	Rare (>1/10000, <1/1000)
Hemic and Lymphatic				Eosinophilia
Metabolic and nutritional			Thirst	Lactic dehydrogenase increase
Musculoskeletal			Joint disorder, leg cramps	Myalgia myasthenia
Nervous	Somnolence	Agitation, akathisia, dizziness, dystonia, extrapyramidal syndrome, hypertonia, tremor	Cogwheel rigidity, paresthesia, speech disorder, tardive dyskinesia,.	Abnormal dreams, abnormal gait, akinesia, ataxia, hallucination, neuropathy, paratysis, vertigo
Respiratory			Rhinitis	
Skin and appendages			Maculopapular rash, rash, urticaria	Psoriasis, skin disorder
Special senses		Abnormal vision		Amblyopia, conjunctivitis, dry eyes
Urogenital				Dysuria, gynaecomastia, impotence, urinary incontinence

Some of the symptoms reported as adverse events may be associated symptoms of uncertying disease.

In short-term and long-term ziprasidone clinical trials, the incidence of 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. 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) 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 placebotreated patients, respectively The incidence of QTc inlerval prolongation above 500msec 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. In long term maintenance treatment in 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 manifestation (e.g. gynaecomastia and breast enlargement) were rare.

4.9 Overdose

Experience with ziprasidone in overdose is limited At the largest confirmed amount, 3240 mg, the only symptoms reported were mild sedation, slurred speech and transitory hypertension (200/95 mmHg) No significant QTc prolongation occurred.

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 arrhyth mias. There is no specific antidote to ziprasidone.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotic, ATC code N05A E04

Ziprasidone has a high affinity for dopamine type 2 (D_2) receptors and substantially higher affinity for serotonin type 2_A ($5HT2_A$) receptors. Receptor blockade, 12 hours after a single dose of 40mg, was greater than 80% for serotonin type 2_A and greater than 50% for D_2 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 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. 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 (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.

Further information on clinical trials

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) 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 1-3kg was observed in ziprasidone-treated patients compared to a 3kg median loss in placebo-treated patients.

In a double-blind comparative 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.

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 to 80 mg twice daily in fed subjects. The absolute bioavailability of a 20 mg dose is 60% in the fed state. The absorption of ziprasidone is reduced by 50% when ziprasidone is administered under fasting conditions.

The mean terminal half-life of ziprasidone after oral administration is 6.6 hours. Mean clearance of ziprasidone administered intravenously is 5ml/min/kg and the volume of distribution is approximately 1.1L/kg. Ziprasidone is more than 99% protein bound in serum. Steady state is reached within 1-3 days.

Ziprasidone is extensively metabolised after oral administration with only a small amount excreted in urine (<1%) or faeces (<4%) as unchanged drug. 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. Approximately 20% of the dose is excreted in urine, and approximately 66% is eliminated in faeces. Unchanged ziprasidone represents about 44% of total drug-related material in serum.

An *in vivo* study suggests that conversion to S-methyl dihydroziprasidone is the major route of metabolism for ziprasidone. *In vitro* studies indicate that this metabolite arises via aldehyde oxidase catalysed reduction, with subsequent S-methylation. Oxidative metabolism, principally via CYP3A4 with potential contribution of CYP1A2, is also involved.

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 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.

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.

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.

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.

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 rats and rabbits, 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 humans given therapeutic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Contents:

Lactose monohydrate, pregelatinised maize starch, magnesium stearate.

- Capsule shell:

Gelatin, titanium dioxide (E171), indigotin (E132) (20 mg, 40 mg, 80 mg capsules).

- Printing ink:

Shellac, ethyl alcohol anhydrous, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, black iron oxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

Product should not be used after the expiry date stated on the outer carton.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister

Ziprasidone capsules are presented in aluminium PVC/PA blisters with aluminium foil lids, in cartons containing 30 capsules.

6.6 Instructions for use and handling

No special requirements

7. DATE OF REVISION OF THE TEXT

May 2002

Manufactured, Packaged and released by Pfizer Manufacturing Deutschland GmbH
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