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SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ZIPSID 20 mg

Ziprasidone hydrochloride 20 mg capsule

ZIPSID 40 mg

Ziprasidone hydrochloride 40 mg capsule

ZIPSID 60 mg

Ziprasidone hydrochloride 60 mg capsule

ZIPSID 80 mg

Ziprasidone hydrochloride 80 mg capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **ZIPSID 20 mg** capsule contains 20 mg ziprasidone hydrochloride monohydrate.

Each **ZIPSID 40 mg** capsule contains 40 mg ziprasidone hydrochloride monohydrate.

Each **ZIPSID 60 mg** capsule contains 60 mg ziprasidone hydrochloride monohydrate.

Each **ZIPSID 80 mg** capsule contains 80 mg ziprasidone hydrochloride monohydrate.

Excipients:

Contains sugar: lactose monohydrate and sucrose.

ZIPSID 20 mg contains 17,2 mg lactose monohydrate and 10 mg sucrose per capsule.

ZIPSID 40 mg contains 34,4 mg lactose monohydrate and 20 mg sucrose per capsule.

ZIPSID 60 mg contains 51,6 mg lactose monohydrate and 30 mg sucrose per capsule.

ZIPSID 80 mg contains 68,8 mg lactose monohydrate and 40 mg sucrose per capsule.

Excipients:

For a full list of excipients, see section 6.1

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3. PHARMACEUTICAL FORM

Capsule.

ZIPSID 20 mg: Blue/White, size 4, hard gelatin capsules imprinted in Black ink with “CL62” on cap and “20 mg” on the body containing pale pink colored powder.

ZIPSID 40 mg: Blue/Blue, size 2, hard gelatin capsules imprinted in Black ink with “CL63” on cap and “40 mg” on the body containing pale pink colored powder.

ZIPSID 60 mg: White/White, size 1, hard gelatin capsules imprinted in Black ink with “CL64” on cap and “60 mg” on the body containing pale pink colored powder.

ZIPSID 80 mg: Blue/White, size 0, hard gelatin capsules imprinted in Black ink with “CL65” on cap and “80 mg” on the body containing pale pink colored powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZIPSID is indicated in the treatment of acute exacerbations and in maintaining the clinical improvement during continuation therapy in patients with schizophrenia.

4.2 Posology and method of administration

Posology:

Adults

The recommended initial **ZIPSID** dose 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 of 80 mg twice daily may be reached as early as day 3 of treatment.

Use in the elderly

There is only limited clinical information in the elderly. Caution should be exercised when **ZIPSID** is administered in the elderly.

Patients with renal impairment:

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No dosage adjustment is required in patients with impaired renal function.

Patients with hepatic impairment:

In patients with mild to moderate hepatic insufficiency, lower doses should be considered. There is lack of experience in patients with severe hepatic insufficiency and **ZIPSID** should be used with caution in this group.

Use in smokers

No dosage adjustment is required in patients who smoke.

Paediatric population

The safety and efficacy of **ZIPSID** in children below the age of 18 years have not been established.

Method of administration

ZIPSID is given orally with food.

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. Dysrhythmias treated with class IA and III antidysrhythmic medicines.

Concomitant treatment with medicines that prolong the QT interval, such as Class IA and III antidysrhythmics, dofetilide, sotalol, quinidine, chlorpromazine, droperidol, probucol, tacrolimus, arsenic trioxide, halofantrine, levomethadyl acetate, mesoridazine, thioridazine, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, dolasetron mesilate, mefloquine, sertindole or cisapride (see sections 4.4 and 4.5).

Pregnancy and lactation, as teratogenicity has been demonstrated in animal studies (see section 4.6).

The safety and efficacy of ZIPSID has not been evaluated in children under the age of 18 years.

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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 section 4.8 and 5.1).

Ziprasidone should not be given together with medicines that are known to prolong the QT-interval (see sections 4.3 and 4.5). In addition, doctors should be alert to the identification of other medicines that have been consistently observed to prolong the QT interval. These medicines should not be prescribed with **ZIPSID**. Caution is advised in patients with significant bradycardia. Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for malignant dysrhythmias 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 dysrhythmias 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 under the age of 18 years 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 ziprasidone. The management of NMS should include immediate discontinuation of all antipsychotic medicines.

Severe Cutaneous Adverse Reactions

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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. 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.

Suicide

Close supervision of high-risk patients for suicide should accompany **ZIPSID** therapy.

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).

ZIPSID containing lactose

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As the capsule contains the excipient lactose (see section 6.1), patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Increased risk of cerebrovascular accidents in the dementia population

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen 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. **ZIPSID** should be used with caution in patients with risk factors for stroke.

Increased Mortality in Elderly people with Dementia

Elderly people with dementia who are treated with antipsychotics are at 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.

ZIPSID 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 ziprasidone. This adverse reaction did not appear to be dose-dependent and did not correlate with the duration of treatment.

Hyperprolactinemia

Ziprasidone may elevate prolactin levels. Disturbances such as galactorrhoea, amenorrhoea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density.

Hyperglycaemia and diabetes mellitus

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Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar non-ketotic coma or death, has been reported in patients treated with ziprasidone.

Patients with an established diagnosis of diabetes mellitus who are started on ziprasidone 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 ziprasidone should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with ziprasidone should undergo fasting blood glucose testing.

In some cases, hyperglycaemia has resolved when ziprasidone was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

4.5 Interaction with other medicines and other forms of interaction

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

CNS medicines/alcohol

Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting medicines (including medicines acting on the dopaminergic and serotonergic systems) and alcohol.

Effect of ziprasidone on other medicines

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

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indicated that ziprasidone may be a modest inhibitor of CYP2D6 and CYP3A4. However, it is unlikely that ziprasidone will affect the pharmacokinetics of medicines 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 dysrhythmias, 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 medicines.

Effects of other medicines on ziprasidone

The CYP3A4 inhibitor ketoconazole (400 mg/day), which also inhibits P-glycoprotein (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, rifampicin and St John´s Wort could cause decreased concentrations of ziprasidone.

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

Cimetidine, a non-specific CYP inhibitor, did not significantly alter the pharmacokinetics of 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.

Pharmacokinetic screening of patients in clinical trials has not revealed any evidence of clinically significant interactions with propranolol or lorazepam.

Pharmacokinetic studies have demonstrated that the bioavailability of ziprasidone is significantly increased in the presence of food. It is therefore recommended that **ZIPSID** should be taken with food.

Serotonergic medicines

There have been reports of serotonin syndrome temporally associated with the therapeutic use of ziprasidone in combination with other serotonergic medicines 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 medicines, nor did ziprasidone alter the binding of these medicines in human plasma. Thus, the potential for medicine interactions with ziprasidone due to displacement is unlikely.

4.6 Fertility, pregnancy and lactation

ZIPSID is contraindicated in pregnancy and lactation (see section 4.3).

Women of childbearing potential

Women of childbearing potential receiving **ZIPSID** should be advised to use an appropriate method of contraception.

Pregnancy

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Safety of use in pregnancy has not been established.

Lactation

Safety of use during lactation has not been established.

Neonates

Neonates exposed to antipsychotic medicines 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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the reported safety profile

The most frequent adverse reactions were insomnia, somnolence, headache and agitation.

Tabulated summary of adverse events

System organ class	**Frequency**	**Undesirable effect**
Infections and infestations	Frequent	Rhinitis
Blood and lymphatic system disorders	Less frequent	Lymphopenia, Eosinophil count increase
Immune system disorders	Less frequent	Hypersensitivity, anaphylactic reaction
Endocrine disorders	Less frequent	Hyperprolactinaemia
Metabolism and nutrition disorders	Less frequent	Appetite increase, hypocalcaemia
Psychiatric disorders	Frequent	Insomnia, mania, agitation, anxiety, restlessness

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	Less frequent	Panic attack, nightmare, nervousness, depressive symptom, libido decreased, hypomania, bradyphrenia, anorgasmia, flat affect
Nervous system disorders	Frequent	Somnolence, headache, dystonia, extrapyramidal disorder, parkinsonism, tardive dyskinesia, dyskinesia, hypertonia, akathisia, tremor, dizziness, sedation
	Less frequent	Syncope, grand mal convulsion, ataxia, akinesia, restless legs syndrome, gait disturbance, drooling, paraesthesia, hypoaesthesia, dysarthria, disturbance in attention, hypersomnia, lethargy, Neuroleptic malignant syndrome, serotonin syndrome, facial droop, paresis
Eye disorders	Frequent	Vision blurred, visual impairment
	Less frequent	Oculogyric crisis, photophobia, dry eye, amblyopia, eye pruritus
Ear and labyrinth disorders	Less frequent	Vertigo, tinnitus, ear pain
Cardiac disorders	Frequent	Tachycardia
	Less frequent	Palpitations, Torsade de pointes
Vascular disorders	Frequent	Hypertension
	Less frequent	Hypertensive crisis, orthostatic hypotension, hypotension, systolic hypertension, diastolic hypertension, labile blood pressure
	Frequency unknown	Embolism venous

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Respiratory, thoracic and mediastinal disorders	Less frequent	Throat tightness, dyspnoea, oropharyngeal pain, laryngospasm, hiccups
Gastrointestinal disorders	Frequent	Vomiting, diarrhoea, nausea, constipation, salivary hypersecretion, dry mouth, dyspepsia.
	Less frequent	Dysphagia, gastritis, gastro-oesophageal reflux disease, abdominal discomfort, tongue disorder, flatulence, loose stools
Skin and subcutaneous tissue disorders	Frequent	Rash
	Less frequent	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	Frequent	Muscle rigidity
	Less frequent	Torticollis, muscle spasms, pain in extremity, musculoskeletal discomfort, joint stiffness, trismus
Renal and urinary disorders	Less frequent	Urinary incontinence, dysuria, urinary retention, enuresis
Pregnancy, puerperium and perinatal conditions	Less frequent	Drug withdrawal syndrome neonatal
Reproductive and breast disorders	Frequent	Male sexual dysfunction
	Less frequent	Galactorrhoea, gynaecomastia, amenorrhea, priapism, erection increased, erectile dysfunction
General disorders and	Frequent	Pyrexia, pain, asthenia, fatigue

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administration site conditions	Less frequent	Chest discomfort, thirst, feeling hot
Investigations	Frequent	Weight decreased, weight increased
	Less frequent	Electrocardiogram QT prolonged, liver function test abnormal, blood lactate dehydrogenase increased

Description of selected adverse reactions

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

The incidence of tonic clonic seizures and hypotension was less frequent.

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

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

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

Treatment

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Treatment is symptomatic and supportive. The possibility of multiple medicine involvement should be considered. 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 dysrhythmias. There is no specific antidote to ziprasidone. Given the high protein binding of ziprasidone, haemodialysis is unlikely to be beneficial in treatment of overdose. Close monitoring and supervision should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

Category and Class: A 2.6.5 Central nervous system depressants – Tranquilisers (Miscellaneous structures).

Pharmacotherapeutic group: Antipsychotic, indole derivatives

ATC code: N05AE04

5.1 Pharmacodynamic properties

Ziprasidone is an atypical antipsychotic medicine.

Ziprasidone has a high affinity for dopamine type 2 (D_2) 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 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 therapeutic activity is mediated, in part, through this combination of antagonist activities. Ziprasidone is also a potent antagonist at $5HT_{2C}$ and $5HT_{1D}$

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receptors, a potent agonist at the 5HT1A receptor and inhibits neuronal reuptake of norepinephrine and serotonin.

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, while absorption is halved in the fasting 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.

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-methyl-dihydroziprasidone. 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-methyldihydro ziprasidone 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-methyldihydro ziprasidone is generated in two steps. These studies indicate

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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-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.

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.

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 twice daily 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.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contains polyethylene glycol 6000, lactose monohydrate, sodium starch glycollate, ammonium chloride, sucrose and sodium lauryl sulfate.

Hard gelatin capsule for **ZIPSID 20 mg**, **ZIPSID 40 mg** and **ZIPSID 80 mg** contain FD & C blue 2 (CI no. 73015), titanium dioxide, gelatin and sodium lauryl sulfate and black edible printing ink.

Hard gelatin capsule for **ZIPSID 60 mg** contains titanium dioxide, gelatin and sodium lauryl sulfate and black edible printing ink.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months from the date of manufacture.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep the blisters in the carton until required for use.

Keep the HDPE container tightly closed.

Store in the original package in order to protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

1) Blister Pack:

Capsules are packed in cold form laminate OPA /Alu foil /PVC as forming material, and plain aluminum foil/heat seal lacquer as lidding materail.

Pack size 14’s, 20’s, 30’s, 50’s, 56’s, 60’s or 100’s capsules.

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2) HDPE Container Pack

Capsules are packed in round, white HDPE container with screw neck with white child-resistant polypropylene or continuous thread closure with pulp and heat seal liner.

Pack size 60's, 100's or 300's capsules

Not all pack sizes are marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office Block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

To be allocated

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated

10. DATE OF REVISION OF THE TEXT

To be advised.

VR