DATA SHEET

ZELDOX®

Generic Name

Ziprasidone hydrochloride monohydrate equivalent to 20, 40, 60, and 80 mg ziprasidone

PRESENTATION

Capsules

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

USES

Actions

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.

Receptor Functional Studies

Additional preclinical studies were carried out to identify agonist or antagonist effects at receptors in which ziprasidone binds with high to moderate affinity. 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. As with other drugs having efficacy in bipolar disorder, the mechanism of action of ziprasidone in bipolar disorder is unknown.

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. The serotonergic and neuronal reuptake properties of ziprasidone are associated with antidepressant activity. In addition, $5HT_{1A}$ agonism has been associated with anxiolytic effects. Potent antagonism at the $5HT_{2C}$ receptor has been associated with antipsychotic activity.

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).

Pharmacokinetics

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 20mg dose is 60% in the fed state. The absorption of ziprasidone is reduced by 50% when ziprasidone is administered under fasting conditions.

Twice daily dosing generally leads to attainment of steady state within 3 days. Systemic exposures at steady state are related to dose.

At steady-state, the mean terminal elimination half-life of ziprasidone is about 6.6 hours following oral dosing. 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.

Ziprasidone is extensively metabolised after oral administration with only a small amount (<1%) excreted in the urine 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 P450 catalyzing the oxidative metabolism of ziprasidone. S-methyl-dihydroziprasidone is generated in two steps catalyzed 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 faecal excretion and CYP3A4 catalyzed metabolism. The sulphoxide is eliminated through renal extraction and by secondary metabolism catalyzed by CYP3A4.

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-methyl-dihydroziprasidone, at the expected Tmax of ziprasidone, was increased by 55% during ketoconazole treatment. No additional QTc prolongation was observed.

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

Pharmacokinetic evaluation of ziprasidone serum concentrations of patients treated orally has not revealed any significant pharmacokinetic differences between smokers and non-smokers.

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. 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), 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.

Indications

Ziprasidone is indicated for the treatment of acute schizophrenia, and maintenance or continuation therapy.

Ziprasidone is also indicated as a monotherapy for the short term treatment of acute manic or mixed episodes associated with bipolar 1 disorder.

DOSAGE AND ADMINISTRATION

Use in Adults

Schizophrenia

The recommended dose in treatment of schizophrenia is 40 mg twice daily to be taken with food (see **Pharmacokinetics**). 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.

Bipolar Mania

The recommended dose in treatment of bipolar mania is 40 mg twice daily to be taken with food (see **Pharmacokinetics**). 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 2 of treatment.

Use in Children

Safety and effectiveness in children under 18 years have not been established.

Use in the Elderly

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

Use in Renal Impairment

No dosage adjustment is required in patients with renal impairment.

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 (see **Pharmacokinetics**).

Use in Smokers

No dosage adjustment is required in patients who smoke.

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 **Warnings and Precautions**).

WARNINGS AND PRECAUTIONS

QT Interval

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

In the pre-marketing clinical trials database for the oral formulation, 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.

In placebo-controlled schizophrenia trials, oral ziprasidone increased the QTc interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg.

A study directly comparing the QT/QTc prolonging effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. In the first phase of the trial, ECGs were obtained at the time of maximum plasma concentration when the drug was administered alone. 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.

In the first phase of the study, the mean change in QTc from baseline was calculated for each drug, 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 study, the effect of oral ziprasidone on QTc length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg twice daily).

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

Some drugs, including Class IA and III antiarrhythmics that prolong the QT/QTc interval greater than 500 msec have been associated with the occurrence of torsade de pointes and with sudden unexplained death (see **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.

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

Ziprasidone should be used with caution in patients with the following risk factors, which can increase the risk for occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval:

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

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 **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, or syncope, the prescriber should initiate further evaluation, e.g., Holter monitoring may be useful.

Neuroleptic Malignant Syndrome (NMS)

In pre-marketing clinical trials there were no reported cases of NMS in patients receiving ziprasidone. NMS, a potentially fatal complex, has been reported in association with antipsychotic drugs, including ziprasidone. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (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, must be discontinued.

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

As with other antipsychotics, 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.

Increased Mortality in Elderly Patient with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis have been shown to be at an increased risk of death compared with placebo when treated with some antipsychotic drugs. 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.

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.

Hyperglycaemia and Diabetes Mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycaemia or diabetes in patients treated with ziprasidone. Although fewer patients have been treated with ziprasidone, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia related adverse events is not completely understood. However, epidemiological studies, which did not include ziprasidone, suggest an increased risk of treatment emergent hyperglycaemia related adverse events in patients treated with atypical antipsychotics included in these studies. Because ziprasidone was not marketed at the time these studies were performed, it is not known if ziprasidone is associated with this increased risk. Precise risk estimates for hyperglycaemia related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued, however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect medicine.

Rash

In premarketing schizophrenia trials with oral ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to dose of 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 etiology 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.

Hyperprolactinaemia

As with other drugs that antagonise dopamine D_2 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 **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.

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.*

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.*

ADVERSE EFFECTS

In short-term placebo-controlled clinical trials, the frequency of adverse events associated with the use of ziprasidone across the therapeutic dose range are identified below:

>1/100

Hypotension, QT interval prolongation, respiratory disorder (including coryzal symptoms)

The table below contains treatment-emergent adverse events which occurred at an incidence of ≥ 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.

	Percentage of Patients Reporting Event	
Body System/Adverse Event	**Ziprasidone (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 Syndrome	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

Agitation, hypertonia and abnormal vision were also reported in the short-term, placebo controlled clinical trials at an incidence of ≥ 1%.*

The following adverse events occurred in placebo-controlled clinical trials at an incidence of less than 1% and greater than placebo.

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 abnormal, thirst. *Rare:* Chest pain, feeling hot, pyrexia, sluggishness.

Cardiac Disorders - *Uncommon:* Bundle branch block right, palpitation.

Gastrointestinal Disorders - *Uncommon:* Dysphagia, flatulence, gastritis. *Rare:* Gastro-oesaphageal reflux, loose stools.

Blood and Lymphatic System Disorders - *Rare:* Lymphopaenia.

Ear and Labyrinth Disorders - *Uncommon:* Tinnitus. *Rare:* Ear pain, vertigo positional.

Eye Disorders - *Uncommon:* Photophobia. *Rare:* Amblyopia, eye pruritus, visual disturbance.

Investigations - *Uncommon:* Hepatic enzyme increased, increased appetite, heart rate increased. *Rare:* Blood lactic dehydrogenase increased, body temperature increased, electrocardiogram QT corrected interval prolonged, eosinophil count increased, eosinophil count abnormal, hypocalcaemia, liver function test abnormal, pulse increased.

Infections and Infestations - *Uncommon:* Rhinitis.

Musculoskeletal and Connective Tissue Disorders - *Uncommon:* Joint stiffness, muscle cramps, pain in extremity. *Rare:* Arthropathy, musculoskeletal discomfort, trismus.

Nervous System Disorders - *Uncommon:* Ataxia, bradykinesia, cogwheel rigidity, disturbance in attention, dizziness postural, drooling, dysarthria, generalised tonic-clonic seizures, hypokinesia, hypersomnia, hypoaesthesia, lethargy, oculogyric crisis, paraesthesia, tardive dyskinesia, vertigo. *Rare:* Akinesia, paresis, restless legs syndrome, torticollis.

Psychiatric Disorders - *Uncommon:* Anxiety, throat tightness, nightmare;
Rare: Anorgasmia, bradyphrenia, flat affect, panic attack, sleep walking.

Respiratory, Thoracic and Mediastinal Disorders - *Uncommon:* Dyspnoea, sore throat.
Rare: Hiccups.

Renal and Urinary Disorders - *Uncommon:* Dysuria, urinary incontinence.

Reproductive System and Breast Disorders - *Rare:* Erectile dysfunction, erection increased, galactorrhoea, gynaecomastia.

Skin and Subcutaneous Tissue - *Uncommon:* Acne, maculopapular rash, rash, 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 **Warnings and Precautions**).

Prolactin Levels

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

Physical and Psychological Dependence

Ziprasidone has not been systemically studied in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behaviour, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which ziprasidone will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse and such patients should be observed closely for signs of ziprasidone misuse or abuse (e.g. development of tolerance, increases in dose, drug seeking behaviour).

Post-Marketing Experience

The following adverse reactions have been reported during post-marketing experience:

Immune System Disorders: allergic reaction

Psychiatric Disorders: insomnia, mania/hypomania

Nervous System Disorders: dystonia, facial droop, neuroleptic malignant syndrome (see **Warnings and Precautions**); serotonin syndrome (alone or in combination with serotonergic medicinal products); tardive dyskinesia

Cardiac Disorders: tachycardia, torsade de pointes (see **Warnings and Precautions**)

Vascular Disorders: postural hypotension, syncope

Gastrointestinal Disorders: vomiting, dysphagia, swollen tongue

Skin and Subcutaneous Tissue Disorders: angioedema, rash

Renal and Urinary Disorders: enuresis, urinary incontinence

Reproductive System and Breast Disorders: galactorrhea, priapism

INTERACTIONS

Class IA and III Antiarrhythmic Drugs (see **Contraindications** and **Warnings and Precautions - QT Interval).**

Concomitant Use with Other Drugs that Prolong QT Interval. 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 oral ziprasidone alone (see **Warnings and Precautions - QT Interval).**

CNS Drugs/Alcohol (see **Warnings and Precautions - CNS Drugs/Alcohol).**

Effect of Ziprasidone on Other Drugs

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* was at least 1000-fold higher than the free concentration that can be expected *in vivo*. Ziprasidone is unlikely to cause clinically important drug interactions mediated by these enzymes.

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.

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 has no effect on the pharmacokinetics of lithium. 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 Drugs on Ziprasidone

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.

Ketoconazole

400 mg/day, a potent inhibitor of CYP3A4, produced an increase of approximately 35% in ziprasidone exposure (AUC and Cmax). These changes produced by ketoconazole are unlikely to be clinically relevant.

Carbamazepine

200 mg twice daily, an inducer of CYP3A4, produced a decrease of 36% in ziprasidone exposure. These changes produced by carbamazepine are unlikely to be clinically relevant.

Cimetidine

A non-specific CYP inhibitor, did not significantly affect ziprasidone pharmacokinetics.

CNS Medicines

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 antacids did not affect the pharmacokinetics of ziprasidone.

Benztropine, Propranolol and 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.

Pregnancy and Lactation

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). There was no evidence of teratogenicity at any dose level (see **Preclinical Data**).

Use in Pregnancy

Category C*.

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.

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-market 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 as possible and as short as possible.*

Use in Lactation

It is not known whether ziprasidone is excreted in breast milk. Patients should be advised not to breast feed an infant if they are receiving ziprasidone.

Effects on Ability to Drive and Use Machines

As with other psychoactive drugs, 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.

OVERDOSAGE

Experience with ziprasidone in 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. In overdose cases in general, the most commonly reported symptoms are extrapyramidal symptoms, somnolence, tremor, and anxiety.

In cases of suspected overdose, the possibility of multiple drug involvement should be considered. 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.

PHARMACEUTICAL PRECAUTIONS

Ziprasidone capsules have a shelf life of 4 years when stored below 30°C. There are no special requirements for storage. No major incompatibilities are known.

MEDICINE CLASSIFICATION

Presciption Medicine.

PACKAGE QUANTITIES

Ziprasidone Capsules contain ziprasidone hydrochloride monohydrate equivalent to 20, 40, 60, and 80 mg ziprasidone. The capsules also contain lactose monohydrate, pregelatinised maize starch, magnesium stearate, gelatin, titanium dioxide (E171), and indigo carmine (E132) (20 mg, 40 mg and 80 mg capsules only).

Ziprasidone capsules are presented in aluminium foil/foil blister strips in cartons containing 60 capsules. A blister pack containing 6 capsules (2 x 40 mg, 2 x 60 mg, 2 x 80 mg) for the purpose of initial titration is also available.

FURTHER INFORMATION

Clinical Trial Data

Schizophrenia

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 hospitalised patients experiencing an acute exacerbation of the illness.

In a 52-week placebo-controlled clinical trial of chronic stable inpatients ziprasidone was significantly effective versus placebo in the prevention of relapse of schizophrenia. Ziprasidone demonstrated continuing improvement in primary negative symptoms and in global (psychological, social and occupational) functioning in this study of inpatient population over a 52-week period.

An analysis of the effect of ziprasidone on patients with clinically significant depressive symptoms, defined as ≥14 on the Montgomery-Asberg Depression Rating Scale (MADRS), was conducted in two multicenter placebo-controlled studies in acute schizophrenia. A statistically significant improvement versus placebo ($p<0.05$) in the MADRS was observed in these two studies in patients receiving 60 mg and 80 mg twice daily.

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 known effect on the QTc interval (see **Warnings and Precautions**) is associated with an increase risk of non-suicide mortality. This study, which was conducted in naturalistic clinical practice settings, showed no difference in its primary endpoint of the rate of non-suicide mortality between ziprasidone and olanzapine treatments.

Bipolar Mania

The efficacy of ziprasidone in bipolar 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 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 coprimary or key secondary efficacy variable in these studies. Ziprasidone treatment (40-80 mg twice daily, 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.

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

General

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.

Preclinical Data

Preclinical trial data 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 number of pups born dead, decreased pup weights and delayed functional development were observed at doses that caused maternal toxicity (e.g. sedation and 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.

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DATE OF PREPARATION

27 January 2012

* Please note changes in Data Sheet