SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

GEODON® 20 mg Capsules

GEODON® 40 mg Capsules

GEODON® 60 mg Capsules

GEODON® 80 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each GEODON 20 mg, 40 mg, 60 mg and 80 mg capsule contains ziprasidone hydrochloride monohydrate equivalent to 20 mg, 40 mg, 60 mg and 80 mg ziprasidone, respectively.

Contains sugar (lactose monohydrate).

Excipients with known effect

Each 20 mg capsule contains 66,10 mg lactose monohydrate.

Each 40 mg capsule contains 87,83 mg lactose monohydrate.

Each 60 mg capsule contains 131,74 mg lactose monohydrate.

Each 80 mg capsule contains 175,66 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

GEODON 20 mg: No. 4 blue/white locking type hard gelatine capsule, imprinted in black with “Pfizer” and “ZDX 20”.

GEODON 40 mg: No. 4 blue locking type hard gelatine capsule, imprinted in black with “Pfizer” and “ZDX 40”.

GEODON 60 mg: No. 3 white locking type hard gelatine capsule, imprinted in black with “Pfizer” and “ZDX 60”.

GEODON 80 mg: No. 2 blue/white locking type hard gelatine capsule, imprinted in black with “Pfizer” and “ZDX 80”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Schizophrenia

GEODON 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

Use in adults

The recommended initial 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.

Special populations

Use in the elderly

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

Use in renal impairment

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

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 GEODON should be used with caution in this group.

Use in smokers

No dosage adjustment is required in patients who smoke (see section 5.2).

Paediatric population

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

Method of administration

GEODON capsules are for oral use.

Capsules should be taken with food and swallowed whole without chewing, crushing or opening beforehand because it may affect the absorption of the medicine.

4.3 Contraindications

GEODON is contraindicated in patients with:

- Known hypersensitivity to ziprasidone or to any of the excipients of GEODON.
- Known QT-interval prolongation including congenital or acquired long QT syndrome.
- Recent myocardial infarction.
- Uncompensated heart failure.
- Cardiac dysrhythmias requiring treatment with Class IA and III anti-dysrhythmic medicines (see section 4.4).
- Pharmacokinetic/pharmacodynamic studies between GEODON and other medicines that prolong the QT interval have not been performed. An additive effect of GEODON and other medicines that prolong the QT interval cannot be excluded. Therefore, GEODON should not be given with dofetilide, sotalol, quinidine, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus. GEODON is also contraindicated with medicines that have demonstrated QT prolongation as one of their pharmacodynamic effects (see section 4.4).
- Pregnancy and lactation, as teratogenicity has been demonstrated in animal studies (see section 4.6).
- The safety and efficacy of GEODON has not been evaluated in children under the age of 18 years.

4.4 Special warnings and precautions for use

QT interval

GEODON use should be avoided in combination with other medicines that are known to prolong the QT_c interval (see sections 4.3 and 4.5). Additionally, medical practitioners should be alert to the identification of other medicines that have been consistently observed to prolong the QT_c interval. Such medicines should not be prescribed with GEODON. GEODON should also be

avoided in patients with congenital long QT syndrome and in patients with a history of cardiac dysrhythmias (see section 4.3*).*

A study directly comparing the QT/QT_c prolonging effect of oral GEODON with several other medicines 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 medicine was administered alone. In the second phase of the trial, ECGs were obtained at the time of maximum plasma concentration while the medicine was co-administered with an inhibitor of the CYP4503A4 metabolism of the medicine.

In the first phase of the study, the mean change in the mean QT_c from baseline was calculated for each medicine, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QT_c from baseline for GEODON ranged from approximately 9 to 14 msec greater than for four of the comparator medicines (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 GEODON on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg twice daily).

In placebo-controlled trials, oral GEODON increased the mean QT_c interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. 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 GEODON treatment. Persistently prolonged QT_c intervals may also increase the risk of further prolongation and dysrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, GEODON should be avoided in patients with histories of significant cardiovascular illness e.g. QT prolongation, recent acute myocardial infarction, uncompensated heart failure or cardiac dysrhythmia (see section 4.3*). GEODON should be discontinued in patients who are found to have persistent QT_c measurements > 500 msec.

For patients taking GEODON who experience symptoms that could indicate the occurrence of Torsade de Pointes e.g. dizziness, palpitations, or syncope, the medical practitioner should

initiate further evaluation e.g. Holter monitoring may be useful. There have been post-marketing reports of Torsade de Pointes in patients with multiple confounding risk factors taking GEODON. A causal relationship with GEODON has not been established.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicines. 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 GEODON and preventive measures undertaken.

Neuroleptic malignant syndrome (NMS)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal complex has been reported in association with GEODON. The management of NMS should include immediate discontinuation of all antipsychotic medicines, including GEODON.

Severe cutaneous adverse reactions

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported with GEODON 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 GEODON exposure.

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

Tardive dyskinesia

Although in clinical trials the incidence of treatment emergent tardive dyskinesia was comparable in patients receiving GEODON and placebo, the risk of tardive dyskinesia may increase with long-term exposure. Therefore, if signs or symptoms of tardive dyskinesia appear in a patient on GEODON, a dose reduction or discontinuation of GEODON should be considered. These symptoms can temporarily deteriorate or even arise after discontinuation of treatment.

Falls

GEODON 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 GEODON therapy.

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 compared with placebo when treated with some atypical antipsychotic medicines. GEODON is not approved for the treatment of elderly patients with dementia-related psychosis.

Cardiovascular disease

Safety and effectiveness in patients with cardiovascular disease have not been established (see section 4.3).

Priapism

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

Hyperprolactinaemia

As with other medicines that antagonise dopamine D2 receptors, GEODON may elevate prolactin levels. Disturbances such as galactorrhoea, amenorrhoea, gynaecomastia and impotence have been reported with prolactin-elevating medicines. Long-standing hyperprolactinaemia when associated with hypogonadism may lead to decreased bone density.

Hyperglycaemia and diabetes mellitus

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

Patients with an established diagnosis of diabetes mellitus who are started on GEODON 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 GEODON should be monitored for symptoms of hyperglycaemia including polydipsia,

polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with GEODON should undergo fasting blood glucose testing.

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

Contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Class IA and III anti-dysrhythmics – See sections 4.3 and 4.4.

Concomitant use with other medicines that prolong QT interval – See sections 4.4 and 4.8.

CNS medicines/alcohol

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

Effect of GEODON on other medicines

Using human liver microsomes, GEODON demonstrated no inhibitory effect on CYP1A2, CYP2C9 or CYP2C19. The concentration of GEODON required to inhibit CYP2D6 and CYP3A4 *in vitro* is at least 1 000-fold higher than the free concentration that can be expected *in vivo*. GEODON is unlikely to cause clinically important medicine interactions mediated by these enzymes.

Dextromethorphan

The pharmacokinetics and metabolism of dextromethorphan, a CYP2D6 substrate, was unaffected by GEODON.

Oral contraceptives

GEODON administration resulted in no significant change to the pharmacokinetics of estrogen (ethinylestradiol, a CYP3A4 substrate), or progesterone components.

Lithium

Co-administration of GEODON has no effect on the steady state or renal clearance of lithium.

Protein binding

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

Effect of other medicines on GEODON

GEODON is metabolised 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 GEODON exposure (AUC and C_{max}). These changes produced by ketoconazole are unlikely to be clinically relevant.

Other inhibitors of CYP3A4 would be expected to have similar effects.

In vitro data indicate that GEODON is a P-glycoprotein (P-gp) substrate. The *in vivo* relevance is unknown. Co-administration with inducers of CYP3A4 and P-gp such as carbamazepine, rifampicin and St John´s Wort could cause decreased concentrations of GEODON. Carbamazepine 200 mg twice daily, an inducer of CYP3A4, produced a decrease of 36 % in GEODON exposure. These changes produced by carbamazepine are unlikely to be clinically relevant.

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

Antacid

Multiple doses of aluminium- and magnesium-containing antacid did not affect the pharmacokinetics of GEODON.

In addition, 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 GEODON is significantly increased in the presence of food. It is therefore recommended that GEODON should be taken with food.

Serotonergic medicines

In isolated cases, there have been reports of serotonin syndrome temporally associated with the therapeutic use of GEODON 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

GEODON is not recommended in pregnancy and lactation (see section 4.3).

Safety in pregnancy and lactation has not been demonstrated – teratogenicity was demonstrated in animal studies (see section 4.3).

Women of childbearing potential

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

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.

Breastfeeding

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

4.7 Effects on ability to drive and use machines

GEODON may cause somnolence. Patients likely to drive or operate other machines should therefore be cautioned appropriately.

4.8 Undesirable effects

Summary of the safety profile

GEODON capsules have been administered in clinical trials to approximately 6 500 subjects. The most common adverse reactions in schizophrenia clinical trials were sedation and akathisia. In other clinical trials, the most common adverse reactions were sedation, akathisia, extrapyramidal disorder and

dizziness.

Tabulated summary of adverse reactions

The table below contains adverse events based on combined short-term (4 – 6 week), fixed dose, schizophrenia studies and short-term (3 week), flexible dose studies with a probable or possible relationship to treatment with GEODON and which occur at an incidence greater than placebo.

All adverse reactions are listed by class and frequency: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 and < 1/1 000); very rare (< 1/10 000). The adverse reactions listed below may also be associated with the underlying disease and/or concomitant medicines.

MedDRA System Organ Class	**Frequency**	**Adverse reactions**
Infections and infestations	Rare	Rhinitis
Metabolism and nutrition disorders	Uncommon	Increased appetite
	Rare	Hypocalcaemia
Psychiatric disorders	Very common	Insomnia
	Common	Restlessness, anxiety
	Uncommon	Nightmare, nervousness, libido decreased
	Rare	Panic attack, depressive symptom, bradyphrenia, flat affect, anorgasmia
Nervous system disorders	Very common	Somnolence, headache
	Common	Dystonia, akathisia, extrapyramidal disorder, parkinsonism (including cogwheel rigidity, bradykinesia, hypokinesia), tremor, dizziness, dyskinesia, hypertonia
	Uncommon	Generalised tonic clonic seizures, drooling, ataxia, dysarthria, disturbance in attention, hypersomnia, hypoaesthesia, paraesthesia, lethargy
	Rare	Paresis, akinesia, restless legs syndrome
Blood and lymphatic system	Rare	Lymphopenia

disorders		
Cardiac disorders	Uncommon	Palpitations
Eye disorders	Common	Vision blurred, visual impairment, abnormal vision
	Uncommon	Oculogyric crisis, photophobia
	Rare	Amblyopia, visual disturbance, eye pruritus, dry eyes
Ear and labyrinth disorders	Uncommon	Vertigo, tinnitus
	Rare	Ear pain
Vascular disorders	Uncommon	Hypertensive crisis, hypertension, hypotension
	Rare	Systolic hypertension, diastolic hypertension, labile blood pressure
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea, sore throat
	Rare	Laryngospasm, hiccups
Gastrointestinal disorders	Common	Nausea, vomiting, constipation, dyspepsia, dry mouth, salivary hypersecretion
	Uncommon	Diarrhoea, gastritis, gastrointestinal discomfort, tongue disorder, flatulence
	Rare	Gastroesophageal reflux, loose stools
Skin and subcutaneous tissue disorders	Uncommon	Urticaria, rash macula-papular, acne
	Rare	Psoriasis, dermatitis allergic, alopecia, swelling face, erythema, rash papular, skin irritation
Musculoskeletal and connective tissue disorders	Common	Muscle rigidity
	Uncommon	Torticollis, musculoskeletal discomfort, muscle cramp, pain in extremity, joint stiffness
	Rare	Trismus

Renal and urinary disorders	Rare	Urinary retention, dysuria
Reproductive system and breast disorders	Common	Male sexual dysfunction
	Uncommon	Gynaecomastia
	Rare	Erectile dysfunction, increased erection
General disorders and administration site conditions	Common	Asthenia
	Uncommon	Chest discomfort, gait abnormal, pain, thirst
	Rare	Pyrexia, feeling hot
Investigations	Uncommon	Increased hepatic enzyme
	Rare	Liver function test abnormal, blood lactate dehydrogenase increased, eosinophil count increased

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

Other findings

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

A low incidence of body weight gain and loss has been reported during clinical trials.

Post-marketing experience

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

MedDRA System organ class	**Adverse reactions**
Immune system disorders	Hypersensitivity
Endocrine disorders	Hyperprolactinaemia
Psychiatric disorders	Mania/hypomania, agitation
Nervous system disorders	Syncope, facial weakness, neuroleptic malignant syndrome (see section 4.4), serotonin syndrome (alone or in combination with serotonergic medicines), sedation, tardive dyskinesia (see section 4.4), facial droop

Cardiac disorders	Tachycardia, Torsade de Pointes (see section 4.4 – QT interval)
Vascular disorders	Orthostatic hypotension, venous thromboembolism (VTE) (see section 4.4)
Gastrointestinal disorders	Dysphagia, tongue oedema
Skin and subcutaneous tissue disorders	Angioedema, rash, drug reaction with eosinophilia and systemic symptoms (DRESS)
Renal and urinary disorders	Enuresis, urinary incontinence
Reproductive system and breast disorders	Priapism, galactorrhoea, amenorrhoea
General disorders and administration site conditions	Fatigue
Investigations	Electrocardiogram QT prolonged, weight decreased, weight increased

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

Experience with GEODON overdosage is limited. The largest confirmed single ingestion is 12 800 mg. In this case, extrapyramidal symptoms and a QT_c 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, 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. Given the high protein binding of GEODON, haemodialysis is unlikely to be beneficial in the treatment of overdose. Close medical monitoring and supervision should continue until the patient recovers. There is no specific antidote to GEODON.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.6.5 Central nervous system depressants: Tranquillisers (Miscellaneous structures)

Mechanism of action

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 ($5HT2_A$) receptors. Ziprasidone also interacts with serotonin $5HT_{2C}$, $5HT1_D$ 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 at 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.

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.

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.

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

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

The absolute bioavailability of a 20 mg dose is 60 % in the fed state, while absorption is halved in the fasting state.

There are no clinically significant differences in the pharmacokinetics of ziprasidone in young and elderly, male or female subjects.

Distribution

Ziprasidone is greater than 99 % protein bound. Twice daily dosing generally leads to attainment of steady state after 1 to 3 days. Systemic exposures at steady state are related to dose. Ziprasidone has a volume of distribution of approximately 1,5 L/kg when administered intravenously.

Biotransformation

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

Ziprasidone is primarily metabolised by two pathways: reduction and methylation to generate S-methyldihydroziprasidone which accounts for approximately two-thirds of the metabolism, and oxidative metabolism accounting for the other third. *In vitro* studies using human liver subcellular fractions indicate that S-methyldihydroziprasidone is generated in two steps. These studies indicate that the first step is mediated primarily by chemical reduction by glutathione as well as by enzymatic reduction by aldehyde oxidase. The second step is methylation mediated by thiol methyltransferase. *In vitro* studies indicate that CYP3A4 is the major cytochrome P450 catalysing the oxidative metabolism of ziprasidone. Ziprasidone, S-methyl-dihydroziprasidone, and ziprasidone sulphoxide, when tested *in vitro*, share properties which may predict a QT_c prolonging effect. S-methyl-dihydroziprasidone is mainly eliminated by faecal excretion and CYP3A4 catalysed metabolism. The sulphoxide is eliminated through renal extraction and by secondary metabolism catalysed 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 T_{max} of ziprasidone, was increased by 55 % during ketoconazole treatment. No additional QT_c prolongation was observed.

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

Elimination

The mean terminal phase half-life of ziprasidone after multiple dosing of normal volunteers and schizophrenic patients was 6,6 hours and 9,8 hours respectively, in the range 3 to 18 hours. Mean systemic clearance of ziprasidone administered intravenously is approximately 7,5 mL/min/kg. No marked differences in the pharmacokinetics of oral ziprasidone have been observed in patients with decreased kidney function (creatinine clearance > 10 mL/min). 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 cirrhosis, 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 serum concentrations of the metabolites is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Lactose monohydrate

Magnesium stearate

Pregelatinised maize starch

Capsule shells

Gelatine

Titanium dioxide

Printing ink

Indigotin/indigo carmine (20 mg, 40 mg and 80 mg)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

GEODON capsules are available in the following containers:

Blister strips (PVC/foil) containing 14, 20, 30, 50, 56, 60 or 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Upjohn South Africa (Pty) Ltd

85 Bute Lane

Sandton

2196

South Africa

Tel.: +27(0)11 320 6000/0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

GEODON 20 mg: 32/2.6.5/0584

GEODON 40 mg: 32/2.6.5/0585

GEODON 60 mg: 32/2.6.5/0586

GEODON 80 mg: 32/2.6.5/0587

9. DATE OF FIRST AUTHORISATION

02 April 2004

10. DATE OF REVISION OF THE TEXT

09 May 2022

BOTSWANA: S2

GEODON 20 mg – Reg. No.: BOT0701000

GEODON 40 mg – Reg. No.: BOT0701001

GEODON 60 mg – Reg. No.: BOT0701002

GEODON 80 mg – Reg. No.: BOT0701003