SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

ZOPISLEEP, 7,5 mg (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 7,5 mg zopiclone

Excipient with known effect: ZOPISLEEP contains lactose monohydrate.

Contains sugar (lactose monohydrate 30,8 mg per tablet).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

White, odourless, round, biconvex film-coated tablet, plain on one side and a division mark on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ZOPISLEEP is indicated for the short-term treatment of insomnia in adults in which the disorder is severe, disabling or subjecting the individual to extreme stress.

4.2 Posology and method of administration

Treatment should be started with the lowest recommended dose and the maximum dose should not be exceeded.

Adults: 7,5 mg orally, shortly before retiring. This dose should not be exceeded.

Elderly patients and patients with impaired hepatic function or chronic respiratory insufficiency:

The lower dose of 3,75 mg ZOPISLEEP should be used initially in these patients, and if necessary, the dose may be increased to 7,5 mg.

Treatment should be started with the lowest recommended dose and the maximum dose should not be exceeded.

Renal insufficiency:

Patients with impaired renal function should start treatment with 3,75 mg, although accumulation of ZOPISLEEP or its metabolites has not been seen during treatment of insomnia in patients with renal insufficiency.

ZOPISLEEP therapy should be for as short a time as possible. Generally, the duration of treatment varies from a few days to two weeks, with a maximum, including tapering off process, of four weeks. Use for any longer periods requires re-evaluation of the patient.

4.3 Contraindications

ZOPISLEEP is contraindicated in patients with

- Hypersensitivity to zopiclone or to any of the excipients in ZOPISLEEP
- Respiratory failure
- Severe sleep apnoea syndrome
- Severe hepatic insufficiency
- Myasthenia gravis

ZOPISLEEP should not be used in children under the age of 18 years.

Safety in pregnancy and lactation has not been established.

4.4 Special warnings and precautions for use

ZOPISLEEP should be used with extreme caution in patients with a history of drug or alcohol abuse.

Specific patient groups

Use in hepatic insufficiency

A reduced dosage is recommended, see Posology. Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy (see section 4.3)

Use in renal insufficiency

A reduced dosage is recommended, see Posology.

Use in respiratory insufficiency

If ZOPISLEEP is prescribed to patients with compromised respiratory function (see section 4.8), precautions should be observed because hypnotics have the capacity to depress respiratory drive. A lower dose is recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Use in paediatric population

ZOPISLEEP should not be used in children and adolescents less than 18 years. The safety and efficacy of ZOPISLEEP in children and adolescents aged less than 18 years have not been established.

Use in elderly patients

Elderly should be given a reduced dose (see section 4.2).

Dependence

There is a potential for abuse and the development of physical and psychological dependence, especially with prolonged use and high doses. The risk of dependence is also greater in patients with a history of psychiatric disorders and/or alcohol, substance or drug abuse. ZOPISLEEP should be used with extreme caution in patients with current or a history of alcohol, substance or drug abuse or dependence.

Once physical dependence has developed, abrupt termination of therapy will result by withdrawal symptoms (see section 4.8).

Withdrawal

The termination of treatment with ZOPISLEEP is unlikely to be associated with withdrawal effects when duration of treatment is limited to 4 weeks. Patients may benefit from tapering off the dose before discontinuation (see section 4.8).

Suicidal ideation/suicide attempt/suicide depression

Some epidemiological studies show an increased incidence of suicidal ideation, suicide attempt and suicide in patients with or without depression, and treated with benzodiazepines and other hypnotics, including zopiclone (e.g. ZOPISLEEP). However, a causal relationship has not been established.

ZOPISLEEP does not constitute a treatment for depression and may even mask its symptoms (suicide may be precipitated in such patients).

ZOPISLEEP is not recommended for primary treatment of psychotic illness.

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

Any underlying cause of the insomnia should also be addressed before symptomatic treatment to avoid under treating potentially serious effects of depression.

Tolerance

Some loss of efficacy to the hypnotic effect of benzodiazepines and benzodiazepine-like medicines may develop after repeated use for a few weeks.

However, with ZOPISLEEP there is an absence of any marked tolerance during treatment periods of up to 4 weeks.

Rebound insomnia and withdrawal phenomena

A transient syndrome where the symptoms which led to treatment with a benzodiazepine or benzodiazepine-like medicine recur in an enhanced form on discontinuation of therapy. It may be accompanied by other reactions including mood changes, anxiety and restlessness. The risk of such phenomena is greater after abrupt discontinuation of ZOPISLEEP, especially after prolonged treatment. It is, therefore, recommended to decrease the dosage gradually and to advise patient accordingly. (See section 4.8)

A course of treatment should employ the lowest effective dose for the minimum length of time necessary for effective treatment. See Posology for guidance on possible treatment regimen. A course of treatment should not continue for longer than 4 weeks including any tapering off (see section 4.8).

Some loss of efficacy may develop after repeated use.

Amnesia

Amnesia is rare, but anterograde amnesia may occur, especially when sleep is interrupted or when retiring to bed is delayed after taking the tablet. To minimise the risk of anterograde amnesia and mental confusion, ZOPISLEEP should be taken only when the patient's schedule will allow for a full night's sleep (7 to 8 hours).

Psychomotor impairment

ZOPISLEEP has central nervous system depressant effects. The risk of psychomotor impairment, including impaired driving ability, should be taken into account (see sections 4.5 and 4.7).

Risks from concomitant use with opioids

Concomitant use of opioids with benzodiazepines or other sedative-hypnotic medicines, including zopiclone 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 ZOPISLEEP concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation (see section 4.5).

Other psychiatric and paradoxical reactions

Other psychiatric and paradoxical reactions have been reported (see section 4.8), like restlessness, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, inappropriate behaviour and other adverse behavioural effects are known to occur when using sedative/hypnotic medicines like ZOPISLEEP. Should this occur, use of ZOPISLEEP 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, or making phone calls, with amnesia for the event, have been reported in patients who have taken zopiclone as contained in ZOPISLEEP and were not fully awake. The use of alcohol and other CNS-depressants with ZOPISLEEP appears to increase the risk of such behaviours, as does the use of ZOPISLEEP at doses exceeding the maximum recommended dose. Discontinuation of ZOPISLEEP should be strongly considered for patients who report such behaviours (see section 4.5).

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

4.5 Interaction with other medicines and other forms of interaction

- Alcohol: Concomitant use may enhance the sedative effect of ZOPISLEEP.

- Central Nervous System (CNS) depressant medicines such as neuroleptics, hypnotics, anxiolytics/sedatives, antidepressant medicines, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative antihistaminics: Concurrent use with ZOPISLEEP may produce additive CNS depressant effects.
- In the case of narcotic analgesics, enhancement of euphoria may also occur leading to an increase in psychic dependence. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines and benzodiazepine-like medicines.
- Hepatic enzyme inhibitors including erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and cimetidine: Inhibitors of cytochrome P450 enzymes may increase the effects of ZOPISLEEP. A dose reduction for ZOPISLEEP may be required when it is co-administered with CYP3A4 inhibitors.
- Hepatic enzyme inducers such as rifampicin, carbamazepine, phenobarbital, phenytoin and St. John's wort.: CYP3A4 inducers may decrease the plasma concentrations of ZOPISLEEP. Therefore, a dose increase for ZOPISLEEP may be required when it is co-administered with CYP3A4 inducers.
- Opioids: The concomitant use of benzodiazepines and other sedative-hypnotic medicines, including ZOPISLEEP, and opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

If ZOPISLEEP is prescribed to a woman of childbearing potential, she should be warned to contact her medical practitioner regarding discontinuation of ZOPISLEEP if she intends to become or suspects that she is pregnant.

Pregnancy

Insufficient data are available on ZOPISLEEP to assess its safety during human pregnancy and lactation. If ZOPISLEEP is used during the last three months of pregnancy or during labour, due to pharmacological action of the product, effects on the neonate, such as hypothermia, hypotonia, and respiratory depression can be expected. The use of ZOPISLEEP during pregnancy is not recommended. (See section 4.3)

Breastfeeding

Although the concentration of ZOPISLEEP in the breast milk is very low, ZOPISLEEP should not be used by breastfeeding mothers. (See section 4.3)

4.7 Effects on ability to drive and use machines

Because of its pharmacological properties and its effect on central nervous system, ZOPISLEEP may adversely affect the ability to drive or to use machines. The risk of psychomotor impairment, including impaired driving ability, is increased if:

- ZOPISLEEP is taken within 12 hours of performing activities that require mental alertness,
- a dose higher than the recommended dose is taken, or
- is co-administered with other CNS depressants, alcohol, or with other medicines that increase the blood levels of ZOPISLEEP.

4.8 Undesirable effects

Immune system disorders

Less frequent:

Angiooedema, anaphylactic reaction

Psychiatric disorders

Less frequent:

Nightmares, agitation, confusion, libido disorder, irritability, aggression, hallucinations

Frequency unknown:

Restlessness, delusion, anger, depressed mood, abnormal behaviour (possibly associated with amnesia) and somnambulism (see section 4.4: somnambulism and associated behaviour), dependence (see section 4.4), withdrawal syndrome (see below)

Nervous system disorder

Frequent:

Dizziness, residual somnolence, drowsiness and incoordination on waking

Less frequent:

Headache, anterograde amnesia (especially when sleep is interrupted, or when tablet is taken too early before retiring), (see section 4.4)

Frequency unknown:

Ataxia, paraesthesia, cognitive disorders such as memory impairment, disturbance in attention, speech disorder

Eye disorders

Frequency unknown:

Diplopia

Respiratory, thoracic and mediastinal disorders

Less frequent:

Dyspnoea (see section 4.4)

Frequency unknown:

Respiratory depression (see section 4.4)

Gastrointestinal disorders

Frequent:

Bitter taste in the mouth, dyspepsia, nausea and dry mouth.

Hepato-biliary disorders

Less frequent:

Increased transaminases and/or blood alkaline phosphatase increased (mild to moderate)

Skin and subcutaneous tissue disorders

Less frequent:

Pruritus, rash (may be a sign of hypersensitivity).

Musculoskeletal and connective tissue disorders

Frequency unknown:

Muscular weakness

General disorders and administration site conditions

Less frequent:

Fatigue

Frequency unknown:

Light headedness, incoordination

Injury, poisoning and procedural complications

Less frequent:

Fall (predominantly in elderly patients)

Other:

Rebound effects: Discontinuation of treatment of ZOPISLEEP may result in a transient syndrome of restlessness and mood changes, as well as an enhancement of symptoms that led to the treatment with ZOPISLEEP. (See section 4.2)

Withdrawal syndrome has been reported upon discontinuation of ZOPISLEEP (see section 4.4.). Withdrawal symptoms vary and may include rebound insomnia, muscle pain, extreme anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, hallucinations, panic attacks, muscle aches/cramps, gastrointestinal disturbances and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis (abnormal acute hearing), numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms of overdose:

(See sections 4.4 and 4.8)

Overdose is usually manifested by varying degrees of central nervous system depression according to the quantity ingested. In mild cases, symptoms include drowsiness, confusion, and lethargy; in more

serious cases, symptoms may include ataxia, hypotonia; hypotension, respiratory depression and coma. Overdose may be life-threatening especially when combined with other CNS depressants (including alcohol). Other risk factors such as the presence of concomitant illness and the debilitated state of the patient may contribute to the severity of the symptoms and can result in fatal outcome.

Treatment of overdose:

Symptomatic and supportive treatment in an adequate clinical environment is recommended, with special attention being paid to respiratory and cardiovascular functions.

Gastric lavage is only useful when performed soon after ingestion.

Haemodialysis is of no value due to the large volume of distribution of ZOPISLEEP. Flumazenil may be a useful antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N05C F01

Zopiclone is a cyclopyrrolone hypnotic medicine. It has sedative, anxiolytic, muscle relaxant, hypnotic and anticonvulsant properties. These effects are related to a specific agonist action at central receptors belonging to the gamma-antinobutyric acid (GABA) macromolecular complex in the brain modulating the opening of the chloride ion channel.

5.2 Pharmacokinetic properties

Absorption

Zopiclone is rapidly absorbed. Peak concentration (30 to 60 mg/ml after doses of 3,75 mg) are reached within 1,5 to 2 hours. Absorption is not affected by co-administration with food.

Distribution

Plasma protein binding is weak (approximately 45 %) and non-saturable. Zopiclone is distributed into breastmilk, its concentration being approximately 50 % that of plasma concentrations.

Biotransformation

After repeated administration there is no accumulation of zopiclone and its metabolites Inter-individual variations appear to be low.

Zopiclone is extensively metabolised in humans to two major metabolites, N-oxide zopiclone (pharmacologically active in animals) and N-desmethyl zopiclone (pharmacologically inactive in animals). An in vitro study indicates that cytochrome P450 (CYPO 3A4 is the major isoenzyme involved in the metabolism of zopiclone to both metabolites, and that CYP2C8 is also involved with N-desmethyl zopiclone formation.

Elimination

At recommended doses, the elimination half-life of the zopiclone is approximately 5 hours. Approximately 80 % of zopiclone is eliminated renally, mainly in the form of free metabolites (N-oxide and N-demethyl derivations). Faecal elimination is approximately 16 %.

Characteristics in specific groups of subjects or patients

In renal insufficiency, no accumulation of zopiclone or its metabolites has been detected after prolonged administration. Zopiclone is removed by haemodialysis.

In cirrhotic patients, the plasma clearance of zopiclone is reduced by approximately 40 % in relation to the decrease of the demethylation process. Therefore, dosage will have to be modified in these patients.

In elderly patients, notwithstanding a slight decrease in hepatic metabolism and lengthening of elimination half-life to approximately 7-hour, various studies have not shown plasma accumulation of the medicine substance on repeated dosing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Calcium hydrogen phosphate (dihydrate)
Carmellose sodium
Lactose monohydrate
Magnesium stearate
Maize starch

Film coating

Instacoat Universal 05R04331 White

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a cool dry place, below 25 °C, protected from light.

6.5 Nature and contents of container

3 x 10 tablets in a PVC/PVDC/Al blister strip packed into a carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd.
124 Elevation Avenue
Randjesfontein
MIDRAND
1683
SOUTH AFRICA

8 REGISTRATION NUMBER

37/2.2/0375.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: March 2005

10 DATE OF REVISION OF THE TEXT

01 December 2019