PROFESSIONAL INFORMATION FOR ZIPDON

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ZIPDON Powder for solution for injection (vials)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL vial contains 20 mg Ziprasidone Mesylate.

Sugar free.

For the full list of excipients, *(see section 6.1)*.

3. PHARMACEUTICAL FORM

Injection

Off white to Pale pink lyophilized powder/cake in a Type-I clear tubular glass vial with 20 mm Grey rubber stopper and sealed with 20 mm aluminium seal having blue colour polypropylene disc.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZIPDON intramuscular (IM) is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with ZIPDON 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 ZIPDON for more than 3 consecutive days has not been studied.

If long-term therapy is indicated, oral Ziprasidone, 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

ZIPDON 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 ZIPDON 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

ZIPDON 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 ziprasidone and other medicines that prolong the QT interval have not been performed. An additive effect of ZIPDON and other medicines that prolong the QT interval cannot be excluded. Therefore, ZIPDON 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. ZIPDON 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 ZIPDON injection has not been evaluated in children under the age of 18 years.

4.4 Special warnings and precautions for use

QT interval

ZIPDON 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 ZIPDON. ZIPDON 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 ziprasidone 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 increases in QT_C from baseline for ziprasidone 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 ziprasidone on QT_C length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg twice daily).

In placebo-controlled trials, oral ziprasidone 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 ZIPDON 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, ZIPDON 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)*. ZIPDON should be discontinued in patients who are found to have persistent QT_C measurements > 500 msec.

For patients taking ZIPDON 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 ZIPDON. A causal relationship with ZIPDON has not been established.

Elderly (> 65 years)

Elderly patients have not been included in clinical studies 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 ziprasidone. The management of NMS should include immediate discontinuation of all antipsychotic medication, including ZIPDON.

Severe cutaneous adverse reactions

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 ZIPDON 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 ziprasidone. Single cases of hypertension have also been reported. Caution should be exercised, particularly in ambulatory patients.

Tardive dyskinesia

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

Falls

ZIPDON 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.

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 section 4.2 and 5.2)*.

Increased Mortality in Elderly people with Dementia

Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small 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.

ZIPDON is not registered for the treatment of dementia-related behavioural disturbances.

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. ZIPDON 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 ZIPDON and preventive measures undertaken.

Priapism

Cases of priapism have been reported with antipsychotic use, including ziprasidone mesylate. 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 data of mortality

Fatalities with the use of ziprasidone, generally in patients with multiple confounding risk factors have been reported. Although a causal relationship has not been established in the studies, ziprasidone 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 ziprasidone.
Patients with an established diagnosis of diabetes mellitus who are started on ZIPDON 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 ZIPDON should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with ZIPDON 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.

Increased risk of cerebrovascular accidents in the dementia population

In studies, a roughly 3-fold increased risk of cerebrovascular adverse events has been observed in randomized placebo-controlled trials of dementia patients using certain atypical antipsychotics. The reason for this elevated risk is not yet understood. It's important to note

that an increased risk cannot be ruled out for other antipsychotics or different patient groups. Consequently, ziprasidone should be used with caution in patients with stroke risk factors.

ZIPDON contains sodium.

ZIPDON 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 ZIPDON, 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 ZIPDON on other medicines

All interaction studies have been conducted with oral ziprasidone.

An *in vivo* study with dextromethorphan showed no marked inhibition with CYP2D6 at plasma concentrations 50 % lower than those obtained after 40 mg ziprasidone twice daily. *In vitro* data indicated that ziprasidone may be a modest inhibitor of CYP2D6 and CYP3A4. However, it is unlikely that ZIPDON 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 estradiol, a CYP3A4 substrate) or progesterone components.

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

Effects of other medicines on ZIPDON

The CYP3A4 inhibitor ketoconazole (400 mg/day) increased the serum concentrations of ziprasidone by < 40 %. The serum concentrations of S-methyl-dihydroziprasidone and ziprasidone sulphoxide, at the expected T_{max} of ZIPDON, 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. Carbamazepine therapy, 200 mg twice daily for 21 days, resulted in a decrease of approximately 35 % in the exposure to ziprasidone.

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

Serotonergic medicines

In isolated cases, 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

ZIPDON 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 ZIPDON due to displacement is unlikely.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential receiving ZIPDON should use an appropriate method of contraception.

Pregnancy

ZIPDON 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).

Breastfeeding

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

Fertility

There are no adequate and well-controlled studies in women and men exposed to ziprasidone.

4.7 Effects on ability to drive and use machines

Administration of ZIPDON 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 most frequent reactions were nausea, sedation, dizziness, injection site pain, headache and somnolence.

Tabulated summary of adverse reactions

System organ class	Frequency	Adverse reaction
Immune system disorders	Frequency unknown	Anaphylactic reaction, Hypersensitivity
Metabolism and nutrition disorders	Less frequent	Decreased appetite
Psychiatric disorders	Frequent	Agitation, Insomnia
	Less frequent	Mania, psychotic disorder, antisocial behaviour, tic, personality disorder, psychosis
	Frequency unknown	Hypomania
Nervous system disorders	Frequent	Dystonia, extrapyramidal disorder, akathisia, tremor, somnolence, headache, dizziness, sedation
	Less frequent	Syncope, Dyskinesia, parkinsonism, cogwheel rigidity, dysarthria, dyspraxia, postural dizziness, aphasia

	Frequency unknown	Neuroleptic malignant syndrome, serotonin syndrome, tardive dyskinesia, facial droop
Ear and labyrinth disorders	Less frequent	Vertigo
Cardiac disorders	Less frequent	Bradycardia
	Frequency unknown	Tachycardia, torsade de pointes
Vascular disorders	Frequent	Hypertension, hypotension,
	Less frequent	Orthostatic hypotension, Flushing
	Frequency unknown	Venous embolism
Respiratory, thoracic and mediastinal disorders	Less frequent	Laryngospasm
Gastrointestinal disorders	Frequent	Vomiting, nausea, constipation, dry mouth
	Less frequent	Diarrhoea, loose stools
	Frequency unknown	Dysphagia, tongue oedema
Skin and subcutaneous tissue disorders	Less frequent	Hyperhidrosis, rash
	Frequency unknown	Allergic reaction, drug reaction with eosinophilia and systemic symptoms (DRESS), angioedema
	Less frequent	Hyperhidrosis, Rash
Musculoskeletal and	Frequent	Muscle rigidity

connective tissue disorders		
Renal and urinary disorders	Less frequent	Dysuria
	Frequency unknown	Urinary incontinence, enuresis
General disorders and administration site conditions	Frequent	Asthenia, injection site pain, injection site burning, fatigue
	Less frequent	Medicine withdrawal syndrome, influenza like illness, injection site discomfort, injection site irritation
Reproductive system and breast disorders	Frequency unknown	Galactorrhoea
	Less frequent	Priapism
Investigations	Less frequent	Decreased blood pressure, increased hepatic enzyme

In short-term and long-term ziprasidone clinical studies, the incidence of seizures and hypotension was uncommon, occurring in less than 1 % of ziprasidone treated patients.
In long-term maintenance treatment in clinical studies, 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 manifestation (e.g., gynaecomastia and breast enlargement) was 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. Healthcare providers

are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Experience with ziprasidone 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 ZIPDON.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pharmacotherapeutic group: Antipsychotic, indole derivatives.

ATC code: NO5A E04.

Mechanism of action

Ziprasidone has a high affinity for dopamine type 2 (D_2) receptors and substantially higher affinity for serotonin type 2A ($5HT_{2A}$) 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 type2 (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

Sulfobutylether beta 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

24 months

6.4 Special precautions for storage

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

- Keep the container in the outer carton.
- Do not freeze.
- For storage of the reconstituted product, *(see section 6.3)*.
- KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of the container

Off white to Pale pink lyophilized powder/cake in a Type-I clear tubular glass vial with 20 mm Grey rubber stopper and sealed with 20 mm aluminium seal having blue colour polypropylene disc.

Pack size: 10 single vials in a box.

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 ZIPDON 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

PPS PHARMACEUTICALS (PTY) LTD.

23 Kiaat Street, ERF 926, Extension 7,

Noordwyk, Midrand, Gauteng,

South Africa, 1687

8. REGISTRATION NUMBERS

59/2.6.5/0507

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 June 2026

10. DATE OF REVISION OF TEXT

Not yet revised.