PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

ZOLPIDEM MR SUN (Modified Release tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated two layer tablet contains:

Zolpidem tartrate USP 12,5 mg

For full list of excipients, see section 6.1

Contains sugar: lactose monohydrate 80,687 mg per tablet.

3 PHARMACEUTICAL FORM

Modified release tablets.

Round biconvex bi-layer coated tablets with yellow layer and white layer and imprinted with “308” on one side and other side plain, with no delamination of tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term treatment of insomnia.

ZOLPIDEM MR SUN is indicated in adults below the age of 65 years, and only when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Posology

Adults (< 65 years): The recommended daily dose is 12,5 mg.

The lowest effective daily dose of ZOLPIDEM MR SUN should be used and must not exceed 12,5 mg.

Treatment should be as short as possible. Generally, the duration of treatment varies from four 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.

Special populations

Elderly: As zolpidem as in ZOLPIDEM MR SUN has not been evaluated in elderly patients (≥ 65 years), ZOLPIDEM MR SUN is not recommended in this population.

Renal impairment: No dosage adjustment is required.

Hepatic impairment: ZOLPIDEM MR SUN should not be used in patients with severe hepatic impairment (see section 4.3 and 4.4).

Paediatric population

Safety and effectiveness of ZOLPIDEM MR SUN in paediatric patients under the age of 18 have not been established. Therefore ZOLPIDEM MR SUN should not be used in this population (see section 4.3).

Method of administration

ZOLPIDEM MR SUN acts rapidly and therefore should be taken immediately before bedtime or in bed. For a faster sleep onset, ZOLPIDEM MR SUN should not be administered with or immediately after a meal (see section 5.2).

Tablets should not be halved, crushed or chewed.

ZOLPIDEM MR SUN should be taken in a single intake and not be readministered during the same night.

4.3 Contraindications

ZOLPIDEM MR SUN is contraindicated in patients with:

- Hypersensitivity to zolpidem tartrate or to any other excipient listed in section 6.1;
- Children under the age of 18 years;
- Sleep apnoea syndrome;
- Myasthenia gravis;
- Severe hepatic impairment;
- Acute and/or severe respiratory impairment;
- Pregnancy and lactation (see section 4.6)

4.4. Special warnings and precautions for use

General information related to effects seen following administration of hypnotics, which should be taken into account by the prescribing medical practitioner, are described below:

The cause of insomnia should be identified wherever possible and the underlying factors treated before a hypnotic is prescribed.

The failure of insomnia to remit after a 7-14 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.

Respiratory Impairment:

As hypnotics have the capacity to depress respiratory drive, precautions should be observed if ZOLPIDEM MR SUN is prescribed to patients with mild to moderate compromised respiratory function.

Risks from concomitant use with opioids:

Concomitant use of benzodiazepines and other sedative-hypnotic medicines, including ZOLPIDEM MR SUN, with opioids may result in sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe ZOLPIDEM MR SUN concomitantly with opioids, prescribe the lowest effective dosages and minimum duration of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation.

Amnesia:

ZOLPIDEM MR SUN may induce anterograde amnesia. The condition occurs most often several hours after ingesting ZOLPIDEM MR SUN and therefore to reduce the risk, patients should ensure that they get a full night's sleep (7-8 hours) before being active.

Other psychiatric and paradoxical reactions:

Other psychiatric and paradoxical reactions like restlessness, exacerbated insomnia, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, abnormal behaviour and other behavioural effects are known to occur when using ZOLPIDEM MR SUN. Should this occur, use of ZOLPIDEM MR SUN should be discontinued. These reactions are more likely to occur in the elderly.

Somnambulism and associated behaviours:

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 have been reported in patients who have taken ZOLPIDEM MR SUN and were not fully awake. The use of alcohol and other CNS-depressants with ZOLPIDEM MR SUN appears to increase the risk of such behaviours, as does the use of ZOLPIDEM MR SUN at doses exceeding the maximum recommended dose. Discontinuation of ZOLPIDEM MR SUN should be strongly considered for patients who report such behaviours.

Tolerance:

Some loss of efficacy to the hypnotic effects of ZOLPIDEM MR SUN may develop after repeated use for a few weeks.

Psychomotor impairment:

The risk of psychomotor impairment, including impaired driving ability, is increased if: ZOLPIDEM MR SUN is taken within less than 7– 8 hours before performing activities that require mental alertness, a dose higher than the recommended dose is taken, or ZOLPIDEM MR SUN is co-administered with other CNS depressants, alcohol, or with other medicines that increase the blood levels of ZOLPIDEM MR SUN.

Dependence:

Use of ZOLPIDEM MR SUN may lead to the development of physical and psychological dependence. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of psychiatric disorders and/or alcohol or drug abuse. Patients with a history of psychiatric disorders should be under careful surveillance when receiving ZOLPIDEM MR SUN. Patients with a history of alcohol or drug abuse – see Patients with a history of alcohol and drug abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches or muscle pain, extreme anxiety and tension, restlessness, confusion and irritability. 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. Dependence has been reported with ZOLPIDEM MR SUN (see section 4.8).

Rebound insomnia:

A transient syndrome, whereby the symptoms that led to treatment with ZOLPIDEM MR SUN recur in an enhanced form, may occur on withdrawal of ZOLPIDEM MR SUN treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness. There are indications that, in the case of ZOLPIDEM MR SUN with a short duration of action, withdrawal phenomenon can become manifest within the dosage interval, especially when the dosage is high. The rebound phenomenon, if it occurs with ZOLPIDEM MR SUN, was limited to the first night after the drug discontinuation in reported clinical studies (see section 5.1).

It is important that the patient should be aware of the possibility of rebound phenomenon, thereby minimising anxiety over such symptoms should they occur when ZOLPIDEM MR SUN is discontinued.

Patients with a history of alcohol or drug abuse:

ZOLPIDEM MR SUN should not be used in patients with a history of alcohol or drug abuse (see section 4.5 and section 4.7).

Hepatic impairment:

ZOLPIDEM MR SUN should be used with caution in patients with mild to moderate hepatic impairment. ZOLPIDEM MR SUN must not be used in patients with severe hepatic impairment as it may contribute to encephalopathy (see section 4.3).

Psychotic illness:

ZOLPIDEM MR SUN is not recommended for the primary treatment of psychotic illness.

Suicidality and Depression:

Several epidemiological studies show an increased incidence of suicide and suicide attempt in patients with or without depression, treated with benzodiazepines and other hypnotics, including ZOLPIDEM MR SUN. A causal relationship has not been established.

ZOLPIDEM MR SUN should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

As suicidal tendencies may be present, the least amount of ZOLPIDEM MR SUN that is feasible, should be supplied to these patients because of the possibility of intentional overdosage by the patient.

A pre-existing depression may be unmasked during the use of zolpidem. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

Severe injuries:

Due to its pharmacological properties, ZOLPIDEM MR SUN can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries.

Patients with Long QT syndrome:

An *in vitro* cardiac electrophysiological study showed that under experimental conditions using very high concentration and pluripotent stem cells ZOLPIDEM MR SUN may reduce the hERG

(human ether-a-go-go-related gene) related potassium currents. The potential consequence in patients with congenital long QT syndrome is unknown. As a precaution, the benefit/risk ratio of ZOLPIDEM MR SUN treatment in patients with known congenital long QT syndrome should be carefully considered.

Severe Anaphylactic and Anaphylactoid Reactions

Cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zolpidem as in ZOLPIDEM MR SUN. Some patients have had additional symptoms such as dyspnoea, throat closing or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department.

If angioedema involves the throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with ZOLPIDEM MR SUN should not be rechallenged with the medicine.

Lactose :

ZOLPIDEM MR SUN contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Alcohol:

Concomitant use with alcohol is not recommended. The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

CNS depressants:

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant medicines, narcotic analgesics, antiepileptic medicines, anaesthetics and sedative antihistamines.

Concomitant use of ZOLPIDEM MR SUN with these medicines may increase drowsiness and psychomotor impairment, including impaired driving ability.

Concomitant use with hypnotics may enhance the euphoric effect of narcotic analgesics, which may lead to an increase in psychological dependence. Co-administration of fluvoxamine may increase blood levels of ZOLPIDEM MR SUN; concurrent use is not recommended (see section 4.5: CYP450 inhibitors and inducers).

Opioids:

The concomitant use of benzodiazepines and other sedative-hypnotic medicines, including ZOLPIDEM MR SUN , and opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

CYPP450 inhibitors and inducers:

Compounds, which inhibit cytochrome P450 may enhance the activity of zolpidem as in ZOLPIDEM MR SUN. Co-administration of ZOLPIDEM MR SUN with ketoconazole (200 mg twice daily), a potent CYP3A4 inhibitor, has been reported to produce a 64 % increase in zolpidem as in ZOLPIDEM MR SUN plasma levels. A routine dosage adjustment of ZOLPIDEM MR SUN is not necessary, but patients should be advised that the sedative effects might be enhanced.

However, co-administration of ZOLPIDEM MR SUN with itraconazole or fluconazole did not produce any significant changes in zolpidem pharmacokinetics and pharmacodynamics.

Fluvoxamine is a strong inhibitor of CYP1A2 and a moderate to weak inhibitor of CYP2C9 and CYP3A4. Co-administration of fluvoxamine may increase blood levels of zolpidem as in ZOLPIDEM MR SUN; concurrent use is not recommended.

Ciprofloxacin has been shown to be a moderate inhibitor of CYP1A2 and CYP3A4. Coadministration of ciprofloxacin may increase blood levels of zolpidem; concurrent use is not recommended.

The pharmacodynamic effect of zolpidem as in ZOLPIDEM MR SUN is decreased when it is administered with a CYP3A4 inducer such as rifampicin due to an increase in liver metabolism.

The pharmacodynamic effect of zolpidem as in ZOLPIDEM MR SUN is decreased when it is administered with a CYP3A4 inducer such as St John's Wort. Co-administration of St. John's Wort may decrease blood levels of zolpidem; concurrent use is not recommended.

Other:

No significant pharmacokinetic interactions were reported, when zolpidem as in ZOLPIDEM MR SUN was administered with warfarin, digoxin, ranitidine or cimetidine.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety in pregnancy have not been established. The use of ZOLPIDEM MR SUN during pregnancy is contraindicated (see section 4.3).

If ZOLPIDEM MR SUN is prescribed to a woman of childbearing potential, she should be warned to contact her medical practitioner about stopping ZOLPIDEM MR SUN if she intends to become, or suspects that she is pregnant.

If for compelling medical reasons ZOLPIDEM MR SUN is administered during the late phase of pregnancy or during labour, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected due to the pharmacological action of zolpidem.

Infants born to mothers who took hypnotics including ZOLPIDEM MR SUN, chronically during the latter stages of pregnancy may have developed physical dependence and may be at risk of developing withdrawal symptoms in the postnatal period.

Breastfeeding:

As zolpidem is excreted in breast milk, the use of ZOLPIDEM MR SUN in breast feeding mothers is contraindicated (see section 4.3).

Fertility

No data available.

4.7 Effects on ability to drive and use machines:

Vehicle drivers and machine operators should be warned that, there may be a possible risk of adverse reactions including drowsiness, prolonged reaction time, dizziness, sleepiness, blurred/double vision, reduced alertness and impaired driving the morning after therapy. In order to minimise this risk a full night of sleep (7 - 8 hours) is recommended. Furthermore, the co-administration of ZOLPIDEM MR SUN with alcohol and other CNS depressants increases the risk of such effects. Patients should be warned not to use alcohol or other psychoactive substances when taking ZOLPIDEM MR SUN (see sections 4.4. and 4.5).

4.8 Undesirable effects

a. Summary of the safety profile

There is evidence of a dose-relationship for adverse effects associated with ZOLPIDEM MR SUN use, particularly for certain CNS events. They have been reported most frequently in elderly patients.

b. Tabulated list of adverse reactions

System organ class	**Frequency**	**Undesirable effect**
Infections and infestations	Frequent Less frequent	Influenza Gastroenteritis, labyrinthitis, lower respiratory tract infection, otitis externa, upper respiratory tract infection
Immune system disorders	Frequency not known	Angioedema
Metabolism and nutrition disorders	Less frequent	Appetite disorder
Psychiatric disorders **Psychiatric disorders**	Frequent Less frequent	Anxiety, psychomotor retardation, disorientation Depression, hallucination, apathy, binge eating, confusional state, depersonalisation, depressed mood, disinhibition, euphoric mood, hallucination visual, hypnagogic hallucination, mood swings, nightmares, stress symptoms

	Frequency not known	Restlessness, aggression, delusion, anger, abnormal behaviour, somnambulism (see section 4.4), dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation), libido disorder Most of these psychiatric undesirable effects are related to paradoxical reactions.
Nervous system disorders	Frequent Less frequent Frequency not known	Headache, somnolence, dizziness, memory disorders (memory impairment, amnesia, anterograde amnesia), disturbance in attention Balance disorder, hypoaesthesia, paraesthesia, ataxia, burning sensation, dizziness postural, dysgeusia, muscle contractions involuntary, tremor Depressed level of consciousness, speech disorder
Eye disorders	Frequent Less frequent	Visual disturbance Eye redness, vision blurred,

		altered visual depth perception, asthenopia
Ear and labyrinth disorders	Less frequent	Vertigo, tinnitus
Cardiac disorders	Less frequent	Palpitations
Respiratory, thoracic and mediastinal disorders	Less frequent Frequency not known	Cough, dry throat, throat irritation Respiratory depression
Gastrointestinal disorders	Frequent Less frequent	Nausea, constipation Vomiting, abdominal discomfort, flatulence, frequent bowel movements, gastro-oesophageal reflux disease
Hepatobiliary disorders:	Frequency not known	Hepatocellular, cholestatic or mixed liver injury
Skin and subcutaneous tissue disorders	Less frequent	Rash, urticaria, dermatitis contact, skin wrinkling
Musculoskeletal and connective tissue disorders	Frequent Less frequent Frequency not known	Myalgia, muscle cramp, neck pain, back pain Arthralgia Muscular weakness
Renal and urinary	Less frequent	Dysuria

disorders		
Reproductive system and breast disorders	Less frequent	Dysmenorrhoea, menorrhagia, vulvovaginal dryness
General disorders and administration site conditions	Frequent Less frequent Frequency not known	Fatigue Asthenia, chest discomfort, feeling drunk, influenza-like illness, lethargy, pain, pyrexia Gait disturbances, drug tolerance, fall
Investigations	Less frequent	Blood pressure increased, body temperature increased, heart rate increased.

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 via the '**6.04 Adverse Drug Reaction Reporting form'**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8.

4.9 Overdose

Signs and symptoms

In cases of overdose involving ZOLPIDEM MR SUN alone or with other CNS-depressant agents (including alcohol), impairment of consciousness up to coma, and more severe symptomatology, including fatal outcomes have been reported.

Management

General symptomatic and supportive measures should be used. Activated charcoal should be given to reduce absorption. Sedating medicines should be withheld even if excitation occurs. Use of flumazenil may be considered where serious symptoms are reported. However, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).

Zolpidem is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 2.2 Sedatives, hypnotics. ATC Code: N05C F02

Zolpidem is a benzodiazepine receptor agonist. Benzodiazepine receptor agonists (BZRAs) exert their pharmacological effects by binding to a site associated with GABA-A receptors. Zolpidem shows selectivity for a subtype of GABA-A receptors containing alpha-1 subunits. Reported scientific evidence suggests that this receptor subtype mediates drug-induced sedative/hypnotic effects.

5.2 Pharmacokinetic properties

Absorption:

After oral intake, the absolute bioavailability is reported to be around 70 % and the peak plasma concentration is reached between 1,5 and 2,5 hours. The inter-individual variability (CV) is reported to be around 40 – 60 % for AUC and 30 – 40 % for C_{max}.

When zolpidem is administered after food C_{max} and AUC are reported to be decreased by 30 and 23 % respectively and the time to maximal plasma concentration is delayed by 2 hours.

Distribution:

The *in vitro* plasma protein binding is reported to be around 92 %. The distribution volume in adults is reported to be 0,54 L/kg following intravenous administration.

Metabolism:

Zolpidem is mainly metabolised by the hepatic cytochrome P450 CYP 3A4 (around 60 % of the net CYP - mediated hepatic clearance). Other P450 isoenzymes such as CYP2C9, CYP1A2, CYP2D6 and CYP2C19 also contribute to the oxidation of the drug. All of zolpidem's metabolites are pharmacologically inactive. Zolpidem itself is not a significant inhibitor or inducer of human CYP isoforms.

Elimination:

Zolpidem is excreted in the form of inactive metabolites in urine (around 60 %) and faeces (around 40 %). Clearance is reported to be around 212 mL / min. Reduced clearance of 100 mL/min has been reported in elderly.

Zolpidem plasma concentrations were measured approximately 9 hours post-dose on day 1 and day 15 in adult patients who were treated for 3 weeks with zolpidem 12,5 mg. Zolpidem concentrations did not change upon repeated dosing indicating no evidence of accumulation with zolpidem. The elimination $t_{1/2}$ is reported to be 2,8 hours in healthy volunteers.

Hepatic impairment:

In patients with liver impairment, the clearance of zolpidem is reported to be decreased and the elimination half-life is extended (around 10 hours) [see section 4.2]. In liver cirrhosis a 5-fold increase of AUC and a 3-fold increase of half-life have been reported.

Renal impairment:

In patients with renal impairment, whether dialysed or not, a moderate increase (around 30 %) of the volume of distribution is reported compared to healthy subjects. Other pharmacokinetic parameters such as clearance, AUC and elimination half-life are not affected. Therefore, no dose adjustment is necessary in patients with renal impairment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Ferric oxide yellow
- hypromellose (methocel E-5LV premium)
- hypromellose 2910 (methocel E15 premium LV)
- hypromellose 2208 (methocel K4M CR premium)
- isopropyl alcohol
- lactose monohydrate
- magnesium stearate
- microcrystalline cellulose
- opadry II clear 85F19250
- opacode black S-1-17823
- sodium starch glycolate type A
- tartaric acid

Film coating

- Opadry II Clear 85F19250
- Opacode Black S-1-17823
- Isopropyl Alcohol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

Store at or below 25 °C

Keep in the original container in order to protect from light.

Keep out of reach of children.

6.4 Special precautions for storage

This medicine does not require any special storage conditions

6.5 Nature and contents of container

ZOLPIDEM MR SUN is available in a pack of 30 tablets, each Alu-PVC Coated with PVDC Blister Pack or Alu/Alu strip containing 10 tablets, packed in carton along with pack insert.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

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Stormill, Ext 1

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South Africa

8. REGISTRATION NUMBER

54/2.2/0325.324

9. DATE OF FIRST AUTHORISATION

03 October 2023

10. DATE OF REVISION OF THE TEXT