SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

GEODON® IM 20 mg/mL Powder for solution for injection (vials)

2. QUALITATIVE AND QUANTITATIVE 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.

Sugar free.

Sodium free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

GEODON IM 20 mg/mL: A vial containing a white to off-white powder. The reconstituted product is a clear and practically particle-free solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

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 IM 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.

Special populations

Elderly population

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 section 4.4).

Renal impairment

GEODON IM injection should be administered with caution in patients with impaired renal function (see section 5.2).

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 IM should be used with caution in this group (see section 5.2).

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

For intramuscular use only. Intravenous administration must be avoided.

For instructions for reconstitution, see section 6.6.

4.3 Contraindications

GEODON IM 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 dysrhythmias treated with Class IA and III anti-dysrhythmic medicines (see sections 4.4).
- Pharmacokinetic/pharmacodynamic studies between GEODON IM and other medicines that prolong the QT interval have not been performed. An additive effect of GEODON IM and other medicines that prolong the QT interval cannot be excluded. Therefore, GEODON IM 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 IM 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 IM injection has not been evaluated in children under the age of 18 years.

4.4 Special warnings and precautions for use

QT interval

GEODON IM use should be avoided in combination with other medicines that are known to prolong the QT_c interval (see section 4.3 and section 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 IM. GEODON IM 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 IM 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 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 IM 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 IM 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 IM 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 IM 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 IM 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 IM should be discontinued in patients who are found to have persistent QT_c measurements > 500 msec.

For patients taking GEODON IM 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 IM. A causal relationship with GEODON IM 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.

Neuroleptic malignant syndrome (NMS)

Neuroleptic malignant syndrome (NMS), a potentially fatal complex has been reported in association with GEODON IM. The management of NMS should include immediate discontinuation of all antipsychotic medication, including GEODON IM.

Severe cutaneous adverse reactions

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

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

Cardiovascular disease

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

Blood pressure

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

Tardive dyskinesia

Although in clinical trials the incidence of treatment emergent tardive dyskinesia was comparable in patients receiving GEODON IM 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 IM, a dose reduction or medicine discontinuation should be considered. These symptoms can temporarily deteriorate or even arise after discontinuation of treatment.

Falls

GEODON IM 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.

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 and/or potentially, cerebrovascular adverse events compared with placebo when treated with some atypical antipsychotic medicines. GEODON IM is not approved for the treatment of elderly patients with dementia-related psychosis.

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 IM and preventive measures undertaken.

Priapism

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

Post-marketing reports of mortality

Fatalities with the use of GEODON IM, generally in patients with multiple confounding risk factors, have been reported. Although a causal relationship has not been established, GEODON IM should be used with caution.

Suicide

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

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 IM.

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

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

GEODON IM contains sodium

GEODON IM contains less than 1 mmol sodium (23 mg) per mL of reconstituted solution for injection. Patients on low sodium diets can be informed that this medicine is essentially 'sodium free'.

4.5 Interaction with other medicines and other forms of interaction

Class IA and III anti-dysrhythmics – see section 4.3 and section 4.4.

Concomitant use with other medicines that prolong QT interval – see section 4.4.

CNS medicines/alcohol

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

Effect of GEODON IM 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 medicines metabolised by these cytochrome P450 isoforms to a clinically relevant extent.

Oral contraceptives – GEODON administration resulted in no significant change to the pharmacokinetics of estrogen (ethinyl estradiol, 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 IM

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 twice daily for 21 days, resulted in a decrease of approximately 35 % in the exposure to GEODON.

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

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.

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 medicine interactions with GEODON due to displacement is unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

GEODON IM 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 IM should use an appropriate method of contraception.

Breastfeeding

There are no adequate and well-controlled studies in lactating women. A single case report found that GEODON IM was detectable in breast milk. Patients should be advised not to breastfeed an infant if they are receiving GEODON IM.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The table below contains adverse events with possible, probable or unknown relationship to GEODON IM in flexible dose phase 2/3 trials. The most common reactions were nausea, sedation, dizziness, injection site pain, headache and somnolence.

Tabulated summary of adverse reactions

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 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

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

System organ class	**Frequency**	**Adverse reaction**
Immune system disorders	Not known	Anaphylactic reaction
Metabolism and nutrition disorders	Uncommon	Decreased appetite
Psychiatric disorders	Common	Agitation
	Uncommon	Psychotic disorder, antisocial behaviour, tic, personality disorder, psychosis
Nervous system disorders	Common	Extrapyramidal disorder, akathisia, tremor, somnolence, headache, dizziness, sedation
	Uncommon	Dyskinesia, parkinsonism, cogwheel rigidity,

		dysarthria, dyspraxia, postural dizziness, aphasia
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Uncommon	Bradycardia
Vascular disorders	Common	Hypertension
	Uncommon	Flushing
Respiratory, thoracic and mediastinal disorders	Uncommon	Laryngospasm
Gastrointestinal disorders	Common	Nausea, constipation, dry mouth
	Uncommon	Diarrhoea, loose stools
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis
Musculoskeletal and connective tissue disorders	Common	Muscle rigidity
Renal and urinary disorders	Rare	Dysuria
General disorders and administration site conditions	Common	Asthenia, injection site pain, injection site burning, fatigue
	Uncommon	Medicine withdrawal syndrome, influenza like illness, injection site discomfort, injection site irritation
Investigations	Uncommon	Decreased blood pressure, increased hepatic enzyme

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

In long-term maintenance treatment in clinical trials, prolactin levels in patients treated with GEODON IM 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.

Post-marketing experience

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

System organ class	Adverse reaction
Immune system disorders	Hypersensitivity
Psychiatric disorders	Insomnia, mania, hypomania
Nervous system disorders	Dystonia, syncope, neuroleptic malignant syndrome, serotonin syndrome, tardive dyskinesia, facial droop
Cardiac disorders	Tachycardia, torsade de pointes
Vascular disorders	Hypotension, orthostatic hypotension, venous embolism
Gastrointestinal disorders	Vomiting, dysphagia, tongue oedema
Skin and subcutaneous tissue disorders	Allergic reaction, rash, drug reaction with eosinophilia and systemic symptoms (DRESS), angioedema
Renal and urinary disorders	Urinary incontinence, enuresis
Reproductive system and breast disorders	Priapism, galactorrhoea

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 IM 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 dysrhythmias. There is no specific antidote to GEODON IM.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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.

5.2 Pharmacokinetic properties

Absorption

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. Exposure increases in a dose-related manner and following 3 days of intramuscular dosing, little accumulation is observed.

Distribution

The volume of distribution is approximately 1,1 L/kg. Ziprasidone is more than 99 % protein bound in serum.

Biotransformation

The mean terminal half-life on the third day of dosing ranged from 8 to 10 hours. The mean terminal half-life of ziprasidone after intravenous administration is 6 hours. Mean systemic 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.

Elimination

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

Special populations

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.

Renal impairment

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.

Hepatic impairment

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

Sulphobutyl ether β-cyclodextrin sodium

Water for injection

6.2 Incompatibilities

This medicine must NOT be mixed with other medicines or solvents except water for injection (see section 6.6).

6.3 Shelf life

36 months.

GEODON IM 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, GEODON IM 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.

6.4 Special precautions for storage

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

For storage of the reconstituted product, see section 6.3.

6.5 Nature and contents of container

A carton containing a 5 ml or 10 ml clear glass vial of GEODON IM 20 mg/mL Powder for solution for injection.

6.6 Special precautions for disposal and other handling

The contents of the vial should be reconstituted by introduction of 1,2 mL water for injection affording a concentration of 20 mg GEODON IM 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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1609

Tel.: +27(011) 451 1300 / +27(071) 281 2503 (24 hours)

Manufacturer: Pharmacia and Upjohn Company LLC, Kalamazoo, USA

8. REGISTRATION NUMBERS

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

9. DATE OF FIRST AUTHORISATION

GEODON IM 20 mg/mL: 11 December 2003

10. DATE OF REVISION OF THE TEXT

26 August 2021

BOTSWANA: S2

Reg. No.: BOT0701004