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 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.

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3. PHARMACEUTICAL FORM

Orodispersible tablets.

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, and 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.

Special populations

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.

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:

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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 population

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 section 4.3).

PROFESSIONAL INFORMATION

Special populations

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.

PROFESSIONAL INFORMATION

Missed dose:

Doctors should advise patients who forget to take ZOXADON ODT to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

- Hypersensitivity to risperidone or 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 section 4.3).

Increased mortality in elderly people with dementia

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

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. No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Caution is advised in these patients. Dehydration is an overall risk for mortality and should therefore be carefully avoided in elderly patients with dementia. Concomitant use of ZOXADON ODT with other diuretics (mainly thiazide diuretics used in low dose) is not associated with similar findings

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

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.

Extrapyramidal symptoms and psychostimulants - Caution is warranted in patients receiving both psychostimulants (e.g. methylphenidate) and risperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications (see section 4.5).

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

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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

Hyperglycaemia 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.

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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, transient ischaemic attacks and fatalities, in elderly patients with dementia treated with ZOXADON ODT.

The risk of CVAEs was significantly higher in patients with mixed or vascular type of dementia when compared to Alzheimer's dementia. Therefore, patients with types of dementias other than Alzheimer's should not be treated with ZOXADON ODT.

Patients/caregivers should be cautioned to immediately report signs and symptoms of potential CVAEs such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems. All treatment options should be considered without delay, including discontinuation of ZOXADON ODT.

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ZOXADON ODT should only be used short term for persistent aggression in patients with moderate to severe Alzheimer's dementia to supplement non-pharmacological approaches which have had limited or no efficacy and when there is potential risk of harm to self or
others.
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

Events of leukopenia, neutropenia and agranulocytosis have been reported with risperidone, with agranulocytosis reported during post-marketing surveillance.
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.

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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 and has been reported during post-marketing surveillance (see section 4.8).

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.

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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.

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:

PROFESSIONAL INFORMATION

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.

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.

PROFESSIONAL INFORMATION

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 (hypokalaemia, hypomagnesaemia), 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.

Psychostimulants:

The combined use of psychostimulants (e.g. methylphenidate) with ZOXADON ODT can lead to extrapyramidal symptoms upon change of either or both treatments (see section 4.4).

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

Food does not affect the absorption of risperidone.

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.

Strong CYP2D6 inhibitors:

Co-administration of risperidone with a strong CYP2D6 inhibitor may increase the plasma concentrations of ZOXADON ODT, but less so of the active antipsychotic fraction. Higher doses of a strong CYP2D6 inhibitor may elevate concentrations of the risperidone active antipsychotic fraction (e.g., paroxetine, see below). It is expected that other CYP2D6 inhibitors, such as quinidine, may affect the plasma concentrations of ZOXADON ODT in a similar way. When concomitant paroxetine, quinidine, or another strong CYP2D6 inhibitor, especially at higher doses, is initiated or discontinued, the medical practitioner should re-evaluate the dosing of ZOXADON ODT.

CYP3A4 and/or P-gp inhibitors:

Co-administration of risperidone with a strong CYP3A4 and/or P-gp inhibitor may substantially elevate plasma concentrations of the ZOXADON ODT active antipsychotic fraction. When concomitant itraconazole or another strong CYP3A4 and/or P-gp inhibitor is initiated or discontinued, the medical practitioner should re-evaluate the dosing of ZOXADON ODT.

CYP3A4 and/or P-gp inducers:

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Co-administration of risperidone with a strong CYP3A4 and/or P-gp inducer may decrease the plasma concentrations of the ZOXADON ODT active antipsychotic fraction.

When concomitant carbamazepine or another strong CYP3A4 and/or P-gp inducer is initiated or discontinued, the medical practitioner should re-evaluate the dosing of ZOXADON ODT.

CYP3A4 inducers exert their effect in a time-dependent manner and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline.

Highly protein-bound drugs:

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.

When using concomitant medication, the corresponding label should be consulted for information on the route of metabolism and the possible need to adjust dosage.

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. Amitriptyline does not affect the pharmacokinetics of ZOXADON ODT or the active antipsychotic fraction.

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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.

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:

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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:

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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.

Galantamine and donepezil, do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction.

Paediatric population

Interaction studies have only been performed in adults. The relevance of the results from these studies in paediatric patients is unknown.

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.

4.6 Fertility, pregnancy and lactation

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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.

Fertility

Risperidone elevates prolactin level. Hyperprolactinaemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients.

There were no relevant effects observed in non-clinical studies.

4.7 Effects on ability to drive and use machines

ZOXADON ODT can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects (see section 4.8).

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

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4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) defined as very frequent (incidence ≥ 10%) are: Parkinsonism, sedation/somnolence, headache and insomnia.

The ADRs that appeared to be dose-related included parkinsonism and akathisia.

Tabulated summary of adverse reactions

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, acarodermatitis, sinusitis otitis media chronic
Blood and lymphatic system disorders	Less frequent	A decrease in neutrophil and/or thrombocyte count, leukopenia, neutropenia, granulocytopenia, anaemia, decreased haematocrit count, increased eosinophil count
	Frequency unknown	Agranulocytosis
Immune system disorders	Less frequent	Hypersensitivity, drug hypersensitivity
	Frequency unknown	Angioedema*, anaphylactic reaction*

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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), glucose urine present
	Frequency unknown	Body temperature dysregulation
Metabolism and nutrition disorders	Frequent	Weight increase, increase/decrease appetite
	Less frequent	Hyperglycaemia, polydipsia, weight decrease, anorexia, hyperinsulinaemia
	Frequency unknown	Diabetes mellitus*, diabetic ketoacidosis*, hypoglycaemia*, blood cholesterol increase*, blood triglycerides increase*
Psychiatric disorders	Frequent	Insomnia, agitation, anxiety, sleep disorder, impaired concentration, memory problems, mood or mental changes including aggressive behaviour, depression
	Less frequent	Hypomania, confusional state, libido decrease, listless, nervousness, nightmare, blunted affect, anorgasmia
	Frequency unknown	Mania*

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Nervous system disorders	Frequent	Parkinsonism, headache, extrapyramidal disorder, dizziness, sedation, increased dream activity, somnolence, tremor, rigidity, hypersalivation, bradykinesia, oculogyric crisis, akathisia (hyperkinesia) and acute dystonia, hypokinesia, lethargy, dyskinesia
	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, hypoaesthesia, paraesthesia, cerebrovascular disorder, diabetic coma, head titubation, hypersomnia, speech disorder, movement disorder
Nervous system disorders	Frequency unknown	Dysgeusia*, catatonia*, somnambulism*, sleep-related eating disorder*

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Eye disorders	Frequent Less frequent Frequency unknown	Blurred vision Photophobia, dry eyes, increased lacrimation, ocular hyperaemia, glaucoma, eye movement disorder, eye rolling, eyelid margin crusting, conjunctivitis, eye discharge, eye swelling, reduced visual acuity Floppy iris syndrome (intraoperative)*
Ear and labyrinth disorders	Less frequent	Vertigo, tinnitus, ear pain
Cardiac disorders	Frequent Less frequent Frequency unknown	Tachycardia Chest pain, palpitations, atrioventricular block, QT prolongation, abnormal electrocardiogram, conduction disorders, sinus dysrhythmia, bradycardia Atrial fibrillation*
Vascular disorders	Frequent Less frequent	Hypertension Hypotension, orthostatic hypotension, flushing, pulmonary embolism, venous thrombosis

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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, hyperventilation, dysphonia
	Frequency unknown	Sleep apnoea syndrome*
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, swollen tongue, swollen lips, cheilitis
	Frequency unknown	Ileus*, intestinal obstruction*, pancreatitis*
Hepatobiliary disorders	Less frequent	Increased transaminases, gamma-glutamyltransferase and hepatic enzymes
	Frequency unknown	Jaundice*

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Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Skin rash, itching, erythema Dry skin, increased pigmentation, increased sweating, photosensitivity, seborrhoea, urticaria, pruritus, eczema, acne, hyperkeratosis, skin disorder, skin lesions, drug eruption, dandruff, skin discolouration, angioedema Alopecia*
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Back pain, arthralgia, muscle spasms, musculoskeletal pain, pain in extremities Increase in blood creatine phosphokinase, abnormal posture, joint stiffness, joint swelling, muscular weakness, myalgia, neck pain, rhabdomyolysis
Renal and urinary disorders	Frequent Less frequent	Enuresis, micturition disturbances or polyuria Pollakiuria, urinary retention, dysuria, urinary incontinence
Pregnancy, puerperium and perinatal conditions	Frequency unknown	Drug withdrawal syndrome in neonates*

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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 administrative 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, decrease in body temperature, peripheral coldness, drug withdrawal syndrome, face oedema, influenza-like illness
	Frequency unknown	Induration, hypothermia*

Investigations	Frequent Less frequent	Increased blood prolactin, increased weight Abnormal electrocardiogram, increased blood glucose, increased transaminases, decreased white blood cell count, increased body temperature, increased eosinophil count, decreased haemoglobin, increased blood creatine phosphokinase, decreased body temperature
Injury and poisoning	Frequent Less frequent	Fall Procedural pain

*Post marketing adverse events

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.

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.

The safety and efficacy of ZOXADON ODT in children under 5 years of age has not been demonstrated.

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.

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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 online service for adverse drug reaction reporting by following the links:

https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/

https://www.sahpra.org.za/Publications/Index/8.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

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 and convulsions have been reported. Torsade de pointes has been reported in association with combined overdose of oral risperidone and paroxetine. In the case of acute overdosage, the possibility of multiple medicine involvement should
be considered.

Management of overdose:

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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.

Mechanism of action

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:

The ODT tablet disintegrates in the oral cavity, releasing risperidone into saliva prior to swallowing. After ingestion, 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.

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Risperidone is bound to albumin and alpha1-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.

Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal or hepatic impairment.

Risperidone should be used with caution in these groups of patients.

Paediatric population

The pharmacokinetics of risperidone, 9-hydroxyrisperidone and the active moiety in children are similar to those in adults.

5.3 Preclinical safety data

Not applicable.

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.

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6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°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 in 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

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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PROFESSIONAL INFORMATION

8. REGISTRATION NUMBER(S)

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

30 August 2024