PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ZOXADON ODT 0,5 mg orodispersible tablets

ZOXADON ODT 1 mg orodispersible tablets

ZOXADON ODT 2 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

ZOXADON ODT 0,5 mg: Each orodispersible tablet contains 0,5 mg risperidone

ZOXADON ODT 1 mg: Each orodispersible tablet contains 1 mg risperidone

ZOXADON ODT 2 mg: Each orodispersible tablet contains 2 mg risperidone

Excipients with known effect:

ZOXADON ODT contains sweetener (aspartame) in the following quantities: 0,4 mg,

0,8 mg, 1,6 mg and 2,4 mg per 0,5 mg, 1 mg, 2 mg tablet, respectively.

ZOXADON ODT contains sugar (mannitol 27,8 mg, 55,6 mg and 111,2 mg per 0,5 mg, 1 mg

and 2 mg tablet, respectively).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

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ZOXADON ODT 0,5 mg:	Round (diameter = 5 mm), slightly biconvex, pink marbled orodispersible tablet
ZOXADON ODT 1 mg:	Round (diameter = 6 mm), slightly biconvex, pink marbled orodispersible tablet
ZOXADON ODT 2 mg:	Round (diameter = 8 mm), slightly biconvex, pink marbled orodispersible tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZOXADON ODT tablets are indicated for the treatment of:

- Acute and chronic schizophrenic psychoses and related psychosis in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility and suspicion) and/or the negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent.

  ZOXADON ODT tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. In patients who have shown an initial treatment response, ZOXADON ODT tablets are also effective in maintaining the clinical improvement.
- Conduct and other disruptive behaviour disorders in children (aged 5 - 12 years), with sub-average intellectual functioning or mental retardation in whom destructive behaviours (e.g. aggression, impulsivity and self-injurious behaviours) are prominent.

The weight of the child should be 50 kg and above to take ZOXADON ODT.

- Mania in bipolar disorder. These episodes are characterised by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

4.2 Posology and method of administration

Posology

Schizophrenia:

Switching from other antipsychotics to ZOXADON ODT:

When medically appropriate, gradual discontinuation of the previous treatment, while ZOXADON ODT therapy is initiated, is recommended. Also if medically appropriate, when switching patients from depot antipsychotics, initiate ZOXADON ODT therapy in place of the next scheduled injection. The need for continuing existing anti-Parkinson medicines should be re-evaluated periodically.

Adults

ZOXADON ODT may be given once or twice daily. Patients should start with ZOXADON ODT 2 mg/day. The dosage may be increased on the second day to 4 mg/day. From then on, the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses of between 4 mg/day and 8 mg/day. Doses above 6 mg/day (when administered twice daily) were associated with more extrapyramidal symptoms and other adverse effects and are not recommended. In some patients, particularly with first episode

acute psychosis, a slower titration phase and a lower starting and maintenance dose may be appropriate. Doses above 10 mg/day have not been shown to be superior in efficacy to lower doses and may cause an increased incidence of side effects such as extrapyramidal symptoms. Dosages above 10 mg/day should only be considered if the benefits outweigh the risk. The maximum total daily dose is 16 mg/day.

A benzodiazepine may be added to ZOXADON ODT if additional sedation is required.

Elderly

It is recommended to half both the starting dose and the subsequent dose increments in elderly patients.

A starting dose of 0,5 mg twice daily is recommended. This dosage can be individually adjusted with 0,5 mg twice daily increments to 1 - 2 mg twice daily.

Special populations

Paediatric population

Children

Not for children under 15 years as efficacy and safety in children under the age of 15 years have not been demonstrated in schizophrenia.

Mania in bipolar disorders:

Adults

ZOXADON ODT should be administered on a once daily schedule, starting with 2 or 3 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Efficacy was demonstrated in flexible doses over a range

of 1 to 6 mg per day.

The continued use of ZOXADON ODT must be evaluated and justified on an ongoing basis.

Special populations

Paediatric

Experience is lacking in bipolar mania in children and adolescents less than 18 years of age.

Conduct and other disruptive behaviour disorders in children 5 - 12 years of age (50 kg and over)

This formulation is not suitable for the treatment of behavioural disturbances in children under 50 kg.

A starting dose of 0,01 mg/kg once daily is recommended. This dosage can be individually adjusted by increments of 0,01 mg/kg once daily, not more frequently than every other day, if needed. The recommended maintenance dose is 0,02 - 0,04 mg/kg once daily. The mean dose is 0,03 mg/kg once daily.

The continued use of ZOXADON ODT must be evaluated and justified on an ongoing basis.

Experience is lacking in children aged less than 5 years (see **CONTRAINDICATIONS**).

Renal and hepatic impairment

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than normal adults. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone.

Irrespective of the indication, starting and consecutive dosing should be halved, and dose

titration should be slower for patients with renal or hepatic impairment.

ZOXADON ODT should be used with caution in these groups of patients.

Method of administration

ZOXADON ODT can be taken before or after food (see section 5.1)

Only remove a tablet from the blister when it is time to take your medicine. Peel open a blister to expose the tablet.

Do not push the tablet through the foil as the tablet is fragile and may break.

Remove the tablet from the blister with clean dry hands and place the tablet on your tongue straight away.

The tablet will begin to disintegrate immediately. It can then be swallowed with or without water.

4.3 Contraindications

ZOXADON ODT is contraindicated in patients with known hypersensitivity to any of the ingredients of ZOXADON ODT.

Conduct and other disruptive behaviour disorders in children: ZOXADON ODT is contraindicated in children under 5 years of age as efficacy and safety in these children have not been demonstrated.

Safety of ZOXADON ODT tablets in pregnancy or lactating women has not been established (see section 4.6).

Parkinson's disease and Lewy body dementia (see section 4.4).

4.4 Special warnings and precautions for use

This formulation is not suitable for the treatment of behavioural disturbances in children weighing less than 50 kg, and adults with dementia.

Dementia associated with Parkinson's disease and senile dementia

Patients with Parkinson's disease or dementia with Lewy bodies (DLB) may be at risk of neuroleptic malignant syndrome (NMS) as well as an increased sensitivity to antipsychotic medicines such as ZOXADON ODT. Manifestations of this increased sensitivity can include confusion, obtundation, and postural instability with frequent falls, in addition to extrapyramidal symptoms.

In clinical trials, elderly ZOXADON ODT treated patients had a higher mortality than placebo treated elderly patients.

Caution should be used when prescribing ZOXADON ODT to patients with Parkinson's disease since it might cause a deterioration of the disease (see CONTRAINDICATIONS).

Increased mortality in elderly people with dementia

Elderly patients with dementia, when treated with atypical antipsychotics such as ZOXADON ODT, have an increased mortality.

Paediatric population

Before ZOXADON ODT is prescribed to a child or adolescent with a conduct disorder, they

should be carefully assessed for physical and social causes of the aggressive behaviour such as pain or inappropriate environmental demands. The sedative effect should be carefully monitored in this population due to the possible impact on learning ability. A change in the time of administration of ZOXADON ODT could improve the impact of the sedation on attention faculties of children and adolescents.

ZOXADON ODT is associated with increases in body weight and body mass index, therefore baseline weight measurement prior to treatment, and regular weight monitoring, is recommended.

Because of the potential effects of prolonged hyperprolactinaemia on growth and sexual maturation in children and adolescents, regular clinical evaluation of endocrinological status should be considered, including measurements of height, weight, sexual maturation, monitoring of menstrual functioning, and other potential prolactin-related effects.

Regular examination for extrapyramidal symptoms and other movement disorders should also be conducted during treatment with ZOXADON ODT.

Renal and hepatic impairment

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction of ZOXADON ODT than adults with normal renal function. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone (see section 4.2).

Tardive dyskinesia

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Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible, involuntary dyskinetic movements predominantly of the face and tongue, may develop in patients treated with ZOXADON ODT. Although this syndrome of TD appears to be most prevalent in the elderly, especially elderly females, it is impossible to predict at the onset of treatment which patients are likely to develop TD.

It has been suggested that the occurrence of Parkinsonian side effects is a predictor for the development of TD. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of ZOXADON ODT administered to the patient increases. However, the syndrome can develop, although less commonly, after relatively brief periods of treatment at low doses.

There is no known treatment for an established case of TD. The syndrome may remit partially or completely if ZOXADON ODT is withdrawn.

ZOXADON ODT treatment itself, however, may suppress the signs and symptoms of TD, thereby masking the underlying process. The effect of symptom suppression upon the long-term course of TD is unknown. In view of these considerations, ZOXADON ODT should be prescribed in a manner that is most likely to minimise the risk of TD. ZOXADON ODT should be reserved for patients who appear to be obtaining substantial benefit from the medicine. In such patients the smallest dose and the shortest duration of treatment should be sought.

The benefit for continued treatment should be reassessed periodically. If signs and symptoms of TD appear in a patient, ZOXADON ODT discontinuation should be considered. However, some patients may require treatment despite the presence of this syndrome.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a potentially fatal symptom complex that has been reported in association with the use of ZOXADON ODT. Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, cardiac dysrhythmias and diaphoresis). Additional signs may include elevated creatine phosphokinase (CPK) levels, myoglobinuria (rhabdomyolysis), and acute renal failure.

In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illnesses (e.g. pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, medicine fever and primary central nervous system pathology. The management of NMS should include:

1. Immediate discontinuation of all antipsychotic medicines and other medicines not essential to concurrent therapy;
2. Intensive symptomatic treatment and medical monitoring; and
3. Treatment of any concomitant serious medical problems for which specific treatments are available.

There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires ZOXADON ODT treatment after recovery from NMS, the potential reintroduction of the medicine should be carefully considered. The patient should be carefully

monitored, since recurrences of NMS have been reported.

Hyperprolactinaemia

Hyperprolactinaemia is a common side effect of treatment with ZOXADON ODT. A dose-dependent increase in plasma prolactin concentration may occur. Evaluation of the prolactin plasma level is recommended in patients with evidence of possible prolactin-related side effects (e.g. gynaecomastia, menstrual disorders, anovulation, fertility disorder, decreased libido, erectile dysfunction and galactorrhoea).

Cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics such as ZOXADON ODT has so far been demonstrated, caution is recommended in patients with relevant medical history. ZOXADON ODT should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

Premenopausal women who develop secondary amenorrhoea of greater than six months duration should receive appropriate preventative therapy to avoid hypo-oestrogenic bone loss.

Hyperglycaemia and diabetes mellitus

Hyperglycemia and exacerbation of pre-existing diabetes mellitus have been reported on ZOXADON ODT treatment.

Hyperglycaemia, in some cases extreme and associated with ketoacidosis and hyperosmolar coma or death, has been reported in patients treated with

ZOXADON ODT. Patients with an established diagnosis of diabetes mellitus who are started on ZOXADON ODT 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 ZOXADON ODT should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with ZOXADON ODT should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when ZOXADON ODT was discontinued. However, some patients required continuation of antidiabetic treatment despite discontinuation of ZOXADON ODT.

Cerebrovascular adverse events

Cerebrovascular adverse events, including cerebrovascular accidents and transient ischaemic attacks, have been reported during treatment with ZOXADON ODT. There is a higher incidence of cerebrovascular adverse events, including cerebrovascular accidents and transient ischaemic attacks, in elderly patients with dementia treated with ZOXADON ODT. Caution is advised in all patients with risk factors for stroke, and regular assessment for the need for ZOXADON ODT treatment is recommended.

Orthostatic hypotension

Due to the alpha-blocking activity of ZOXADON ODT, (orthostatic) hypotension can occur, especially during the initial dose-titration period. ZOXADON ODT should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction,

conduction abnormalities, dehydration, hypovolaemia or cerebrovascular disease), and the dosage should be gradually titrated, as recommended. A dose reduction should be considered if hypotension occurs.

Leukopenia, neutropenia and agranulocytosis

Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of ZOXADON ODT should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur.

Patients with severe neutropenia (absolute neutropenia count < 1 x 10^9 /l) should discontinue **ZOXADON ODT** and have their WBC followed until recovery.

QT prolongation

QT prolongation has been reported with the use of risperidone, as in ZOXADON ODT.

Caution should be exercised when ZOXADON ODT is prescribed in patients with known cardiovascular disease, family history of QT prolongation, bradycardia or electrolyte disturbances (hypokalaemia, hypomagnesaemia), as it may increase the risk of dysrhythmogenic effects, and in concomitant use with medicines known to prolong the QT interval.

Intraoperative Floppy Iris Syndrome

Cases of intraoperative floppy iris syndrome (IFIS) during cataract surgery have been reported in patients taking risperidone, as in ZOXADON ODT. IFIS may increase the risk of eye complications during and after cataract surgery.

Complications of IFIS during cataract surgery include iris trauma: posterior capsule rupture and vitreous loss.

Post-operative complications include increased intraocular pressure and cystoid macular oedema. It is therefore recommended to verify pre-surgery data gathering on patient history and the previous or current use of ZOXADON ODT.

Seizures

Seizures have been reported after treatment with ZOXADON ODT. Caution is recommended when treating patients with epilepsy or other conditions that potentially lower the seizure threshold.

Priapism

Priapism may occur with ZOXADON ODT treatment due to its alpha-adrenergic blocking effects.

Body temperature regulation

ZOXADON ODT may disrupt the body's ability to reduce core body temperature. ZOXADON ODT should be used with caution in patients who experience conditions that contribute to an increase in core body temperature, e.g. strenuous exercise, exposure to extreme heat,

concomitant use with anticholinergic medicines, or being subject to dehydration.

Antiemetic effect

ZOXADON ODT may have an antiemetic effect which could mask the signs and symptoms of overdosage with certain medicines or conditions such as intestinal obstruction, Reye's syndrome and brain tumour.

Weight gain

Weight gain has been reported with ZOXADON ODT use. Weight should be monitored regularly.

Venous thromboembolism (VTE)

Since patients treated with antipsychotics, such as ZOXADON ODT, often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with ZOXADON ODT, and preventative measures taken.

Concomitant use with furosemide

There is a higher mortality in elderly patients with dementia treated with furosemide and risperidone, when compared to patients treated with ZOXADON ODT alone. Dehydration is an overall risk for mortality. Concomitant use of ZOXADON ODT with other diuretics (mainly thiazide diuretics used in low dose) is not associated with similar findings.

Stopping ZOXADON ODT treatment:

Gradual withdrawal of ZOXADON ODT is recommended because of the risk of withdrawal symptoms, including sweating, nausea, vomiting and rebound psychosis, with abrupt cessation of treatment.

Information on excipients of ZOXADON ODT:

ZOXADON ODT contains aspartame, which is a source of phenylalanine, and may be harmful to patients with phenylketonuria.

ZOXADON ODT contains mannitol which may have a mild laxative effect

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic-related interactions

Medicines known to prolong the QT interval:

Caution is advised when prescribing ZOXADON ODT with medicines known to prolong the QT interval, such as antidysrhythmics (e.g. quinidine, dysopiramide, procainamide, propafenone, amiodarone, sotalol), tricyclic antidepressants (i.e. amitriptyline), tetracyclic antidepressants (i.e. maprotiline), some antihistamines, other antipsychotics, some antimalarials (i.e. quinine and mefloquine) and with medicines causing electrolyte imbalance (hypokalemia, hypomagnesiaemia), bradycardia, or those which inhibit the hepatic metabolism of ZOXADON ODT. This list is indicative and not exhaustive.

Centrally-acting medicines and alcohol:

Given the primary CNS depressive effects of ZOXADON ODT, it should be used with caution in combination with alcohol and other centrally acting medicines, including opiates, antihistamines and benzodiazepines due to increased risk of sedation.

Levodopa and dopamine agonists:

ZOXADON ODT may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Medicines with hypotensive effect:

Clinically significant hypotension has been observed with concomitant use of ZOXADON ODT and antihypertensive treatment.

Paliperidone:

Concomitant use of ZOXADON ODT with paliperidone is not recommended as paliperidone is the active metabolite of risperidone, and the combination of the two may lead to additive antipsychotic fraction exposure.

Pharmacokinetic-related interactions

Risperidone, as in ZOXADON ODT, is mainly metabolised through CYP2D6, and to a lesser extent through CYP3A4. Both risperidone and its active metabolite 9-hydroxyrisperidone are substrates of P-glycoprotein (P-gp) activity. Substances that modify CYP2D6 activity, or substances strongly inhibiting or inducing CYP3A4 and P-gp, may influence the pharmacokinetics of risperidone active antipsychotic fraction.

Effects of other medicines on the pharmacokinetics of ZOXADON ODT:

Antiepileptics:

Carbamazepine**,** a strong CYP3A4 inducer and P-gp inducer decreases the plasma levels of the active antipsychotic fraction of risperidone by about 50 %. Similar effects may be observed with other hepatic enzyme inducers e.g. phenytoin and phenobarbitone. On discontinuation of carbamazepine or other hepatic enzyme inducers the dosage of ZOXADON ODT should be re-evaluated and, if necessary, decreased.

Valproate: valproate T_{max} increases from 1,3 hours to 2,0 hours showing no clinically relevant effect.

Topiramate: modest decrease in risperidone bioavailability, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.

Antipsychotics:

Phenothiazines may increase the plasma concentration of risperidone but not that of the antipsychotic fraction.

SSRIs and tricyclic antidepressants:

Fluoxetine and paroxetine, strong CYP2D6 inhibitors, increase the plasma concentration of risperidone but less so of the antipsychotic fraction. Doses of paroxetine higher than 20 mg/day may elevate the concentrations of the risperidone active antipsychotic fraction. Fluoxetine kinetics were not changed in combination with ZOXADON ODT. When concomitant fluoxetine or paroxetine is initiated or discontinued, the dosing of ZOXADON ODT should be re-evaluated.

Tricyclic antidepressants may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

Sertraline, a weak inhibitor of CYP2D6, and fluvoxamine, a weak inhibitor of CYP3A4, at dosages up to 100 mg/day, are not associated with clinically significant changes in concentrations of the risperidone active antipsychotic fraction. However, doses higher than 100 mg/day of sertraline or fluvoxamine may elevate concentrations of the risperidone active antipsychotic fraction.

Venlafaxine: risperidone AUC increased and risperidone clearance decreased, but there is no effect on 9-hydroxyrisperidone and the active moiety.

Quetiapine: no significant interaction.

Clozapine: no significant interaction.

Psychostimulants:

The combined use of psychostimulants, e.g. methylphenidate, with ZOXADON ODT in children and adolescents did not alter the pharmacokinetics and efficacy of ZOXADON ODT.

Antibacterials:

Erythromycin, a moderate CYP3A4 inhibitor and P-gp inhibitor, does not change the pharmacokinetics of risperidone and the antipsychotic fraction.

Rifampicin, a strong CYP3A4 inducer and a P-gp inducer, decreases the plasma concentrations of the active antipsychotic fraction.

Antifungals:

Itraconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increases the plasma concentrations of the active antipsychotic fraction by about 70 %, at risperidone doses of 2 to 8 mg/day.

Ketoconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of

200 mg/day increases the plasma concentrations of risperidone and decreases plasma concentrations of 9-hydroxyrisperidone.

Antivirals:

Protease inhibitors: No formal study data are available, however, since ritonavir is a strong CYP3A4 inhibitor and a weak CYP2D6 inhibitor, ritonavir and ritonavir-boosted protease inhibitors potentially raise concentrations of the risperidone active antipsychotic fraction.

Anticholinesterases:

There were non-significant effects on risperidone kinetics or that of the active antipsychotic fraction in combination with donepezil or galantamine, both CYP2D6 and CYP3A4 substrates.

Beta blockers:

Some beta blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

Calcium channel blockers:

Verapamil, a moderate inhibitor of CYP3A4 and an inhibitor of P-gp, increases the plasma concentration of risperidone and the antipsychotic fraction.

Gastrointestinal medicines:

Cimetidine and ranitidine, both weak inhibitors of CYP2D6 and CYP3A4, increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction.

Effect of ZOXADON ODT on the pharmacokinetics of other medicines:

Diuretics:

Furosemide: increases mortality in elderly patients with dementia (see section 4.4**)**.

Antiepileptics:

ZOXADON ODT shows no clinically relevant effect on the pharmacokinetics of valproate or topiramate.

Antipsychotics:

Aripiprazole, a CYP2D6 and CYP3A4 substrate: ZOXADON ODT shows no effect on the pharmacokinetics of aripiprazole or its active metabolite, dehydroaripiprazole.

Lithium: C_{max} and AUC of lithium are non-significantly increased, but T_{max} of lithium is increased from 2,4 hours to 3,0 hours. ZOXADON ODT shows no clinically relevant effect on the pharmacokinetics of lithium.

When ZOXADON ODT is taken together with other highly protein-bound medicines (e.g. diazepam, warfarin, digoxin, imipramine and propranolol), there is no clinically relevant displacement of either medicine from the plasma proteins.

4.6 Fertility, pregnancy and lactation

The safety of ZOXADON ODT in pregnancy and lactating women has not been established (see section 4.3).

Pregnancy

Reversible extrapyramidal symptoms, including hypertonia, hypotonia, jitteriness, tremor, muscle rigidity, twitching and convulsions, feeding disorder and withdrawal symptoms have been observed in neonates following use of risperidone, as in ZOXADON ODT, during the last trimester of pregnancy.

Breastfeeding

Risperidone and 9-hydroxyrisperidone are excreted in human breast milk. Therefore, women

receiving ZOXADON ODT should not breastfeed their infants.

4.7 Effects on ability to drive and use machines:

ZOXADON ODT may impair mental alertness. Patients should therefore be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) (incidence .10%) are:

Parkinsonism, headache, and insomnia.

Tabulated list of adverse effects

System Organ Class	Frequency	Side effects
Infections and Infestations	Frequent	Urinary tract infection, pneumonia, influenza, bronchitis, upper respiratory tract infection
	Less frequent	Respiratory tract infection, cystitis, eye infection, ear infection, otitis media, tonsillitis, onychomycosis, cellulitis localised infection, viral infection, acrodermatitis

Blood and lymphatic system disorders	Less frequent	A decrease in neutrophil and/ or thrombocyte count, leukopenia, neutropenia, granulocytopenia, anaemia, decreased haemocrit count, increased eosinophil count
	Frequency unknown	Agranulocytosis
Immune system disorders	Less frequent	Hypersensitivity, drug hypersensitvity
	Frequency unknown	Angioedema, anaphylactic reaction
Endocrine disorders	Frequent	Increased plasma prolactin levels and associated manifestations
	Less frequent	Water intoxication, either due to polydipsia or the syndrome of inappropriate secretion of the antidiuretic hormone (SIADH)
	Frequency unknown	Body temperature dysregulation
Metabolism and nutrition disorders	Frequent	Weight increase, increase/decrease appetite
	Less frequent	Diabetes mellitus, hyperglycaemia, polydipsia, weight decrease, anorexia, blood cholesterol increase, hypoglycaemia, hyperinsulinaemia, blood triglycerides increase, diabetic ketoacidosis

Psychiatric disorders	Frequent	Insomnia, agitation, anxiety, sleep disorder, impaired concentration, memory problems, mood or mental changes including aggressive behaviour, depression
	Less frequent	Mania, hypomania, confusional state, libido decrease, listless, nervousness, nightmare, blunted affect
Nervous system disorders	Frequent	Parkinsonism, headache, extrapyramidal disorder, dizziness, sedation, increased dream activity, somnolence. Dose dependant extrapyramidal symptoms including tremor, rigidity, hypersalivation, bradykinesia, oculogyric crisis, akathisia (hyperkinesia) and acute dystonia, hypokinesia.
	Less frequent	Tardive dyskinesia, neuroleptic malignant syndrome, cerebro-vascular incidents, cerebral ischaemia, unresponsive to stimuli, loss of consciousness, decreased level of consciousness, convulsion, syncope, psychomotor hyperactivity, balance disorder, abnormal co-ordination, postural dizziness, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paraesthesia, cerebrovascular disorder, diabetic coma, head titubation
Eye disorders	Frequent	Blurred vision

	Less frequent	Photophobia, dry eyes, increased lacrimation, ocular hyperaemia, glaucoma, eye movement disorder, eye rolling, eyelid margin crusting, floppy iris syndrome (intraoperative), conjunctivitis
Ear and labyrinth disorders	Less frequent	Vertigo, tinnitus, ear pain
Cardiac disorders	Frequent	Tachycardia
	Less frequent	Chest pain, palpitations, atrial fibrillation, aterioventricular block, QT prolongation, abnormal electrocardiogram, conduction disorders, sinus dysrhythmia, bradycardia
Vascular disorders	Frequent	Hypertension
	Less frequent	Hypotension, orthostatic hypotension, flushing, pulmonary embolism, venous thrombosis
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, rhinitis, cough, pharyngolaryngeal pain, pharyngitis, epistaxis, nasal congestion
	Less frequent	Pneumonia aspiration, pulmonary congestion, respiratory tract congestion, rales, wheezing, dysphonia, sinusitis, upper respiratory tract infection, respiratory disorder, sleep apnoea syndrome, hyperventilation

Gastrointestinal disorders	Frequent	Constipation, dyspepsia, nausea, decreased salivation, diarrhoea, vomiting, abdominal pain, abdominal discomfort, dry mouth, toothache
	Less frequent	Hypersalivation, faecal incontinence, faecaloma, gastroenteritis, dysphagia, flatulence, intestinal obstruction, pancreatitis, swollen tongue, swollen lips, cheilitis
	Frequency unknown	Ileus
Hepato-biliary disorders	Less frequent	Increased transaminases, gammaglutamyltransferase and hepatic enzymes, jaundice
Skin and subcutaneous tissue disorders	Frequent	Skin rash, itching, erythema
	Less frequent	Dry skin, increased pigmentation, increased sweating, photosensitivity, seborrhoea, urticaria, pruritus, alopecia, eczema, acne, hyperkeratosis, skin disorder, skin lesions, drug eruption, dandruff, skin discolouration
Musculoskeletal, connective tissue and bone disorders	Frequent	Back pain, arthralgia, muscle spasms, musculoskeletal pain, pain in extremities
	Less frequent	Increase in blood creatine phosphokinase, abnormal posture, joint stiffness, joint swelling, muscular weakness, myalgia, neck pain, rhabdomyolysis

Renal and urinary disorders	Frequent	Enuresis, micturition disturbances or polyuria
	Less frequent	Pollakiuria, urinary retention, dysuria, urinary incontinence
Pregnancy, puerperium, and neonatal conditions	Frequency unknown	Drug withdrawal syndrome in neonates
Reproductive system and breast disorders	Less frequent	Erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, priapism, gynaecomastia, galactorrhoea, disturbances in the menstrual cycle, amenorrhoea, sexual dysfunction, breast pain, breast discomfort, breast enlargement, breast discharge, vaginal discharge
	Frequency unknown	Priapism
General disorders and administration site conditions	Frequent	Fatigue, pyrexia, chest pain, asthenia, peripheral oedema
	Less frequent	Chills, increase in body temperature, abnormal gait, thirst, chest discomfort, malaise, feeling abnormal, discomfort, hypothermia, decrease in body temperature, peripheral coldness, drug withdrawal syndrome, face oedema
	Frequency unknown	Induration

Injury, poisoning and procedural complications	Frequent	Fall
	Less frequent	Procedural pain

a. Description of selected adverse reactions

Extrapyramidal disorder may occur: Parkinsonism (salivary hypersecretion,musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, and glabellar reflex abnormal),akathisia (akathisia,restlessness, hyperkinesia, and restless leg syndrome), tremor, dyskinesia (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia.

Dystonia includes dystonia, muscle spasms, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus. Tremor includes tremor and parkinsonian rest tremor. It should be noted that a broader spectrum of symptoms are included, that do not necessarily have an extrapyramidal origin.

b. Paediatric population

The following ADRs were reported with a frequency ≥5% in paediatric patients (5 to 17 years) and with at least twice the frequency seen in clinical trials in adults: somnolence/sedation, fatigue, headache, increased appetite, vomiting, upper respiratory tract infection, nasal congestion, abdominal pain, dizziness, cough, pyrexia, tremor, diarrhoea, and enuresis.

c. Other special populations

Elderly patients with dementia:

Transient ischaemic attack and cerebrovascular accident were ADRs reported in clinical trials with a frequency of 1.4% and 1.5%, respectively, in elderly patients with dementia. In addition, the following ADRs were reported with a frequency ≥5% in elderly patients with dementia and with at least twice the frequency seen in other adult populations: urinary tract infection, peripheral oedema, lethargy, and cough.

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms:

Reported signs and symptoms have been those resulting from an exaggeration of ZOXADON ODT's known pharmacological effects. Symptoms of acute overdosage include drowsiness, sedation, hypotension, tachycardia and extrapyramidal symptoms. In overdose, cases of QT-prolongation have been reported. In the case of acute overdosage, the possibility of multiple

medicine involvement should be considered.

Management of overdose:

Establish and maintain a clear airway and ensure adequate oxygenation and ventilation.

Administration of activated charcoal together with a laxative should be considered.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible dysrhythmias.

Since there is no known antidote if accidental poisoning or overdosage is suspected, appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic medicines. In case of severe extrapyramidal symptoms, anticholinergic medicine should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antipsychotics

ATC code: N05AX08

Pharmacological classification: A.2.6.5 Central nervous system depressants. Miscellaneous structures.

Risperidone is an antipsychotic of the benzisoxazol derivatives. It is a selective monoaminergic antagonist. Risperidone has affinity for serotonin-5-HT2, dopamine-D2, H1-histamine, alpha1- and alpha2-adrenergic receptors. Risperidone has no affinity for

cholinergic receptors. It is a potent D2 antagonist.

5.2 Pharmacokinetic properties

Absorption:

ZOXADON ODT disintegrates in the oral cavity, releasing risperidone into saliva prior to swallowing. After ingestion of the ZOXADON ODT, risperidone is released into the gastro-intestinal tract and is available for absorption.

Risperidone is completely absorbed after oral administration. Food does not affect the absorption of risperidone.

Distribution:

Peak plasma concentrations are attained within 1 to 2 hours. Steady state is reached within 1 day for risperidone in most patients and 4 - 5 days for 9-hydroxyrisperidone.

Biotransformation:

Risperidone is metabolised by cytochrome CYP2D6 to 9-hydroxyrisperidone which has a similar pharmacological activity to risperidone. Risperidone and 9-hydroxyrisperidone form the active antipsychotic fraction.

After oral administration, the half-life of risperidone is about 3 hours. The elimination half-life of 9-hydroxyrisperidone and the active antipsychotic fraction is 24 hours.

Following 6 mg or 8 mg once daily, peak levels of the active moiety are about 30 % higher and trough levels about 30 % lower than the peaks and troughs following 3 mg and 4 mg twice daily.

Risperidone is bound to albumin and alpha$_1$-acid glycoprotein. Plasma protein binding of risperidone is 88 %, and 77 % for 9-hydroxyrisperidone.

Elimination:

One week after administration, 70 % of the dose is excreted in the urine and 14 % in the faeces. In urine, risperidone and 9-hydroxyrisperidone represent 35 - 45 % of the dose.

Linearity/non-linearity:

Risperidone plasma concentration is dose-proportional within the therapeutic dose-range.

Pharmacokinetics in special patient groups

Risperidone shows significantly higher active plasma concentrations and slower elimination in the elderly and in patients with moderately severe renal insufficiency. The plasma concentrations of risperidone are normal in patients with mild to moderate liver insufficiency. The pharmacokinetics of risperidone, 9-hydroxyrisperidone and the active moiety in children are similar to those in adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame

Basic butylated methacrylate copolymer

Calcium silicate

Crospovidone

Flavour peppermint

Flavour spearmint

Hydroxypropyl cellulose

Iron oxide red

Magnesium stearate

Mannitol

Microcrystalline cellulose

Povidone

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

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

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

ZOXADON ODT is packed into silver perforated peel blisters consisting of cold formed

OPA/AL/PVC film and PET/Al peel off foil in packs of 30's in an outer carton.

6.6 Special precautions for disposal of a used medicine or waste materials derived

from such medicine and other handling of the product

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBERS

ZOXADON ODT 0,5 mg: 46/2.6.5/0362

ZOXADON ODT 1 mg: 46/2.6.5/0363

ZOXADON ODT 2 mg: 46/2.6.5/0364

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 May 2019

10. DATE OF REVISION OF THE TEXT

06 April 2022