Zoxadon 0,5 mg, 1, 2, 3 and 4 mg
Pharma Dynamics (Pty) Ltd
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Implementation (67 working days from the date of submission)
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PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ZOXADON 0,5 mg tablets

ZOXADON 1 mg tablets

ZOXADON 2 mg tablets

ZOXADON 3 mg tablets

ZOXADON 4 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZOXADON 0,5 mg tablets: Each tablet contains 0,5 mg risperidone.

ZOXADON 1 mg tablets: Each tablet contains 1 mg risperidone.

ZOXADON 2 mg tablets: Each tablet contains 2 mg risperidone.

ZOXADON 3 mg tablets: Each tablet contains 3 mg risperidone.

ZOXADON 4 mg tablets: Each tablet contains 4 mg risperidone.

Each 0,5 mg tablet contains sugar (lactose anhydrous 61,70 mg).

Each 1 mg tablet contains sugar (lactose anhydrous 61,25 mg).

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Each 2 mg tablet contains sugar (lactose anhydrous122,50 mg).

Each 3 mg tablet contains sugar (lactose anhydrous 183,75 mg).

Each 4 mg tablet contains sugar (lactose anhydrous 245,00 mg).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet.

ZOXADON 0,5 mg: Light yellow, oval, biconvex, scored, film coated tablets, marked T. Size 8 x 5 mm

ZOXADON 1 mg: White, oval, biconvex, scored, film coated tablets, marked T1. Size 8 x 5 mm

ZOXADON 2 mg: White, oval, biconvex, scored, film coated tablets, marked T2. Size 10 x 5 mm

ZOXADON 3 mg: White, oval, biconvex, scored, film coated tablets, marked T3. Size 11 x 6,5 mm

ZOXADON 4 mg: White, oval, biconvex, scored, film coated tablets, marked T4. Size 14 x 7,5 mm

4. CLINICAL PARTICULARS

PROFESSIONAL INFORMATION

4.1 Therapeutic indications

ZOXADON 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 tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. In patients who have shown an initial treatment response, ZOXADON tablets are also effective in maintaining the clinical improvement
- 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
- 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.

4.2 Posology and method of administration

Schizophrenia

ZOXADON may be given once or twice daily.

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Patients should start with ZOXADON 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 generally 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 if additional sedation is
required.

Elderly patients and patients with renal and hepatic impairment

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.

Children

PROFESSIONAL INFORMATION

Schizophrenia: 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

ZOXADON 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 must be evaluated and justified on an ongoing basis.

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

Conduct and other disruptive behaviour disorders in children 5 - 12 years of age

Patients < 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 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 liver 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.

Caution should be exercised with these groups of patients as clinical experience is lacking in these patient populations. It is recommended to halve both the starting dose and the subsequent dose increments.

Method of administration

ZOXADON is for oral administration, food does not affect the absorption.

Switching from other antipsychotics to ZOXADON:

When medically appropriate, gradual discontinuation of the previous treatment, while ZOXADON therapy is initiated, is recommended.

Also, if medically appropriate, when switching patients from depot antipsychotics, initiate ZOXADON therapy in place of the next scheduled injection. The need for continuing existing anti-Parkinson

medicines should be re-evaluated periodically.

PROFESSIONAL INFORMATION

Missed dose:

Doctors should advise patients who forget to take ZOXADON 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
- conduct and other disruptive behaviour disorders in children: ZOXADON is contraindicated in children under 5 years of age as efficacy and safety in these children have not been demonstrated
- parkinson's disease and Lewy body dementia (see section 4.2).

4.4 Special warnings and precautions for use

Elderly Patients with Dementia

Overall Mortality:

Elderly patients with dementia treated with atypical antipsychotic medicines have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic medicines, including risperidone. In placebo-controlled trials with oral

risperidone, the incidence of mortality was 4,0 % for risperidone -treated patients compared to 3,1 % for placebo-treated patients. The mean age (range) of patients who died was 86 years (range 67-100 years).

PROFESSIONAL INFORMATION

Concomitant use with furosemide

In risperidone, as in ZOXADON, placebo-controlled trials in elderly patients with dementia, there was a higher mortality in patients treated with furosemide and ZOXADON when compared to patients treated
with ZOXADON 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 was an overall risk for mortality and should be carefully avoided in these patients.

Cerebrovascular Adverse Events

Cerebrovascular adverse events (CVAE), including cerebrovascular accidents and transient ischaemic attacks have been reported during treatment with ZOXADON. In placebo-controlled clinical trials in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events, including cerebrovascular accidents, transient ischaemic attacks and fatalities, in patients treated with ZOXADON compared to patients receiving placebo (mean age 85 years; range 73 - 97 years).

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 other types of dementias other than Alzheimer's should not be treated with ZOXADON.

PROFESSIONAL INFORMATION

Risk predictors for stroke in the individual patient should be taken into account before prescribing ZOXADON to elderly patients with dementia. 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.

ZOXADON 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.
Patients should be reassessed regularly, and the need for continuing treatment reassessed.

Hypotension

Due to the alpha-blocking activity of ZOXADON, (orthostatic) hypotension can occur, especially during the initial dose-titration period. ZOXADON should be used with caution in patients with known cardiovascular disease, and the dosage should be gradually titrated, as recommended. A dose reduction should be considered if hypotension occurs.

PROFESSIONAL INFORMATION

Leukopenia, neutropenia, and agranulocytosis

Events of leukopenia, neutropenia and agranulocytosis have been reported with the use of ZOXADON. Agranulocytosis has been reported during post-marketing surveillance. Patients with a history of a clinically significant low white blood cell count or a medicine-induced leukopenia/neutropenia should be monitored during therapy, and discontinuation of ZOXADON should be considered at the first sign of a clinically significant decline in white blood cells 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 neutrophil count < 1 x 109 /L) should discontinue ZOXADON and have their white blood cells followed until recovery.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with ZOXADON. 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 ZOXADON and preventative measures undertaken.

Tardive dyskinesia /extrapyramidal symptoms (TD/EPS)

Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible, involuntary dyskinetic movements may develop in patients treated with ZOXADON. 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.

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 treatment is withdrawn.

ZOXADON 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 should be prescribed in a manner that is most likely to minimise the risk of TD.

ZOXADON 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, ZOXADON 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. 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.

The management of NMS should include:

1. Immediate discontinuation of all antipsychotic medicines including ZOXADON and other medicines not essential to concurrent therapy;
2. Intensive symptomatic treatment and medical monitoring;
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 antipsychotic medicine treatment after recovery from NMS, the potential reintroduction of medicine therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

PROFESSIONAL INFORMATION

Dementia associated with Parkinson's disease and senile dementia

(See section 4.3).

Prescribing ZOXADON to patients with Parkinson's disease or Dementia with Lewy Bodies (DLB) is not recommended since both groups may be at risk of Neuroleptic Malignant Syndrome (NMS) as

well as having an increased sensitivity to antipsychotic medications such as ZOXADON (see section 4.3).

Manifestations of this increased sensitivity can include confusion, obtundation, and postural instability with frequent falls, in addition to extrapyramidal symptoms. In addition, in clinical trials, risperidone-treated elderly patients had a higher mortality than placebo-treated elderly patients.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis and hyperosmolar coma or death, and exacerbation of pre-existing diabetes mellitus have been reported in patients treated with ZOXADON. Patients with an established diagnosis of diabetes mellitus who are started on ZOXADON 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 should be monitored for symptoms of hyperglycaemia including polydipsia,

polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with ZOXADON should undergo fasting blood glucose testing. In some cases, hyperglycaemia was resolved when ZOXADON was discontinued. However, some patients required continuation of antidiabetic treatment despite discontinuation of ZOXADON.

Weight gain

Patients may be advised to refrain from excessive eating in view of the possibility of weight gain. Significant weight gain has been reported, therefore careful monitoring is advised.

Hyperprolactinemia

Hyperprolactinemia is a common side effect of treatment with ZOXADON. 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, galactorrhoea).
Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in
patients with relevant medical history.
ZOXADON should be used with caution in patients with pre-existing

hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

QT interval

Caution should be exercised when ZOXADON is prescribed in patients with a history of cardiac dysrhythmias, in patients with congenital long QT syndrome, 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.

Priapism

Medicines with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with ZOXADON during post-marketing surveillance (see section 4.8).

Body temperature regulation

Disruption of the body's ability to reduce the core body temperature may occur. Appropriate care is advised when prescribing ZOXADON to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity or being subject to dehydration.

Antiemetic effect

PROFESSIONAL INFORMATION

An antiemetic effect was observed in preclinical studies with risperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain medicines or of conditions
such as intestinal obstruction, Reye's syndrome, and brain tumour.

Intraoperative Floppy Iris Syndrome

Cases of intraoperative floppy iris syndrome (IFIS) during cataract surgery have been reported in patients taking risperidone, such as in ZOXADON. 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. Postoperative 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 risperidone.

Elderly patients and patients with renal and hepatic impairment

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction 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).
It is recommended to halve both the starting dose and the subsequent dose increments in patients and patients with renal or liver insufficiency.

PROFESSIONAL INFORMATION

Pituitary adenomas

Benign pituitary adenomas have been reported during post-marketing surveillance. No causal association could be detected.

Seizures

ZOXADON should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Information on excipients of ZOXADON

ZOXADON contains lactose. Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ZOXADON.

ZOXADON contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Paediatric population

Before ZOXADON is prescribed to a child or adolescent with conduct disorder, they should be fully assessed for physical and social causes of the aggressive behaviour such as pain or inappropriate environmental demands.

The sedative effect of ZOXADON should be closely monitored in this population because of possible consequences on learning ability. A change in the time of

administration of risperidone could improve the impact of the sedation on attention faculties of children and adolescents.

Risperidone was associated with mean increases in body weight and body mass index (BMI). Baseline weight measurement prior to treatment and regular weight monitoring are recommended. Changes in height in the long-term open-label extension studies were within expected age-appropriate norms. The effect of long-term ZOXADON treatment on sexual maturation and height has not been adequately studied.

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.

Results from a small post-marketing observational study showed that risperidone-exposed subjects between the ages of 8-16 years were on average approximately 3.0 to 4.8 cm taller than those who received other atypical antipsychotic medications. This study was not adequate to determine whether exposure to risperidone had any impact on final adult height, or whether the result was due to a direct effect of risperidone on bone growth, or the effect of the underlying disease itself on bone growth, or the result of better control of the underlying

disease with resulting increase in linear growth. During treatment with ZOXADON regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.

For specific posology recommendations in children and adolescents see section 4.2.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic-related interactions

Medicines known to prolong the QT interval

As with other antipsychotics, caution is advised when prescribing risperidone, as in ZOXADON, with medicines known to prolong the QT interval, such as antiarrhythmics (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 risperidone. This list is indicative and not exhaustive.

Centrally-acting medicines and alcohol

Risperidone, as in ZOXADON, should be used with caution in combination with other centrally-acting substances, notably including alcohol, opiates, antihistamines, and benzodiazepines, due to the
increased risk of sedation.

PROFESSIONAL INFORMATION

Levodopa and dopamine agonists

ZOXADON 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 post-marketing with concomitant use of risperidone, as in ZOXADON, and antihypertensive treatment (see section 4.4).

Psychostimulants

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

Paliperidone

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

Pharmacokinetic-related interactions

Risperidone is mainly metabolised through CYP2D6, and to a lesser extent through CYP3A4. Both risperidone and its active metabolite 9-hydroxy-risperidone are substrates of P-glycoprotein (P-gp).

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Substances that modify CYP2D6 activity, or substances strongly inhibiting or inducing CYP3A4 and/or P-gp activity, may influence the pharmacokinetics of the risperidone active antipsychotic fraction.

Strong CYP2D6 inhibitors

Co-administration of ZOXADON with a strong CYP2D6 inhibitor may increase the plasma concentrations of risperidone, 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 risperidone in a similar way. When concomitant paroxetine, quinidine, or another strong CYP2D6 inhibitor, especially at higher doses, is initiated or discontinued, the physician should re-evaluate the dosing of ZOXADON.

CYP3A4 and/or P-gp inhibitors

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

CYP3A4 and/or P-gp inducers

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

initiated or discontinued, the physician should re-evaluate the dosing of ZOXADON.

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 medicines

When ZOXADON is taken together with highly protein-bound ~~drugs~~ medicines, there is no clinically relevant displacement of either medicine ~~drug~~ 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.

Effect of other medicines on the pharmacokinetics of risperidone

Antibacterials:

- erythromycin, a moderate CYP3A4 inhibitor and P-gp inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction
- rifampicin, a strong CYP3A4 inducer and a P-gp inducer, decreased the plasma concentrations of the active antipsychotic fraction.

Anticholinesterases:

Donepezil and galantamine, both CYP2D6 and CYP3A4 substrates, do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction.

Antiepileptics:

- carbamazepine, a strong CYP3A4 inducer and a P-gp inducer, has been shown to decrease the plasma concentrations of the active antipsychotic fraction of risperidone. Similar effects may be observed with e.g., phenytoin and phenobarbital which also induce CYP3A4 hepatic enzyme, as well as P-glycoprotein. On discontinuation of carbamazepine or other hepatic enzyme inducers, the dosage of ZOXADON should be re-evaluated and, if necessary, decreased
- topiramate modestly reduced the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance
- ZOXADON does not show a clinically relevant effect on the pharmacokinetics of valproate or topiramate.

Antifungals:

- itraconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased 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 increased the plasma concentrations of risperidone and decreased the plasma concentrations of 9-hydroxy-risperidone.

Antipsychotics:

- phenothiazines may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

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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.

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 active antipsychotic fraction.

Gastrointestinal medicines:

- h2-receptor antagonists: Cimetidine and ranitidine, both weak inhibitors of CYP2D6 and CYP3A4, increased the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction.

Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants:

- fluoxetine, a strong CYP2D6 inhibitor, increases the plasma concentration of risperidone, but less so of the active antipsychotic fraction. When concomitant fluoxetine is initiated or discontinued, the dosing of ZOXADON should be re-evaluated.
- paroxetine, a strong CYP2D6 inhibitor, increases the plasma concentrations of risperidone, but, at dosages up to 20 mg/day, less so of the active antipsychotic

fraction. However, higher doses of paroxetine may elevate concentrations of the risperidone active antipsychotic fraction. When concomitant paroxetine is initiated or discontinued, the dosing of ZOXADON 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 risperidone or 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.

Effect of risperidone on the pharmacokinetics of other ~~medicinal products~~ medicines

Antiepileptics:

- risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate or topiramate.

Antipsychotics:

- aripiprazole, a CYP2D6 and CYP3A4 substrate: Risperidone tablets or injections did not affect the pharmacokinetics of the sum of aripiprazole and its active metabolite, dehydroaripiprazole.

Digitalis glycosides:

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- risperidone does not show a clinically relevant effect on the pharmacokinetics of digoxin.

Lithium:

- risperidone does not show a clinically relevant effect on the pharmacokinetics of lithium.

Concomitant use of risperidone with furosemide

- see section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Venlafaxine administered under steady-state conditions at 150 mg/day inhibited the CYP2D6-mediated metabolism of ZOXADON (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32 % increase in risperidone AUC. However, venlafaxine co-administration did not significantly alter the pharmacokinetic profile of the total active antipsychotic fraction.

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

Food does not affect the absorption of ZOXADON.

Paediatric population

PROFESSIONAL INFORMATION

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 in children and adolescents did not alter the pharmacokinetics and efficacy of ZOXADON.

4.6 Fertility, pregnancy, and lactation

Pregnancy

The safety of ZOXADON in pregnancy and lactating women has not been established. Reversible extrapyramidal symptoms, including hypertonia, hypotonia, jitteriness, tremor, muscle rigidity, twitching and convulsions, feeding disorder and withdrawal symptoms have been observed in neonates following post-marketing use of ZOXADON during the last trimester of pregnancy.

Breastfeeding

Risperidone and 9-hydroxy-risperidone are excreted in human breast milk. Therefore, women receiving ZOXADON should not breastfeed.

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 the non-clinical studies.

PROFESSIONAL INFORMATION

4.7 Effects on ability to drive and use machines

ZOXADON 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 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

a. 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.

b. Tabulated summary of adverse reactions

System Organ Class	Frequency	Side effects
Infections and Infestations	Frequent	Pneumonia, bronchitis, upper respiratory tract infection, urinary tract infection, influenza
	Less frequent	Sinusitis, ear infection, respiratory tract infection, cystitis, eye infection, tonsillitis, otitis media, onychomycosis, cellulitis, localised infection, viral infection, acarodermatitis, infection, otitis media chronic

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Blood and lymphatic system disorders	Less frequent Frequency unknown	Neutropenia, white blood cell count decreased, anaemia, haematocrit decreased, eosinophil count increased Thrombocytopenia*, agranulocytosis*
Immune system disorders	Less frequent Frequency unknown	Hypersensitivity Anaphylactic reaction*, angioedema*
Endocrine disorders	Frequent Less frequent Frequency unknown	Hyperprolactinaemia Increased plasma prolactin levels and associated manifestations, glucose urine present Inappropriate antidiuretic hormone secretion*
Metabolism and nutrition disorders	Frequent Less frequent Frequency unknown	Weight increased, increased appetite, decreased appetite Anorexia, polydipsia, hyperglycaemia, weight decreased, hyperinsulinaemia Diabetes mellitus*, blood cholesterol increased*, water intoxication*, hypoglycaemia*, blood triglycerides increased*, diabetic ketoacidosis*

PROFESSIONAL INFORMATION

Psychiatric disorders	Frequent Less frequent Frequency unknown	Insomnia, sleep disorder, agitation, depression, anxiety Confusional state, libido decreased, nervousness, nightmare, blunted affect, anorgasmia, Mania*
Nervous system disorders	Frequent Less frequent	Dizziness, sedation/somnolence, parkinsonism, headache, akathisia, dystonia, dyskinesia, tremor Tardive dyskinesia, neuroleptic malignant syndrome, cerebral ischaemia, unresponsive to stimuli, loss of consciousness, depressed level of consciousness, convulsion, syncope, psychomotor hyperactivity, balance disorder, coordination abnormal, dizziness postural, disturbance in attention,

PROFESSIONAL INFORMATION

Nervous system disorders continued…	Frequency unknown	dysarthria, hypoaesthesia, paraesthesia, cerebrovascular accident, transient ischaemic attack, hypersomnia, speech disorder, head titubation, psychomotor hyperactivity, diabetic coma, cerebrovascular disorder, movement disorder Dysgeusia*, catatonia*, somnambulism*, sleep-related eating disorder*
Eye disorders	Frequent Less frequent Frequency unknown	Blurred vision, Conjunctivitis photophobia, dry eye, lacrimation increased, ocular hyperaemia, glaucoma, eye movement disorder, eye rolling, eyelid margin crusting, eye discharge, eye swelling, reduced visual acuity Floppy iris syndrome (intraoperative)*
Ear and labyrinth disorders	Less frequent	Vertigo, tinnitus, ear pain

PROFESSIONAL INFORMATION

Cardiac disorders	Frequent Less frequent Frequency unknown	Tachycardia Atrial fibrillation, atrioventricular block, conduction disorder, bundle branch block, bradycardia, electrocardiogram abnormal, palpitations, sinus arrhythmia Electrocardiogram QT prolonged*
Vascular disorders	Frequent Less frequent	Hypertension Hypotension, orthostatic hypotension, flushing, pulmonary embolism, venous thrombosis
Respiratory, thoracic, and mediastinal disorders	Frequent Less frequent Frequency unknown	Dyspnoea, pharyngolaryngeal pain, cough, epistaxis, nasal congestion Pneumonia aspiration, pulmonary congestion, respiratory tract congestion, rales, wheezing, dysphonia, respiratory disorder, hyperventilation Sleep apnoea syndrome*
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Constipation, dyspepsia, nausea abdominal discomfort, vomiting, diarrhoea, dry mouth, toothache Faecal incontinence, faecaloma, gastroenteritis, dysphagia, flatulence, swollen tongue, cheilitis, lip swelling Intestinal obstruction*, pancreatitis*, paralytic ileus*

PROFESSIONAL INFORMATION

Hepatobiliary disorders	Less frequent Frequency unknown	Transaminases increased, gamma-glutamyltransferase increased, hepatic enzyme increased Jaundice*
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Skin rash, erythema Urticaria, pruritus, alopecia, hyperkeratosis, eczema, dry skin, skin discolouration, acne, seborrhoeic dermatitis, skin disorder, skin lesion, drug eruption, dandruff, angioedema Alopecia*
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Muscle spasms, musculoskeletal pain, back pain, arthralgia Blood creatine phosphokinase increased, posture abnormal, joint stiffness, joint swelling muscular weakness, neck pain, rhabdomyolysis
Renal and urinary disorders	Frequent Less frequent	Enuresis Pollakiuria, urinary retention, dysuria, urinary incontinence
Pregnancy, puerperium, and perinatal conditions	Frequency unknown	Neonatal drug withdrawal syndrome*

PROFESSIONAL INFORMATION

Reproductive system and breast disorders	Less frequent	Erectile dysfunction, ejaculation disorder, amenorrhoea, menstrual disorder, gynaecomastia, galactorrhoea, sexual dysfunction, breast pain, breast discomfort, vaginal discharge, menstruation delayed, breast engorgement, breast enlargement, breast discharge
	Frequency unknown	Priapism*
General disorders and administrative site conditions	Frequent	Oedema, pyrexia, chest pain, asthenia, fatigue, pain, peripheral oedema
	Less frequent	Face oedema, chills, body temperature increased, gait abnormal, thirst, chest discomfort, malaise, feeling abnormal, discomfort, body temperature decreased, peripheral coldness, drug withdrawal syndrome, induration, influenza-like illness, sluggishness
	Frequency unknown	Hypothermia*
Injury, poisoning and procedural complications	Frequent	Fall
	Less frequent	Procedural pain

*Post marketing adverse events.

c. Paediatric population

PROFESSIONAL INFORMATION

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

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 link: 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'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.

Torsade de pointes has been reported in association with combined overdose of oral risperidone and paroxetine.

PROFESSIONAL INFORMATION

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 arrhythmias. 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 medication 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.

PROFESSIONAL INFORMATION

It is a selective monoaminergic antagonist.

Risperidone has affinity for serotonin-5-HT_2, dopamine- D_2, H_1-histamine, alpha1- and alpha2- adrenergic receptors.

Risperidone has no affinity for cholinergic receptors. It is a potent D_2 antagonist.

5.2 Pharmacokinetic properties

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.

Following 6 mg or 8 mg once daily, peak levels of the active moiety were about 30 % higher and trough levels about 30 % lower than the peaks and troughs following 3 and 4 mg twice daily. The bioavailability of the 6 mg tablet is not equivalent to that of 2 by 3 mg and the bioavailability of the 8 mg tablet is not equivalent to that of the 2 by 4 mg tablets. Therefore, these tablet strengths cannot be used interchangeably.

Steady state is reached within 1 day for risperidone in most patients and 4 - 5 days for 9-hydroxy-risperidone. Risperidone plasma concentration is dose-proportional within the therapeutic dose-range.

Risperidone is bound to albumin and alpha1-acid glycoprotein. Plasma protein binding of risperidone is 88 % and 77 % for 9-hydroxyl- risperidone.

Biotransformation:

PROFESSIONAL INFORMATION

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

Elimination:

After oral administration, the half-life of risperidone is about 3 hours.

The elimination half-life of 9-hydroxy- risperidone and the active antipsychotic fraction is 24 hours.

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

Risperidone showed significantly higher active plasma concentrations and slower elimination in the elderly and in patients with moderately severe renal insufficiency. The plasma concentrations of risperidone were normal in patients with mild to moderate liver insufficiency.

Pharmacokinetics in special patient groups

Patients with hepatic impairment:

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 hepatic impairment.

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

Patients with renal impairment:

PROFESSIONAL INFORMATION

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than normal adults. Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal impairment.

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

Paediatric population

The pharmacokinetics of risperidone, 9-hydroxy-risperidone 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

Core

Lactose anhydrous

Magnesium stearate

Microcrystalline cellulose

Pregelatinised starch.

Coating [Opadry white 03F28470 (1/2/3/4 mg) or Opadry yellow 03F32566 (0,5 mg)]:

Hypromellose 6

PROFESSIONAL INFORMATION

Macrogol 6000

Titanium dioxide

Iron oxide yellow (0,5 mg only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

For tablets in blisters: Keep the blisters in the carton until required for use.

For tablets in containers: keep well closed in the original container.

6.5 Nature and contents of container

ZOXADON is packed into transparent PVC-PVDC/Al heat sealed blisters.

ZOXADON is also packed into HDPE containers with a snap-on LDPE cap with a tamper evident ring.

Pack size: 20 or 30 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

PROFESSIONAL INFORMATION

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 NUMBER(S)

ZOXADON 0,5 mg: A41/2.6.5/0468

ZOXADON 1 mg: A41/2.6.5/0445

ZOXADON 2 mg: A41/2.6.5/0446

ZOXADON 3 mg: A41/2.6.5/0469

ZOXADON 4 mg: A41/2.6.5/0470

9. DATE OF FIRST AUTHORISATION

09 December 2008

10. DATE OF REVISION OF THE TEXT

06 March 2024

PROFESSIONAL INFORMATION

NAMIBIA:

ZOXADON 0,5 mg: 10/2.6.5/0021

ZOXADON 1 mg: 10/2.6.5/0022

ZOXADON 2 mg: 10/2.6.5/0023

ZOXADON 3 mg: 10/2.6.5/0024

ZOXADON 4 mg:10/2.6.5/0025

ZOXADON 6 mg: 10/2.6.5/0026