PROFESSIONAL INFORMATION FOR:

ZOPIVANE

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ZOPIVANE (7,5 mg film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each tablet contains zopiclone 7,5 mg.

Contains sugar: lactose monohydrate 40,000 mg per tablet.

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM

Film-coated tablets

White, film coated, oblong-shaped, shallow convex tablets with central breakline on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZOPIVANE is indicated for the short-term treatment of insomnia in adults.

4.2 Posology and method of administration

Posology

Adults:

7,5 mg (one tablet) taken orally shortly before retiring at night.

This dose should not be exceeded.

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

Special populations

Elderly patients and patients with hepatic and chronic respiratory insufficiency:

3,75 mg taken orally shortly before retiring at night, initially. This may be increased to 7,5 mg depending on the effectiveness and tolerance of the tablets.

Renal insufficiency:

Although accumulation of zopiclone has not been observed in patients with renal insufficiency, it is recommended that treatment should be initiated with 3,75 mg.

Paediatric population

ZOPIVANE should not be prescribed to children younger than 18 years old.

4.3 Contraindications

ZOPIVANE is contraindicated in patients with:

- hypersensitivity to zopiclone or to any other excipients of ZOPIVANE (see **section 6.1**)
- myasthenia gravis
- respiratory failure
- severe hepatic insufficiency
- sleep apnoea syndrome
- patients with pre-existing CNS depression or coma.

Safety in pregnancy has not been established (see **section 4.6**).

ZOPIVANE should not be prescribed to breastfeeding mothers (see **section 4.6**).

ZOPIVANE should not be prescribed to children younger than 18 years old.

4.4 Special warnings and precautions for use

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

Drowsiness and inco-ordination on waking may occur. Patients should be cautioned about driving motor vehicles or operating machinery, until it has been established that their performance is not affected (see **section 4.7**).

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 ZOPIVANE 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

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

Use in elderly patients

ZOPIVANE should be given with care to the elderly or debilitated patients who may be more prone to adverse effects.

Dependence

The development of dependence or abuse cannot be excluded and should be kept in mind when zopiclone is prescribed. Dependence is particularly likely in patients with a history of alcohol and/or drug abuse and in patients with marked

personality disorders. The risk of dependence or abuse increases with dose and duration of treatment and the use with alcohol and other psycotropics.

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

Withdrawal

The termination of treatment with ZOPIVANE 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. ZOPIVANE). However, a causal relationship has not been established.

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

ZOPIVANE is not recommended for primary treatment of psychotic illness.

ZOPIVANE should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present therefore the least amount of ZOPIVANE 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 ZOPIVANE. 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 ZOPIVANE 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 ZOPIVANE, 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, ZOPIVANE should be taken only when the patient’s schedule will allow for a full night’s sleep (7 to 8 hours).

Psychomotor impairment

ZOPIVANE 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 ZOPIVANE 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 ZOPIVANE. Should this occur, use of ZOPIVANE 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 ZOPIVANE and were not fully awake. The use of alcohol and other CNS-depressants with ZOPIVANE appears to increase the risk of such behaviours, as does the use of ZOPIVANE at doses exceeding the maximum recommended dose. Discontinuation of ZOPIVANE should be strongly considered for patients who report such behaviours (see **section 4.5**).

ZOPIVANE contains lactose monohydrate

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take ZOPIVANE.

4.5 Interaction with other medicinal products and other forms of interaction

- The concomitant use of alcohol is not recommended since the sedative effect of zopiclone may be enhanced.
- Caution is advised when prescribing zopiclone to patients using central depressant medication such as neuroleptics, anxiolytic/sedatives, hypnotics, antidepressant medicines, antiepileptic medication, anaesthetics, narcotic analgesics and sedative antihistaminics as the central depressive effects of zopiclone may be enhanced by these medicines.
- 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 ZOPIVANE. A dose reduction for ZOPIVANE 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 ZOPIVANE. Therefore, a dose increase for ZOPIVANE may be required when it is co-administered with CYP3A4 inducers.
- Opioids: The concomitant use of benzodiazepines and other sedative-hypnotic medicines, including ZOPIVANE, 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**).
- Sedative effects of zoplicone may be enhanced by cisapride.
- Zopiclone may be removed by dialysis.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

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

Pregnancy

Insufficient data are available on ZOPIVANE to assess its safety during human pregnancy and lactation. If ZOPIVANE 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 ZOPIVANE during pregnancy is not recommended. (see **section 4.3**).

Breastfeeding

Although the concentration of ZOPIVANE in the breast milk is very low, ZOPIVANE 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, ZOPIVANE may adversely affect the ability to drive or to use machines (see **section 4.4**). The risk of psychomotor impairment, including impaired driving ability, is increased if:

- ZOPIVANE 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 ZOPIVANE.

4.8 Undesirable effects

Summary of the safety profile

Sedation, ataxia, drowsiness and inco-ordination on waking, are the most frequent side-effects. They generally decrease on continued administration of zopiclone.

Tabulated summary of adverse reactions

The following adverse reactions have been classified according to the following categories, frequent, less frequent and frequency unknown.

MedDRA system organ Class	**Frequency**	**Side 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 ZOPIVANE may result in a transient syndrome of restlessness and mood changes, as well as an enhancement of symptoms that led to the treatment with ZOPIVANE (see **section 4.2**).

Withdrawal syndrome has been reported upon discontinuation of ZOPIVANE (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. Health care 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 and to Cipla Medpro (Pty) Ltd at drugsafetysa@cipla.com or telephone 080 222 6662 (toll free).

4.9 Overdose

Symptoms of overdose

Overdosage usually presents with varying degrees of central nervous system depression, ranging from drowsiness to coma, 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. When the overdosage is combined with alcohol or other CNS depressants, it may be life-threatening. 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 to respiratory and cardiovascular functions. Gastric lavage is of value only if performed soon after ingestion. Flumazenil may be useful as an antidote. Haemodialysis is of no value due to the large volume of distribution of ZOPIVANE.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.2.2. Sedatives, hypnotics

ATC Code: N05C F01

Zopiclone belongs to the chemical group the cyclopyrrolones, and is reported to have similar amnesic, anxiolytic, muscular relaxant, sedative and anti-convulsant properties to those of the benzodiazepines, although it is chemically distinct from them.

The pharmacological actions of zopiclone are mediated by the enhancement of the activity of aminobutyric acid (GABA) in the brain. It binds to the same receptor component of the GABA receptor in the brain as the benzodiazepines, but at a different site.

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:

Colloidal silicon dioxide (Aerosil 200)

Lactose monohydrate

Magnesium stearate

Maize starch

Sodium starch glycolate

Tablet coating:

Opadry QX321A180025

Opadry QX321A180025:

Glycerol monocaprylocaprate

Macrogol (PEG) Polyvinyl alcohol graft copolymer

Polyvinyl alcohol

Talc

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a cool, dry place at or below 25 °C. Protect from light.

6.5 Nature and contents of container

ZOPIVANE tablets are supplied in blister strips of 10 tablets, packed in 30's in a carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

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Customer Care: 080 222 6662

8. REGISTRATION NUMBER

35/2.2/0021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 January 2023

10. DATE OF REVISION OF THE TEXT