SCHEDULING STATUS:

S5 (GEODON IM 20 mg/ml Powder for Solution for Injection)

S1 (PFIZER WATER FOR INJECTIONS)

PROPRIETARY NAME AND DOSAGE FORM:

GEODON® IM 20 mg/ml Powder for Solution for Injection (vials)

WATER FOR INJECTIONS (ampoules)

COMPOSITION:

Each single-use vial contains a lyophile of ziprasidone mesylate complexed with sulphobutyl ether β-cyclodextrin sodium. After reconstitution with 1,2 ml water for injection, each ml contains ziprasidone mesylate trihydrate equivalent to 20 mg ziprasidone.

Excipients: Sulphobutyl ether β-cyclodextrin sodium.

Each ampoule of PFIZER WATER FOR INJECTIONS contains an extractable volume of 1,2 ml sterile water for injections.

PHARMACOLOGICAL CLASSIFICATION:

A 2.6.5 Central nervous system depressants: Miscellaneous structures

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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 oral 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 at histamine H_1- and $alpha_1$-receptors. Ziprasidone demonstrates negligible affinity for muscarinic M_1-receptors.

Ziprasidone has been shown to be an antagonist at both serotonin type 2_A ($5HT_{2A}$) and dopamine type 2 (D_2) receptors. It is proposed that the antipsychotic activity is mediated, in part, through this combination of antagonist activities. Ziprasidone is also a potent antagonist at $5HT_{2C}$ and $5HT_{1D}$ receptors, a potent agonist at the $5HT_{1A}$ receptor and inhibits neuronal reuptake of norepinephrine and serotonin.

Pharmacokinetic properties:

The bioavailability of ziprasidone administered intramuscularly is 100 %. After intramuscular administration of single doses, peak serum concentrations typically occur at approximately 30 – 60 minutes post-dose. The mean half-life ($t_{1/2}$) ranges from approximately 2 to 5 hours. Exposure increases in a dose-related manner and following 3 days of intramuscular dosing, little accumulation is observed. Mean systemic clearance of ziprasidone administered intravenously is 5 ml/min/kg and the volume of distribution is approximately 1,1 L/kg.

Ziprasidone is more than 99 % protein bound in serum.

Ziprasidone is extensively metabolised after oral administration with only a small amount excreted in urine (< 1 %) or faeces (< 4 %) as unchanged drug.

Ziprasidone is primarily cleared via three proposed metabolic routes to yield four major circulating metabolites, benzisothiazole piperazine (BITP) sulphoxide, BITP sulphone, ziprasidone sulphoxide and S-methyl-dihydroziprasidone. Approximately 20 % of the dose is excreted in urine, and approximately 66 % is eliminated in faeces. Unchanged ziprasidone represents about 44 % of total drug-related material in serum.

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

Ziprasidone, S-methyl-dihydroziprasidone, and ziprasidone sulphoxide, when tested *in vitro,* share properties that may predict a QT_c-prolonging effect. S-methyl-dihydroziprasidone is mainly eliminated in faeces presumably by biliary excretion with a minor contribution by CYP3A4 catalysed metabolism. Ziprasidone sulphoxide is eliminated through renal excretion and by secondary metabolism catalysed by CYP3A4.

Pharmacokinetic screening of patients treated orally has not revealed any significant pharmacokinetic differences between smokers and non-smokers.

No clinically significant age- or gender-differences in the pharmacokinetics were observed following oral administration.

No marked differences in the pharmacokinetics of oral ziprasidone have been observed in patients with decreased renal 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.

INDICATIONS:

GEODON intramuscular is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with GEODON is appropriate and who need intramuscular antipsychotic medication for rapid control of the agitation.

CONTRAINDICATIONS:

GEODON is contraindicated in patients with:

Known hypersensitivity to ziprasidone or any of the excipients.

Known QT interval prolongation including congenital long QT syndrome.

Recent myocardial infarction.

Uncompensated heart failure.

Cardiac arrhythmias treated with Class IA and III anti-arrhythmic medicines (see WARNINGS AND SPECIAL PRECAUTIONS and SIDE EFFECTS).

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 WARNINGS AND SPECIAL PRECAUTIONS).

Pregnancy and lactation, as teratogenicity has been demonstrated in animal studies.

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

WARNINGS AND SPECIAL PRECAUTIONS:

QT interval:

GEODON use should be avoided in combination with other medicines that are known to prolong the QT_c interval (see CONTRAINDICATIONS and INTERACTIONS). Additionally, physicians 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 arrhythmias (see CONTRAINDICATIONS). 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 CYP450A4 metabolism of the medicine.

In the first phase of the study, the mean change in the 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 BD).

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 futher prolongation and arrhythmia, 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 arrhythmia (see CONTRAINDICATIONS*)*. 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 physician 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.

Elderly (> 65 years):

Elderly patients have not been included in clinical trials in sufficient numbers. Thus, no recommendations as regards dosing could be given and intramuscular treatment in these patients is not recommended.

Cardiovascular disease:

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

Seizures:

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

Suicide:

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

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 medication, 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 drug discontinuation should be considered. These symptoms can temporarily deteriorate or even arise after discontinuation of treatment.

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.

Effects on ability to drive and use machines:

Administration of GEODON results in somnolence. Patients should be instructed not to drive or operate machines until this effect has resolved.

INTERACTIONS:

Interaction with other medicines and other forms of interaction:

Class IA and III anti-arrhythmics – see CONTRAINDICATIONS and WARNINGS AND SPECIAL

PRECAUTIONS.

Concomitant use with other medicinal products that prolong QT interval – see WARNINGS AND SPECIAL PRECAUTIONS.

CNS drugs/alcohol:

Given the primary CNS effects of GEODON, 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.

Effect of GEODON on other medicines:

All interaction studies have been conducted with oral GEODON.

An *in vivo* study with dextromethorphan showed no marked inhibition with CYP2D6 at plasma concentrations 50 % lower than those obtained after 40 mg GEODON twice daily. *In vitro* data indicated that GEODON may be a modest inhibitor of CYP2D6 and CYP3A4. However, it is unlikely that GEODON will affect the pharmacokinetics of drugs metabolised by these cytochrome P450 isoforms to a clinically relevant extent.

Oral contraceptives – GEODON administration resulted in no significant change to the pharmacokinetics of oestrogen (ethinyl oestradiol, a CYP3A4 substrate) or progesterone components.

Lithium – Co-administration of GEODON had no effect on the pharmacokinetics of lithium.

Effects of other medicines on GEODON:

The CYP3A4 inhibitor ketoconazole (400 mg/day) increased the serum concentrations of GEODON by < 40 %. The serum concentrations of S-methyl-dihydroziprasidone and ziprasidone sulphoxide, at the expected T_{max} of GEODON, were increased by 55 % and 8 % respectively. No additional QT_c prolongation was observed. Changes in pharmacokinetics due to co-administration of potent CYP3A4 inhibitors are unlikely to be of clinical importance.

Carbamazepine therapy, 200 mg b.i.d. for 21 days, resulted in a decrease of approximately 35 % in the exposure to GEODON.

Antacid – multiple doses of aluminium and magnesium containing antacid did not affect the pharmacokinetics of GEODON.

PREGNANCY AND LACTATION:

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

Women of child-bearing potential receiving GEODON should use an appropriate method of contraception.

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.

DOSAGE AND DIRECTIONS FOR USE:

GEODON IM is for intramuscular use only.

Treatment with the intramuscular formulation should only be used in patients where treatment with an oral formulation is considered to be inappropriate.

Use in adults:

The recommended dose is 10 mg – 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every 2 hours. Some patients may require an initial dose of 20 mg, which can be followed by a further dose of 10 mg after 4 hours. Thereafter, doses of 10 mg may be given every 2 hours up to a maximum daily dose of 40 mg. Intramuscular administration of GEODON for more than 3 consecutive days has not been studied.

If long-term therapy is indicated, oral GEODON capsules, up to 80 mg twice daily, should replace the intramuscular administration as soon as possible.

Use in children:

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

Use in the elderly:

Safety and effectiveness in the elderly (65 years and over) have not been established. Treatment with intramuscular injection is not recommended to these patients (see WARNINGS AND SPECIAL PRECAUTIONS and SIDE EFFECTS).

Use in renal impairment:

GEODON intramuscular injection should be administered with caution in patients with impaired renal function (see Pharmacokinetic properties).

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 (see Pharmacokinetic properties).

Use in smokers:

No dosage adjustment is required in patients who smoke (see Pharmacokinetic properties).

Reconstitution:

The contents of the vial should be reconstituted by introduction of 1,2 ml of the supplied WATER FOR INJECTIONS, affording a concentration of 20 mg GEODON per ml, and shaking until complete dissolution has occurred (approximately one minute). Only clear solutions, free of visible particles, should be used. Only one dose (0,5 ml corresponding to the 10 mg dose, or 1 ml corresponding to the 20 mg dose), should be withdrawn from each vial and the remainder discarded.

This product does not contain an antimicrobial preservative. Chemical and physical in-use stability of the reconstituted product has been demonstrated for 24 hours up to 25 °C and 7 days at 2 – 8 °C. However, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 – 8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Incompatibilities:

This medicinal product must NOT be mixed with other medicinal products or solvents except WATER FOR INJECTIONS.

SIDE EFFECTS:

GEODON IM has been administered in clinical trials to over 1 000 subjects. The table below contains adverse events with possible, probable or unknown relationship to in flexible dose phase 2/3 trials. The most common reactions were injection site pain, nausea, somnolence and dizziness.

Organ system	**Very common (>1/10)**	**Common (>1/100, < 1/10)**	**Uncommon (>1/1 000, < 1/100)**	**Rare (>1/10 000, < 1/1 000)**
Body as a whole		Injection site	Injection site	

		pain, asthenia, headache	reaction, flu syndrome	
Cardiovascular		Hypertension, postural hypotension	Bradycardia, hypotension, vasodilatation, tachycardia	
Digestive		Diarrhoea, nausea	Anorexia, dry mouth, vomiting	
Nervous		Somnolence, dizziness, akathisia	Extrapyramidal syndrome, agitation, aphasia, cogwheel rigidity, dystonia, insomnia, personality disorder, psychosis, speech disorder, vertigo	
Respiratory			Laryngismus	
Skin and appendages			Sweating	

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

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

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

Blood pressure:

Dizziness, tachycardia and postural hypotension are not unusual in patients following intramuscular administration of GEODON. Single cases of hypertension have also been reported. Caution should be exercised, particularly in ambulatory patients.

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

Nervous system disorders: Neuroleptic malignant syndrome.

Skin and subcutaneous tissue disorders: Allergic reaction, rash, drug reaction with eosinophilia and systemic symptoms (DRESS).

Cardiac disorders: Torsade de pointes.

Reproductive system and breast disorders: Galactorrhoea.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Experience with GEODON overdosage is limited. With oral dosing, 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 acute overdosage, establish and maintain an airway and ensure adequate ventilation and oxygenation. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdosage may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. There is no specific antidote to GEODON.

IDENTIFICATION:

GEODON 20 mg/ml Powder for Solution for Injection: A vial containing a white to off-white powder. The reconstituted product is a clear and practically particle-free solution.

WATER FOR INJECTIONS: A clear colourless solvent.

PRESENTATION:

A carton containing 1 clear glass vial of GEODON IM 20 mg/ml Powder for Solution for Injection, and 1 clear glass ampoule of WATER FOR INJECTIONS.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Protect from light. Keep the container in the outer carton. Do not freeze.

This product does not contain an antimicrobial preservative. Chemical and physical in-use stability of the reconstituted product has been demonstrated for 24 hours up to 25 °C and 7 days at 2 – 8 °C. However, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 – 8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions. The reconstituted solution should be protected from light. Keep out of reach of children.

REGISTRATION NUMBERS:

GEODON IM 20 mg/ml: 36/2.6.5/0478

PFIZER WATER FOR INJECTIONS: 36/34/0479

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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85 Bute Lane

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

02 February 2007

BOTSWANA: S2

Reg. No.: BOT0701004