1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE

ZOLNOXS 10 mg TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZOLNOXS 10 mg TABLETS contains 10 mg zolpidem as zolpidem tartrate.

Contains sugar: Lactose monohydrate 49,40 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

White to off-white capsule-shaped film-coated tablet with a breakline on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ZOLNOXS 10 mg TABLETS is indicated in adults for the short-term treatment of insomnia.

ZOLNOXS 10 mg TABLETS, or a short-acting hypnotic, is only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2. Posology and method of administration

Posology

Treatment should be as short as possible. Generally, the duration of treatment varies from a few days to two weeks with a maximum, including the tapering off process, of four weeks.

In certain cases, extension beyond the maximum treatment period may be necessary. If so, it should not take place without re-evaluation of the patient's status. ZOLNOXS 10 mg TABLETS should be taken just before going to bed.

Dose: The recommended daily dose for adult males is 10 mg immediately before bedtime.
The recommended adult dose for females is 5 mg immediately before bedtime.
The risk of impaired mental alertness is higher if ZOLNOXS 10 mg TABLETS is taken with less than a full night of sleep remaining; therefore, a period of at least 8 hours is recommended between taking ZOLNOXS 10 mg TABLETS and performing activities such as driving or operating other machinery (see section 4.7).

Elderly and hepatic impairment

In elderly or debilitated patients who may be especially sensitive to the effects of ZOLNOXS 10 mg TABLETS, and in patients with hepatic insufficiency who do not clear the medicine as rapidly as normal individuals, a dose of 5 mg is recommended, which should be exceeded only under exceptional circumstances. The total dose of ZOLNOXS 10 mg TABLETS should not exceed 10 mg in any patient.

Paediatric population

Safety and effectiveness of ZOLNOXS 10 mg TABLETS in paediatric patients under the age of 18 years have not been established. ZOLNOXS 10 mg TABLETS should not be prescribed in this population (see section 4.3).

Method of administration

For oral administration.

4.3. Contraindications

ZOLNOXS 10 mg TABLETS is contraindicated in:

- Patients with hypersensitivity to zolpidem or to any of the excipients in ZOLNOXS 10 mg (see section 6.1)
- Myasthenia gravis.
- Sleep apnoea syndrome and/or obstructive sleep apnoea.
- Acute and severe pulmonary insufficiency.
- Severe hepatic insufficiency (see section 4.4).
- Patients who have previously experienced an episode of complex sleep behaviour with eszopiclone, zaleplon, or zolpidem, as in ZOLNOXS 10 mg TABLETS (see section 4.4).
- Acute and/or severe respiratory depression.
- Patients with psychotic illness.
- Children under the age of 18.
- Pregnancy and lactation (see section 4.6).

4.4. Special warnings and precautions for use

Risk of serious injuries caused by sleep walking using insomnia-medicines.

Duration of treatment

The cause of insomnia should be identified wherever possible and the underlying factors treated before ZOLNOXS 10 mg TABLETS is prescribed. The failure of insomnia to remit after a 7 to 14-day course of treatment may indicate the presence of a primary psychiatric or physical disorder, and the patient should be carefully re-evaluated at regular intervals. The duration of treatment should be as short as possible and should not exceed 4 weeks, including the tapering off process (see section 4.2). Extensions beyond these periods should not take place without re-evaluation of the situation. It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased.

Tolerance

Some loss of efficacy of the hypnotic effects of ZOLNOXS 10 mg TABLETS may develop after repeated use for a few weeks.

Amnesia

Hypnotic medicines, such as ZOLNOXS 10 mg TABLETS, may induce anterograde amnesia. The condition occurs most often several hours after ingesting ZOLNOXS 10 mg TABLETS and therefore, to reduce this risk, patients should ensure that they will be able to have an uninterrupted sleep of 8 hours. Anterograde amnesia may occur using therapeutic dosages of ZOLNOXS 10 mg TABLETS, the risk increasing at higher dosages. Amnesic effects may be

associated with inappropriate behaviour.

Rebound insomnia

A transient syndrome, whereby the symptoms that led to treatment with sedative hypnotic medicines recur in an enhanced form, may occur on withdrawal of ZOLNOXS 10 mg TABLETS. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

The syndrome is more likely to develop when ZOLNOXS 10 mg TABLETS is discontinued abruptly, and therefore treatment should be withdrawn gradually. Moreover, it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms, should they occur while ZOLNOXS 10 mg TABLETS is being discontinued.

There are indications that, in the case of hypnotics with short duration of action, such as ZOLNOXS 10 mg TABLETS, withdrawal phenomena can manifest within the dosage interval, especially when the dosage is high.

Psychiatric and paradoxical reactions

Reactions like restlessness, exacerbated insomnia, agitation, irritability, aggressiveness, delusion, anger, rages, nightmares, hallucinations, psychoses, inappropriate/abnormal behaviour and other adverse behavioural effects are known to occur when using ZOLNOXS 10 mg TABLETS (see section 4.8). Should this occur, use of ZOLNOXS 10 mg TABLETS should be discontinued. These reactions are more likely to occur in children (see section 4.3) and in the elderly.

Risk from concomitant use of opioids

Concomitant use of ZOLNOXS 10 mg TABLETS and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of ZOLNOXS 10 mg TABLETS with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe ZOLNOXS 10 mg TABLETS concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patient should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

Dependence and abuse

Use of ZOLNOXS 10 mg TABLETS (even at therapeutic doses) may lead to the development of abuse and/or physical and psychological dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see *Rebound insomnia* above).

ZOLNOXS 10 mg TABLETS should be used with extreme caution in patients with current or a history of alcohol, substance or medicine abuse or dependence (see *History of alcohol or medicine abuse* below*)*.

The risk of dependence increases with the dose and duration of treatment, it is also greater in patients with a history of alcohol or medicine abuse. Because persons with a history of

psychiatric disorders or addiction to, or abuse of, medicines or alcohol are at increased risk of habituation and dependence, they should be under careful surveillance when receiving ZOLNOXS 10 mg TABLETS. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms.

Withdrawal syndrome

Withdrawal signs and symptoms may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. Symptoms may range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors and convulsions. In severe cases, the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Specific patient groups:

For the elderly

See section 4.2

Respiratory insufficiency

Caution should be observed when prescribing ZOLNOXS 10 mg TABLETS to patients with compromised respiratory function since hypnotics, such as ZOLNOXS 10 mg TABLETS, have been shown to impair respiratory drive.

Suicidal ideation, suicide attempt, suicide and depression

Increased incidence of suicidal ideation, suicide attempt and suicide in patients with or without depression, and treated with benzodiazepines and other hypnotics, including zolpidem, as in ZOLNOXS 10 mg TABLETS, may occur. However, a causal relationship has not been

established.

ZOLNOXS 10 mg TABLETS should not be used as the primary treatment of depressive syndromes.

ZOLNOXS 10 mg TABLETS should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present, therefore, the least amount of ZOLNOXS 10 mg TABLETS that is feasible, should be supplied to these patients because of the possibility of intentional overdosage by the patient. Pre-existing depression may be unmasked during the use of ZOLNOXS 10 mg TABLETS. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

Psychotic illness

ZOLNOXS 10 mg TABLETS should not be used in patients with psychotic illness (see section 4.3).

History of alcohol or medicine abuse

Extreme caution should be exercised when prescribing ZOLNOXS 10 mg TABLETS for patients with a history of drug or alcohol abuse.

ZOLNOXS 10 mg TABLETS should not be used in the above-mentioned patients. These patients should be under careful surveillance when receiving ZOLNOXS 10 mg TABLETS since they are at risk of habituation and psychological dependence (see *Dependence and abuse* above).

Severe hepatic insufficiency

ZOLNOXS 10 mg TABLETS is not indicated to treat patients with severe hepatic insufficiency as it may precipitate encephalopathy (see section 4.2 and section 4.3).

Abnormal sleep-related events and amnesia

Reports of potentially dangerous, complex sleep related behaviours, amnesia and hallucinations have been associated with zolpidem use, as in ZOLNOXS 10 mg TABLETS. It is advised that, when considering the use of ZOLNOXS 10 mg TABLETS in the management of insomnia, prescribers should advise patients of the contraindications and precautions.

A study concluded that there was an association between zolpidem exposure and parasomnias, amnesia and hallucination.

Somnambulism and associated behaviours

Healthcare providers should not prescribe eszopiclone, zaleplon, or zolpidem, as in ZOLNOXS 10 mg TABLETS, to patients who have previously experienced complex sleep behaviours after taking any of these medicines (see section 4.3). Advise all patients the behaviours caused by these medicines have led to serious injuries or death.

The injuries are a result of sleep behaviours which include: sleepwalking, sleep driving and engaging in other activities while not fully awake.

Tell the patient to discontinue taking these medicines if they experience an episode of complex sleep behaviour.

Sleep walking and other associated behaviours such as “sleep driving”, preparing and eating food, making phone calls or having sex, with amnesia for the event, results in patients who had taken ZOLNOXS 10 mg TABLETS and were not fully awake.

The use of alcohol and other central nervous system (CNS) depressants with ZOLNOXS 10 mg TABLETS appears to increase the risk of such behaviours, as does the use of ZOLNOXS 10 mg TABLETS at doses exceeding the maximum recommended dose.

Discontinuation of ZOLNOXS 10 mg TABLETS should be advised for patients who have such behaviours (for example, sleep driving), due to the risk to the patient and others (see section 4.5 and section 4.8).

Severe injuries

Due to its pharmacological properties, ZOLNOXS 10 mg TABLETS can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries (see section 4.8).

Next-day psychomotor impairment

ZOLNOXS 10 mg TABLETS has CNS depressant effects. The risk of next-day psychomotor impairment, including impaired driving ability, is increased if:

- ZOLNOXS 10 mg TABLETS is taken within less than 8 hours before performing activities that require mental alertness (see section 4.7);
- a dose higher than the recommended dose is taken;

- ZOLNOXS 10 mg TABLETS is co-administered with other CNS depressants or with other medicines that increase the blood levels of ZOLNOXS 10 mg TABLETS, or with alcohol or illicit medicines (see section 4.5).

ZOLNOXS 10 mg TABLETS should be taken in a single intake immediately at bedtime and not be re-administered during the same night (see section 4.2).

Lactose warning

ZOLNOXS 10 mg TABLETS contains lactose monohydrate which may influence the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ZOLNOXS 10 mg TABLETS.

4.5. Interaction with other medicines and other forms of interaction

Not recommended:

Concomitant intake with alcohol.

The sedative effect may be enhanced when ZOLNOXS 10 mg TABLETS is used in combination with alcohol. This affects the ability to drive or use machines (see section 4.7).

Consider:

Combination with CNS depressants

Enhancement of the central depressive effects may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant medicines, narcotic analgesics, anti-epileptic medicines, anaesthetics and sedative antihistamines. Therefore, concomitant use of ZOLNOXS 10 mg TABLETS with these medicines may increase

drowsiness and next-day psychomotor impairment, including impaired driving ability (see section 4.4 and section 4.7).

Also, visual hallucinations in patients taking ZOLNOXS 10 mg TABLETS with antidepressants including bupropion, desipramine, fluoxetine, sertraline and venlafaxine may occur.

Co-administration of fluvoxamine may increase blood levels of ZOLNOXS 10 mg TABLETS, concurrent use is not recommended.

In the case of narcotic analgesics enhancement of euphoria may also occur, leading to an increase in psychological dependence.

Opioids

The concomitant use of sedative medicines such as benzodiazepines or related medicines such as ZOLNOXS 10 mg TABLETS with opioids may increase the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effects. The dosage and duration of concomitant use should be limited (see section 4.4).

CYP450 inhibitors and inducers

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of ZOLNOXS 10 mg TABLETS.

ZOLNOXS 10 mg TABLETS is metabolised via several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2. The pharmacodynamic effect of ZOLNOXS 10 mg TABLETS is decreased when it is administered with a CYP3A4 inducer such

as rifampicin and St. John's Wort. Co-administration of St. John's Wort may decrease blood levels of zolpidem, as in ZOLNOXS 10 mg TABLETS, concurrent use is therefore not recommended.

Routine dosage adjustment of ZOLNOXS 10 mg TABLETS is not considered necessary, but patients, should be advised that use of ZOLNOXS 10 mg TABLETS with ketoconazole may enhance the sedative effects.

Since CYP3A4 plays an important role in ZOLNOXS 10 mg TABLETS metabolism, possible interactions with medicines that are substrates or inducers of CYP3A4 should be considered.

Co-administration of ciprofloxacin may increase blood levels of ZOLNOXS 10 mg TABLETS, concomitant use is not recommended.

Other medicines

When ZOLNOXS 10 mg TABLETS is administered with warfarin, digoxin, ranitidine or cimetidine, there are no significant pharmacokinetic interactions.

4.6. Fertility, pregnancy and lactation

ZOLNOXS 10 mg TABLETS should not be used in pregnancy or lactation.

The safety of ZOLNOXS 10 mg TABLETS in pregnancy and lactation has not been established (see section 4.3).

Women of childbearing potential

If ZOLNOXS 10 mg TABLETS is prescribed to a woman of childbearing potential, she should be warned to contact her health care provider about stopping ZOLNOXS 10 mg TABLETS if she intends to become or suspects that she is pregnant.

Pregnancy

ZOLNOXS 10 mg TABLETS crosses the placenta.

Zolpidem, as in ZOLNOXS 10 mg TABLETS, increased incidence of cleft lip and palate associated with use of benzodiazepines, during pregnancy.

Reduced foetal movement and foetal heart rate variability may occur after administration of ZOLNOXS 10 mg TABLETS during the second and/or third trimester of pregnancy.

If ZOLNOXS 10 mg TABLETS is administered during the late phase of pregnancy, or during labour, effects on the neonate such as hypothermia, hypotonia, feeding difficulties ('floppy infant syndrome') and respiratory depression, due to the pharmacological action of ZOLNOXS 10 mg TABLETS, may occur. Cases of severe neonatal respiratory depression have been reported.

Newborn/neonate

Infants born to mothers who take ZOLNOXS 10 mg TABLETS chronically during the latter stages of pregnancy may develop physical dependence and may be at risk of developing

withdrawal symptoms in the post-natal period (see section 4.3). Appropriate monitoring of the newborn in the postnatal period is recommended.

Breastfeeding

ZOLNOXS 10 mg TABLETS appears in breast milk. ZOLNOXS 10 mg TABLETS should not be administered to breastfeeding mothers (see section 4.3).

Fertility

No data available.

4.7. Effects on ability to drive and use machines

ZOLNOXS 10 mg TABLETS has a major influence on the ability to drive and use machines. Since adverse reactions such as sedation, drowsiness, dizziness and vertigo have been reported in patients receiving ZOLNOXS 10 mg TABLETS, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that ZOLNOXS 10 mg TABLETS does not adversely affect their ability to do so safely (see section 4.8).

If insufficient sleep duration occurs, the likelihood of impaired alertness may increase (see section 4.4).

Driving ability impairment and behaviours such as 'sleep-driving' have occurred with zolpidem, as in ZOLNOXS 10 mg TABLETS, alone at therapeutic doses (see sections 4.4).

Furthermore, the co-administration of ZOLNOXS 10 mg TABLETS with alcohol and other CNS depressants increases the risk of such behaviours (see sections 4.4 and 4.5). Patients should be

warned not to use alcohol or other psychoactive substances when taking ZOLNOXS 10 mg TABLETS.

4.8. Undesirable effects

Tabulated list of adverse reactions for ZOLNOXS 10 mg TABLETS

System organ class	***Frequent***	***Less frequent***	***Unknown***
Infections and Infestations	Upper respiratory tract infection, lower respiratory tract infection		
Immune system disorders		Angioedema (angioneurotic oedema)	
Metabolism and nutrition disorders		Appetite disorder	
Psychiatric disorders	Hallucination, agitation, nightmare, depression, exacerbated insomnia	Confusional state, irritability, restlessness, aggression, somnambulism, euphoric mood, libido disorder, delusion, dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation), anger, psychosis, abnormal behaviour	
Nervous system disorders	Somnolence, headache, dizziness, anterograde amnesia (amnestic effects may be associated with inappropriate behaviour)	Paraesthesia, tremor, disturbance in attention, speech disorder, depressed level of consciousness, day time drowsiness, vertigo, light-headedness	Sleep behaviours which include: sleepwalking, sleep driving and engaging in other activities while not fully awake, parasomnias*
Eye disorders		Diplopia, vision abnormalities, vision blurred, visual impairment	
Respiratory, thoracic and mediastinal disorders		Respiratory depression	

Gastrointestinal disorders	Diarrhoea, nausea, vomiting, abdominal pain		
Hepato-biliary disorders		Elevated liver enzymes, hepatocellular, cholestatic or mixed liver injury	
Skin and subcutaneous tissue disorders		Rash, pruritus, hyperhidrosis, urticaria	
Musculoskeletal and connective tissue disorders	Back pain	Myalgia, muscle spasms, muscular weakness	
General disorders and administration site conditions	Fatigue	Gait disturbance, medicine tolerance, fall, malaise	

* parasomnia is an umbrella term for complex movements or behaviours during sleep, including abnormal dreaming, nightmares (paroniria) and sleepwalking (somnambulism).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

Following an overdose with ZOLNOXS 10 mg TABLETS alone, impairment of consciousness has ranged from somnolence to coma. Overdose cases involving multiple CNS depressant agents (e.g. alcohol), including ZOLNOXS 10 mg TABLETS, have resulted in more severe symptomatology, including fatal outcomes.

Treatment

General symptomatic and supportive measures should be used. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption.

Intravenous fluids should be administered as needed. Sedative medicines should be withheld even if excitation occurs. The value of dialysis in the treatment of overdose has not been determined, although haemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that ZOLNOXS 10 mg TABLETS is not dialysable.

The use of benzodiazepine-antagonists (e.g. flumazenil) may be considered where serious symptoms are observed. Patients should be kept under close observation as further doses of flumazenil may be necessary. Flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).

In the management of overdose with any medicine, it should be borne in mind that multiple medicines may have been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: Central nervous system depresssants

Pharmacotherapeutic group: A 2.2 Sedatives, hypnotics

ATC code: N05CF02

Mechanism of action

Zolpidem is an imidazopyridine compound with sedative/hypnotic effects. These effects are related to a specific agonist action at central receptors belonging to GABA-omega benzodiazepine-1 and benzodiazapine-2 macromolecular receptor complex, modulating the opening of the chloride ion channel. Zolpidem acts primarily upon the omega-1 (benzodiazepine-1) receptor sub-types. The clinical relevance of this is not known.

5.2. Pharmacokinetic properties

Absorption

After oral administration, peak plasma concentrations are about 45 % higher in women than in men given the same oral dose because of lower clearance rate in women. The bioavailability of zolpidem is about 70 %, reaching peak plasma concentration between 0,5 and 3 hours after dosing.

Distribution

At therapeutic dose levels, the pharmacokinetics are linear. The degree of plasma protein binding is about 92 %. The plasma elimination half-life is about 2,5 hours (1,4 to 3,8 hours). The distribution volume in adults is 0,54 ± 0,02 l/kg. The distribution volume decreases to 0,34 ± 0,05 l/kg in the elderly.

Elimination

Zolpidem is excreted in the form of inactive metabolites (hepatic metabolism), mainly in the urine (56 %) and faeces (37 %). It has no inducing effects on hepatic enzymes. In elderly patients, clearance is reduced. The peak concentration is increased by about 50 % and elimination half-life by 32 %. In patients with renal insufficiency, whether dialysed or not, there is a moderate reduction in clearance. The other pharmacokinetic parameters are unaffected.

Special Populations

Hepatic impairment

In patients with hepatic insufficiency, the bioavailability of zolpidem is increased. Clearance is reduced and the elimination half-life prolonged (about 10 hours).

6 PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised starch.

Coating: HMPC 2910/Hypromellose, Macrogol/PEG, titanium dioxide.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store in a dry place at or below 25°C.

Protect from light.

Do not remove the blister strips from the carton until required for use.

6.5. Nature and contents of container

Blister strips composed of clear, transparent PVC backed with aluminium foil containing 10 tablets each. Blister strips are packed into cardboard cartons containing either 30 tablets (3 blister strips of 10 tablets each) or 100 tablets (10 blister strips of 10 tablets each).

Grey, cylindrical, plastic securitainer containing 30 or 100 tablets held down by white, plastic ullage filler with collapsible prongs. The container is sealed with a white snap-on polyethylene cap.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8 REGISTRATION NUMBER

36/2.2/0328

9 DATE OF FIRST AUTHORISATION

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10 DATE OF REVISION OF TEXT

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