PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

ZILSUN MR (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.

ZILSUN MR 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 ZILSUN MR 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 ZILSUN MR has not been evaluated in elderly patients (≥ 65 years), ZILSUN MR is not recommended in this population.

Renal impairment: No dosage adjustment is required.

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

Paediatric population

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

Method of administration

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

Tablets should not be halved, crushed or chewed.

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

4.3 Contraindications

ZILSUN MR 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 ZILSUN MR 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 ZILSUN MR, 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 ZILSUN MR 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:

ZILSUN MR may induce anterograde amnesia. The condition occurs most often several hours after ingesting ZILSUN MR 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 ZILSUN MR. Should this occur, use of ZILSUN MR 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 ZILSUN MR and were not fully awake. The use of alcohol and other CNS-depressants with ZILSUN MR appears to increase the risk of such behaviours, as does the use of ZILSUN MR at doses exceeding the maximum recommended dose. Discontinuation of ZILSUN MR should be strongly considered for patients who report such behaviours.

Tolerance:

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

Psychomotor impairment:

The risk of psychomotor impairment, including impaired driving ability, is increased if: ZILSUN MR 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 ZILSUN MR is co-administered with other CNS depressants, alcohol, or with other medicines that increase the blood levels of ZILSUN MR.

Dependence:

Use of ZILSUN MR 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 ZILSUN MR. 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 ZILSUN MR (see section 4.8).

Rebound insomnia:

A transient syndrome, whereby the symptoms that led to treatment with ZILSUN MR recur in an enhanced form, may occur on withdrawal of ZILSUN MR treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness. There are indications that, in the case of ZILSUN MR 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 ZILSUN MR, 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 ZILSUN MR is discontinued.

Patients with a history of alcohol or drug abuse:

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

Hepatic impairment:

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

Psychotic illness:

ZILSUN MR 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 ZILSUN MR. A causal relationship has not been established.

ZILSUN MR 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 ZILSUN MR 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, ZILSUN MR 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 ZILSUN MR 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 ZILSUN MR 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 ZILSUN MR. 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 ZILSUN MR should not be rechallenged with the medicine.

Lactose:

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

However, co-administration of ZILSUN MR 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 ZILSUN MR; 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 ZILSUN MR 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 ZILSUN MR 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 ZILSUN MR 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 ZILSUN MR during pregnancy is contraindicated (see section 4.3).

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

If for compelling medical reasons ZILSUN MR 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 ZILSUN MR, 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 ZILSUN MR 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 ZILSUN MR 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 ZILSUN MR (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 ZILSUN MR 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	Frequent	Anxiety, psychomotor retardation,

		disorientation
Psychiatric disorders	Less frequent	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	Headache, somnolence, dizziness, memory disorders (memory impairment, amnesia, anterograde amnesia), disturbance in attention

	Less frequent Frequency not known	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 disorders	Less frequent	Dysuria
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 ZILSUN MR 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

ZILSUN MR 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

14 Lautre Road

Stormill, Ext 1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER

54/2.2/0324

9. DATE OF FIRST AUTHORISATION

03 October 2023

10. DATE OF REVISION OF THE TEXT

PROFESSIONELE INLIGTING

SKEDULERINGSTATUS

S5

1 NAAM VAN DIE MEDISYNE

ZILSUN MR (Gemodifiseerde vrystellingtablet)

2 KWALITATIEWE EN KWANTITATIEWE SAMESTELLING

Elke filmbedekte twee-lagige-tablet bevat:

Zolpidemtartraat USP 12,5 mg

Vir volledige lys van onaktiewe bestanddele, sien afdeling 6.1.

Bevat suiker: 80,687 mg laktosemonohidraat per tablet.

3 FARMASEUTIESE VORM

Gemodifiseerde vrystellingtablet.

Ronde bikonvekse twee-lagige bedekte tablette met ‘n geel laag en ‘n wit laag, gepers met “308” op die een kant en ander kant skoon, met geen opsplitsing in lae van die tablet nie.

4 KLINIESE BESONDERHEDE

4.1 Terapeutiese indikasies

Korttermyn-behandeling van slapeloosheid.

ZILSUN MR word aangedui by volwassenes onder die ouderdom van 65 jaar, en slegs wanneer die versteuring ernstig, stremmend is, of die individu blootstel aan uitermatige spanning.

4.2 Posologie en metode van toediening

Posologie

Volwassenes (< 65-jaar): Die aanbevole daaglikse dosis is 12,5 mg.

Die laagste doeltreffende daaglikse dosis van ZILSUN MR moet gebruik word en moet nie 12,5 mg oorskry nie.

Behandeling moet so kort as moontlik wees. Oor die algemeen varieer die duur van behandeling van vier dae tot twee weke met ‘n maksimum, insluitend die afskaalperiode, van vier weke. In sekere gevalle mag die behandelingstydperk, indien nodig, verby die maksimum verleng word; indien so, moet dit nie plaasvind sonder die her-evaluering van die pasiënt se status nie.

Spesiale populasies

Bejaardes: Aangesien zolpidem, soos in ZILSUN MR, nie geëvalueer is by bejaarde pasiënte (≥ 65 jaar) nie, word ZILSUN MR nie aanbeveel by hierdie populasie nie.

Nierontoereikendheid: Geen dosisaanpassing is nodig nie.

Hepatiese ontoereikendheid: ZILSUN MR moet nie gebruik word by pasiënte met ernstige hepatiese ontoereikendheid nie (sien afdelings 4.3 en 4.4).

Pediatriese populasie

Veiligheid en doeltreffendheid van ZILSUN MR by pediatriese pasiënte onder die ouderdom van 18 is nie vasgestel nie. Daarom moet ZILSUN MR nie by hierdie populasie gebruik word nie (sien afdeling 4.3).

Metode van toediening

ZILSUN MR werk vinnig en moet daarom direk voor slapenstyd geneem word of as reeds in die bed is. Vir ‘n vinniger aanvang van slaap, moet ZILSUN MR met, of onmiddellik ná, ‘n maaltyd toegedien word (sien afdeling 5.2).

Tablette moet nie gehalveer, fyngemaak of gekou word nie.

ZILSUN MR moet as ‘n enkeldosis ingeneem word en moet nie weer toegedien word tydens dieselfde aand nie.

4.3 Kontra-indikasies

ZILSUN MR is teenaangedui by pasiënte met:

- Hipersensitiwiteit teen zolpidemtartraat of teen enige van die ander onaktiewe bestanddele gelys in afdeling 6.1;
- Kinders onder die ouderdom van18 jaar;
- Slaapapnee-sindroom;
- Myasthenia gravis;
- Ernstige hepatiese ontoereikendheid; Akute en/of ernstige respiratoriese ontoereikendheid;
- Swangerskap en laktasie (sien afdeling 4.6)

4.4. Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

Algemene inligting verwant aan effekte waargeneem ná toediening van hipnotika, wat deur die voorskrywende dokter in ag geneem moet word, word hieronder beskryf:

Die oorsaak van slapeloosheid moet, indien moontlik, geïdentifiseer word en die onderliggende faktore behandel word voordat ‘n hipnotikum voorgeskryf word.

Die mislukking vir slapeloosheid om te verminder ná ‘n 7-14 dag behandelingskursus kan ‘n aanduiding wees van die teenwoordigheid van ‘n primêre psigiatriese of fisiese versteuring en die pasiënt moet noukeurig met gereelde tussenposes weer geëvalueer word.

Respiratoriese ontoereikendheid:

Aangesien hipnotika die vermoë besit om asemhalingsvermoë te onderdruk, moet voorsorgmaatreëls ingestel word as ZILSUN MR voorgeskryf word aan pasiënte met geringe tot matige gekompromitteerde respiratoriese funksie.

Risiko's van gelyktydige gebruik met opioïede:

Gelyktydige gebruik van bensodiasepiene en ander kalmerende-hipnotika medisyne, insluitend ZILSUN MR, saam met opioïede kan lei tot sedasie, respiratoriese onderdrukking, koma, en die dood. As gevolg van hierdie risiko's, word die gelyktydige voorskryf van opioïede en bensodiasepiene gereserveer vir gebruik by pasiënte vir wie alternatiewe behandelingsopsies onvoldoende is.

As die besluit geneem word om ZILSUN MR gelyktydig met opioïede voor te skryf, skryf die laagste doeltreffende dosisse en minimum duur van gelyktydige gebruik voor, en volg pasiënte noukeurig op vir tekens en simptome van respiratoriese onderdrukking en sedasie.

Amnesie:

ZILSUN MR kan anterograde amnesie induseer. Die toestand kom meer dikwels verskeie ure ná inname van ZILSUN MR voor en om daarom die risiko te verminder, moet pasiënte seker maak dat hulle 'n volle nag se slaap (7-8 uur) ingekry het voordat hulle aktief is.

Ander psigiatriese en paradoksikale reaksies:

Ander psigiatriese en paradoksikale reaksies soos rusteloosheid, verergerde slapeloosheid, agitasie, geïrriteerdheid, aggressie, delusie, woede, nagmerries, hallusinasies, abnormale gedrag en ander gedragseffekte is bekend om voor te kom wanneer ZILSUN MR gebruik word. Indien dit voorkom, moet die gebruik van ZILSUN MR gestaak word. Hierdie reaksies kom meer waarskynlik by bejaardes voor.

Slaapwandelary en geassosieerde gedrag:

Slaapwandel en ander geassosieerde gedrag soos 'bestuur in die slaap', bereiding en eet van voedsel, maak van telefoonoproepe of om seks te beoefen, met amnesie vir die voorval is aangemeld by pasiënte wat ZILSUN MR geneem het en nie ten volle wakker is nie. Die gebruik van alkohol en ander SSS-onderdrukkers saam met ZILSUN MR blyk om die risiko van sulke gedrag te

verhoog, soos wat die gebruik van dosisse van ZILSUN MR is wat die maksimum aanbevole dosis oorskry. Staking van ZILSUN MR moet sterk oorweeg word by pasiënte wat sulke gedrag vertoon.

Toleransie:

Sommige verlies van doeltreffendheid vir die hipnotiese effekte van ZILSUN MR kan ontwikkel ná herhaaldelike gebruik vir ‘n paar weke.

Psigomotoriese ontoereikendheid:

Die risiko van psigomotoriese ontoereikendheid, insluitend ontoereikende bestuursvermoë, word verhoog as ZILSUN MR gebruik word binne minder as 7– 8 uur voordat aktiwiteite beoefen word wat geesteswaaksaamheid vereis, ‘n dosis hoër as die aanbevole dosis geneem word, of ZILSUN MR saam met ander SSS-onderdrukkers, alkohol, of met ander medisyne wat die bloedvlakke van ZILSUN MR verhoog, toegedien word.

Afhanklikheid:

Gebruik van ZILSUN MR kan lei tot die ontwikkeling van fisiese en psigologiese afhanklikheid. Die risiko van afhanklikheid verhoog met dosis en duur van behandeling; dit is ook hoër by pasiënte met ‘n geskiedenis van psigiatriese versteurings en/of alkohol of substansmisbruik. Pasiënte met ‘n geskiedenis van psigiatriese versteurings moet onder noukeurige toesig wees wanneer hul ZILSUN MR ontvang. Pasiënte met ‘n geskiedenis van alkohol of substansmisbruik – sien Pasiënte met ‘n geskiedenis van alkohol en substansmisbruik.

Sodra fisiese afhanklikheid ontwikkel het, sal skielike staking van behandeling met onttrekkingsimptome gepaard gaan. Hierdie kan bestaan uit hoofpyn of spierpyn, uitermatige angstigheid en spanning, rusteloosheid, verwarring en geïrriteerdheid. In ernstige gevalle kan die volgende voorkom: verontwerkliking, depersonalisasie, hiperakoesie, gevoelloosheid en tinteling van die ekstremiteite, hipersensitiwiteit vir lig, geluid en fisiese kontak, hallusinasies of epileptiese toevalle. Afhanklikheid is aangemeld met ZILSUN MR (sien afdeling 4.8).

Terugslag slapeloosheid:

'n Verbygaande sindroom, waarby die simptome wat gelei het tot die behandeling met ZILSUN MR teruggekeer het in 'n versterkte vorm, kan voorkom met onttrekking van ZILSUN MR-behandeling. Dit kan vergesel word deur ander reaksies insluitend gemoedsveranderinge, angstigheid en rusteloosheid. Daar is aanduidings dat, in die geval van ZILSUN MR met 'n kort duur van werking, onttrekkingsfenomeen openbaar gemaak kan word binne die doseringsinterval, veral wanneer die dosering hoog is.

Die terugslagfenomeen, as dit voorkom met ZILSUN MR, was in aangemelde kliniese studies beperk tot die eerste nag nadat die geneesmiddel onttrek is (sien afdeling 5.1).

Dit is belangrik dat die pasiënt bewus moet wees van die moontlikheid van die terugslagfenomeen, waardeur angstigheid oor sulke simptome geminimaliseer word indien dit sou voorkom wanneer ZILSUN MR gestaak word.

Pasiënte met 'n geskiedenis van alkohol- of substansmisbruik:

ZILSUN MR moet nie gebruik word by pasiënte met 'n geskiedenis van alkohol of substansmisbruik nie (sien afdeling 4.5 en afdeling 4.7).

Hepatiese ontoereikendheid:

ZILSUN MR moet met omsigtigheid gebruik word by pasiënte met geringe tot matige hepatiese ontoereikendheid. ZILSUN MR moet nie gebruik word by pasiënte met ernstige hepatiese ontoereikendheid nie, aangesien dit kan bydra tot enkefalopatie (sien afdeling 4.3).

Psigotiese siekte:

ZILSUN MR word nie aanbeveel vir die primêre behandeling van psigotiese siekte nie.

Selfdood en Depressie:

Verskeie epidemiologiese studies het ‘n verhoogde voorkoms van selfdood en selfdoodpogings aangedui by pasiënte met of sonder depressie, behandel met bensodiasepiene en ander hipnotika, insluitend ZILSUN MR. ‘n Oorsaaklike verwantskap is nie vasgestel nie.

ZILSUN MR moet nie as enkelmiddel gebruik word om depressie of angstigheid geassosieer met depressie te behandel nie (selfdood kan in sulke pasiënte gepresipiteer word).

Aangesien selfdoodneigings teenwoordig mag wees, moet die kleinste moontlike hoeveelheid ZILSUN MR aan hierdie pasiënte voorsien word as gevolg van die moontlikheid van doelbewuste oordosering deur die pasiënt.

‘n Voorafbestaande depressie kan ontmasker word tydens die gebruik van zolpidem. Aangesien slapeloosheid ‘n simptoom van depressie kan wees, moet die pasiënt hergeëvalueer word as slapeloosheid aanhou.

Ernstige beserings:

As gevolg van die farmakologiese eienskappe, kan ZILSUN MR lomerigheid en ‘n verlaagde vlak van bewustheid veroorsaak wat kan lei tot val en gevolglike ernstige beserings.

Pasiënte met verlengde QT-sindroom:

In ‘n *in vitro k*ardiale elektrofisiologiese studie is aangetoon dat onder eksperimentele toestande waar ‘n baie hoë konsentrasie en veelmagtige stamselle gebruik is, kan ZILSUN MR die hERG (menslike eter-a-go-go-verwante geen) verwante kaliumstrome verlaag. Die moontlike gevolge by pasiënte met kongenitale verlengde QT-sindroom is onbekend. As ‘n voorsorgmaatreël, moet die voordeel/risiko verhouding van ZILSUN MR-behandeling by pasiënte met bekende kongenitale verlengde QT-sindroom met omsigtigheid oorweeg word.

Ernstige Anafilaktiese en Anafilaktoïede Reaksies

Gevalle van angio-edeem waar die tong, glottis of larinks betrek word, is aangemeld by pasiënte nadat die eerste of daaropvolgende dosisse van sedatiewe-hipnotika, insluitend zolpidem, soos ZILSUN MR, geneem is.

Sommige pasiënte het addisionele simptome soos dispnee, toetrek van die keel of naarheid en braking gehad wat dui op anafilakse. Sommige pasiënte het mediese behandeling in die noodgevalle afdeling benodig.

As angio-edeem die keel, glottis of larinks betrek, kan lugwegobstruksie voorkom en dit kan fataal wees.

Pasiënte wat angio-edeem ná behandeling met ZILSUN MR ontwikkel, moet nie met die medisyne gedaag word nie.

Laktose:

ZILSUN MR bevat laktose. Pasiënte met seldsame oorerflike probleme van galaktose onverdraagsaamheid, totale laktase tekort of glukose-galaktose wanabsorpsie moet nie hierdie medisyne neem nie.

4.5 Interaksie met ander medisyne en ander vorme van interaksie

Alkohol:

Gelyktydige gebruik met alkohol word nie aanbeveel nie. Die sedatiewe effek kan versterk word wanneer die produk in kombinasie met alkohol gebruik word. Dit affekteer die vermoë om te bestuur of masjinerie te hanteer.

SSS-onderdrukkers:

Versterking van die sentrale onderdrukkende effek kan voorkom in gevalle van gelyktydige gebruik met antipsigotika (neuroleptika), hipnotika, angsiolitiese middels/sedatiewe middels, antidepressant-medisyne, narkotiese analgetika, anti-epileptiese medisyne, anestetika en sedatiewe antihistamiene.

Gelyktydige gebruik van ZILSUN MR met hierdie medisyne kan lomerigheid en psigomotoriese ontoereikendheid verhoog, insluitend belemmerde bestuursvermoë.

Gelyktydige gebruik met hipnotika kan die euforiese effek van narkotiese analgetika verhoog, wat kan lei tot ‘n toename in psigologiese afhanklikheid. Gesamentlike toediening van fluvoksamien kan bloedvlakke van ZILSUN MR verhoog; gelyktydige gebruik word nie aanbeveel nie (sien afdeling 4.5: CYP450-inhibeerders en induseerders).

Opioïede:

Die gesamentlike gebruik van bensodiasepiene en ander sedatiewe-hipnotiese medisyne, insluitend ZILSUN MR, en opioïede verhoog die risiko van sedasie, respiratoriese onderdrukking, koma, en sterfte as gevolg van die toegevoegde SSS-onderdrukkende effek. Die dosis en duur van gelyktydige gebruik moet beperk word (sien afdeling 4.4).

CYP450-inhibeerders en -induseerders:

Verbindings wat sitochroomP450 inhibeer, kan die aktiwiteit van zolpidem, soos in ZILSUN MR, versterk. Daar is aangemeld dat gesamentlike toediening van ZILSUN MR met ketokonasool (200 mg twee keer per dag), ‘n kragtige CYP3A4-inhibeerder, ‘n 64 % toename in zolpidem-, soos in ZILSUN MR, plasmavlakke veroorsaak. ‘n Roetine dosisaanpassing van ZILSUN MR is nie nodig nie, maar pasiënte moet ingelig word dat die sedatiewe effekte verhoog kan wees.

Gesamentlike toediening van ZILSUN MR met itrakonasool of flukonasool het egter nie noemenswaardige veranderinge in zolpidem farmakokinetika en farmakodinamika aangebring nie.

Fluvoksamien is ‘n sterk inhibeerder van CYP1A2 en ‘n matige tot swak inhibeerder van CYP2C9 en CYP3A4. Gesamentlike toediening van fluvoksamien kan bloedvlakke van zolpidem, soos in ZILSUN MR, verhoog; gelyktydige gebruik word nie aanbeveel nie.

Siprofloksasien het aangetoon om ‘n matige inhibeerder van CYP1A2 en CYP3A4 te wees. Gesamentlike toediening van siprofloksasien kan bloedvlakke van zolpidem verhoog; gelyktydige

gebruik word nie aanbeveel nie.

Die farmakodinamiese effek van zolpidem, soos in ZILSUN MR, word verlaag wanneer dit saam met ‘n CYP3A4-induseerder, soos rifamisien, toegedien word te wyte aan ‘n verhoogde lewermetabolisme.

Die farmakodinamiese effek van zolpidem, soos in ZILSUN MR, word verlaag wanneer dit saam met ‘n CYP3A4-induseerder soos St Johanneskruid toegedien word. Gesamentlike toediening van St. Johanneskruid kan die bloedvlakke van zolpidem verlaag; gelyktydige gebruik word nie aanbeveel nie.

Ander:

Geen noemenswaardige farmakokinetiese interaksies is aangemeld nie wanneer zolpidem, soos in ZILSUN MR, saam met warfarien, digoksien, ranitidien of simetidien toegedien is nie.

4.6 Fertiliteit, swangerskap en laktasie

Swangerskap:

Veiligheid in swangerskap is nie vasgestel nie. Die gebruik van ZILSUN MR tydens swangerskap is teenaangedui (sien afdeling 4.3).

As ZILSUN MR voorgeskryf word aan ‘n vrou van kinderbarende vermoë, moet sy gewaarsku word dat sy haar dokter moet raadpleeg om ZILSUN MR te staak as sy van plan is om swanger te raak, of vermoed dat sy swanger is.

Indien, vir enige noodsaaklike mediese redes, ZILSUN MR toegedien moet word tydens die laat stadiums van swangerskap of tydens kraam, kan effekte op die pasgeborene soos hipotermie, hipotonie en matige respiratoriese onderdrukking verwag word te wyte aan die farmakologiese werking van zolpidem.

Suigelinge wat gebore word van moeders wat hipnotika, insluitend ZILSUN MR, chronies gebruik het tydens die laaste stadiums van swangerskap mag fisiese afhanklikheid ontwikkel het en mag ‘n risiko besit om onttrekkingsimptome te ontwikkel tydens die postnatale tydperk.

Borsvoeding:

Aangesien zolpidem in borsmelk uitgeskei word, is die gebruik van ZILSUN MR in borsvoedende moeders teenaangedui (sien afdeling 4.3).

Fertiliteit

Geen data beskikbaar nie.

4.7 Effekte op die vermoë om te bestuur en masjinerie te gebruik:

Bestuurders van motorvoertuie en operateurs van masjinerie moet gewaarsku word dat daar ‘n moontlike risiko van ongunstige reaksies, insluitend lomerigheid, verlengde reaksietyd, duiseligheid, slaperigheid, dowwe/dubbelvisie, verlaagde waaksaamheid en belemmerde bestuursvermoë die oggend ná terapie is. Ten einde hierdie risiko te verminder, word ‘n volle nag se slaap (7 - 8 uur) aanbeveel. Verder word die risiko van sulke effekte verhoog met die gelyktydige toediening van ZILSUN MR saam met alkohol en ander SSS-onderdrukkers. Pasiënte moet gewaarsku word om nie alkohol of ander psigo-aktiewe substanse te gebruik wanneer ZILSUN MR geneem word nie (sien afdelings 4.4. en 4.5).

4.8 Ongunstige effekte

a. Opsomming van die veiligheidsprofiel

Daar is bewyse van ‘n dosis-verwantskap vir newe-effekte geassosieer met ZILSUN MR-gebruik, veral vir sekere SSS-voorvalle. Dit word meer dikwels by bejaarde pasiënte aangemeld.

b. Getabulleerde lys van ongewenste reaksies

Sisteem-orgaanklas	**Voorkoms**	**Ongewenste effek**
Infeksies en infestasies	Dikwels Minder dikwels	Griep, gastro-enteritis, labirinitis, onderste lugweginfeksie, otitis eksterna, boonste lugweginfeksie
Immuunstelsel-versteurings	Voorkoms onbekend	Angio-edeem
Metabolisme en voedingsversteurings	Minder dikwels	Aptytversteuring
Psigiatriese versteurings	Dikwels Minder dikwels Voorkoms onbekend	Angstigheid, psigomotoriese vertraging, disoriëntasie Depressie, hallusinasie, apatie, eetversteuring, verwarde toestand, depersonalisasie, bedrukte gemoed, waninhibisie, euforiese gemoed, visuele hallusinasie, hipnagogiese hallusinasie, gemoedskommelinge nagmerries, stres-simptome Rusteloosheid, aggressie, delusie, woede, abnormale gedrag, slaapwandelary (sien afdeling 4.4), afhanklikheid (onttrekkingsimptome, of terugkerende effekte kan

		voorkom ná behandeling gestaak is), libido-versteuring Die meeste van hierdie psigiatriese ongewenste effekte is verwant aan paradoksikale reaksies.
Senuweestelsel-versteurings	Dikwels Minder dikwels Voorkoms onbekend	Hoofpyn, slaperigheid, duiseligheid, geheue-versteurings (ontoereikende geheue, amnesie anterograde amnesie), aandagversteuring Balansversteuring, hipoastesie, para-estesie, ataksie, branderige sensasie, posturale duiseligheid, disgeusie, onwillekeurige spiersametrekkings, bewerigheid Onderdrukte bewussynsvlak, spraakversteuring
Oogversteurings	Dikwels Minder dikwels	Visuele versteuring Oogrooiheid, dowwe visie, veranderde persepsie van visuele diepte, astenopie
Oor- en labirintversteurings	Minder dikwels	Vertigo, tinnitus
Kardiale versteurings	Minder dikwels	Palpitasies

Respiratoriese, torakale en mediastinale versteurings	Minder dikwels Voorkoms onbekend	Hoes, droë keel, keelirritasie Respiratoriese onderdrukking
Gastroïntestinale versteurings	Dikwels Minder dikwels	Naarheid, hardlywigheid Braking, abdominale ongemak, winderigheid, dikwelse ontlasting, gastro-esofageale refluks-siekte
Hepatobiliêre versteurings	Voorkoms onbekend	Hepatosellulêre, cholestatiese of gemengde lewerskade
Vel- en subkutane weefselversteurings	Minder dikwels	Uitslag, urtikarie, kontakdermatitis, velverrimpeling
Muskuloskeletale en bindweefselversteurings	Dikwels Minder dikwels Voorkoms onbekend	Mialgie, spierkrampe, nekpyn, rugpyn Artralgie Spierswakheid
Renale en urinêre versteurings	Minder dikwels	Disurie
Voortplantingstelsel en borsversteurings	Minder dikwels	Dismenorree, oormatige menstruasie, vulvovaginale droogheid
Algemene versteurings en toedienplektoestande	Dikwels Minder dikwels	Moegheid Astenie, borskasongemak, dronk-gevoel, griepagtige siekte,

	Voorkoms onbekend	letargie, pyn, pireksie Stap-/bewegingsversteurings, geneesmiddeltoleransie, val
Ondersoeke	Minder dikwels	Bloeddrukverhoging, verhoging in liggaamstemperatuur, verhoogde hartritme.

Aanmelding van vermoedelike ongunstige reaksies:

Aanmelding van vermoedelike ongunstige reaksies na goedkeuring van die medisyne is belangrik. Dit verseker voortdurende monitering van die voordeel/risiko balans van die medisyne. Gesondheidsorgverskaffers word versoek om vermoedelike ongunstige reaksies by SAHPRA aan te meld *via* die '**6.04 Adverse Drug Reaction Reporting form'**, wat aanlyn beskikbaar is onder SAHPRA se publikasies: https://www.sahpra.org.za/Publications/index/8.

4.9 Oordosis

Tekens en simptome

In gevalle van oordosering waar slegs ZILSUN MR alleen of saam met ander SSS-onderdrukkende middels (insluitend alkohol) betrek word, verswakking van bewussyn tot met koma, en meer ernstige simptomatologie, insluitend fatale uitkoms is aangemeld.

Beheer

Algemene simptomatiese en ondersteunende maatreëls moet toegepas word. Geaktiveerde houtskool moet toegedien word om absorpsie te verminder. Sederende medisyne moet vermy word selfs as opwinding voorkom. Gebruik van flumasenil kan oorweeg word waar ernstige simptome aangemeld is. Toediening van flumasenil kan egter bydra tot die voorkoms van neurologiese simptome (konvulsies).

Zolpidem is nie dialiseerbaar nie.

5 FARMAKOLOGIESE EIENSKAPPE

5.1 Farmakodinamiese eienskappe

Farmakoterapeutiese groep: A 2.2 Sedatiewe middels, hipnotika. ATC Kode: N05C F02

Zolpidem is ‘n bensodiasepien reseptor-agonis. Bensodiasepien reseptor-agoniste (BZRAs) oefen hulle farmakologiese effekte uit deur binding aan ‘n ligging geassosieer met GABA-A reseptore. Zolpidem vertoon selektiwiteit vir ‘n subtipe van GABA-A reseptore wat alfa-1-subeenhede bevat. Aangemelde wetenskaplike bewyse stel voor dat hierdie reseptor-subtipe geneesmiddel-geïnduseerde sedatiewe/hipnotiese effekte bemiddel.

5.2 Farmakokinetiese eienskappe

Absorpsie:

Ná orale inname, is die aangemelde absolute biobeskikbaarheid ongeveer 70 % en die piek plasma-konsentrasie word tussen 1,5 en 2,5 uur bereik. Die inter-individuele varieerbaarheid (CV) is aangemeld om ongeveer 40 – 60 % vir AOK en 30 – 40 % vir K_{maks} te wees.

Wanneer zolpidem ná voedsel toegedien word, is K_{maks} en AOK aangemeld om met 30 en 23 %, respektiewelik, te verlaag en die tyd tot by maksimale plasmakonsentrasie word met 2 uur vertraag.

Verspreiding:

Die *in vitro* plasmaproteïen-binding is aangemeld as ongeveer 92 %. Die verspreidingsvolume by volwassenes is aangemeld om 0,54 L/kg te wees ná intraveneuse toediening.

Metabolisme:

Zolpidem word hoofsaaklik deur die hepatiese sitochroom P450 CYP 3A4 (ongeveer 60 % van die totale CYP-bemiddelde hepatiese opruiming) gemetabolisser. Ander P450-isoënsieme soos CYP2C9, CYP1A2, CYP2D6 en CYP2C19 dra ook by tot die oksidasie van die geneesmiddel. Al die metaboliete van zolpidem is farmakologies onaktief. Zolpidem self is nie ‘n merkwaardige inhibeerder of induseerder van menslike CYP-isovorme nie.

Eliminasie:

Zolpidem word uitgeskei in die vorm van onaktiewe metaboliete in urine (ongeveer 60 %) en feses (ongeveer 40 %). Opruiming is aangemeld om ongeveer 212 mL / min te wees. Verminderde opruiming van 100 mL/min is by bejaardes aangemeld.

Zolpidem-plasmakonsentrasies is ongeveer 9 uur ná dosering op dag 1 en dag 15 by volwasse pasiënte wat vir 3 weke met 12,5 mg zolpidem behandel is, bepaal. Zolpidemkonsentrasies het nie verander met herhaalde dosering nie, wat daarop dui dat daar geen bewys van akkumulasie van zolpidem is nie. Die eliminasie $t_{1/2}$ is aangemeld om 2,8 uur by gesonde proefpersone te wees.

Hepatiese ontoereikendheid:

In pasiënte met lewerontoereikendheid, is die opruiming van zolpidem aangemeld om verlaag te wees en die eliminasie half-leeftyd is verleng (omtrent 10 uur) [sien afdeling 4.2]. By lewersirrose is ‘n 5-voudige toename in AOK en ‘n 3-voudige toename van half-leeftyd aangemeld.

Renale ontoereikendheid:

In pasiënte met renale ontoereikendheid, of dit nou gedialiseer is of nie, is ‘n matige toename (omtrent 30 %) van die volume van verspreiding aangemeld vergeleke met gesonde proefpersone. Ander farmakokinetiese parameters soos opruiming, AOK en eliminasie half-leeftyd word nie geaffekteer nie. Daarom is geen dosisaanpassing nodig by pasiënte met renale ontoereikendheid nie.

6. FARMASEUTIESE BESONDERHEDE

6.1 Lys van onaktiewe bestanddele

- Geel ysteroksied
- hipromellose (methocel E-5LV premium)
- hipromellose 2910 (methocel E15 premium LV)
- hipromellose 2208 (methocel K4M CR premium)
- isopropielalkohol
- laktosemonohidraat
- magnesiumstearaat
- mikrokristallyne sellulose
- Opadry II helder 85F19250
- Opacode swart S-1-17823
- natrium-styselglikolaat tipe A
- wynsteensuur

Filmbedekking

- Opadry II Helder 85F19250
- Opacode Swart S-1-17823
- Isopropielalkohol

6.2 Onverenigbaarhede

Nie van toepassing nie

6.3 Rakleeftyd

24 maande

Bewaar by of benede 25 °C

Hou in die oorspronklike houer om teen lig te beskerm.

Hou buite die bereik van kinders.

6.4 Spesiale voorsorgmaatreëls vir bewaring

Hierdie medisyne benodig nie spesiale bewaringsvereistes nie

6.5 Aard en inhoud van die verpakking

ZILSUN MR is beskikbaar in ‘n pakkie van 30 tablette, elke Alu-PVC-stulpstrook, bedek met PVD, of Alu/Alu-strook bevat 10 tablette, verpak in ‘n karton saam met ‘n professionele inligtingstuk.

6.6 Spesiale voorsorgmaatreëls vir vernietiging en ander hantering

Geen spesiale vereistes nie

7. HOUER VAN DIE REGISTRASIESERTIFIKAAT

Ranbaxy Pharmaceuticals (Pty) Ltd

Lautreweg 14

Stormill, Uitbreiding 1

Roodepoort, 1724

Suid-Afrika

8. REGISTRASIENOMMER

9 DATUM VAN EERSTE GOEDKEURING

10 DATUM VAN HERSIENING VAN DIE TEKS