PROFESSIONAL INFORMATION

SCHEDULING STATUS S5

1. NAME OF THE MEDICINE

Sandoz® Zopiclone 7,5 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SANDOZ ZOPICLONE 7,5 tablet contains: 7,5 mg zopiclone.

Contains lactose monohydrate (78,5 mg per tablet).

3. PHARMACEUTICAL FORM

White to off white, oval, biconvex, film-coated tablets with break-line.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SANDOZ ZOPICLONE 7,5 is only indicated when the disorder is severe, disabling or subjecting the individual to extreme stress.

SANDOZ ZOPICLONE 7,5 is used in the short-term treatment of insomnia in adults.

Safety in long-term treatment has not been demonstrated

4.2 Posology and method of administration

Posology

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

The treatment duration should be as short 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.

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.

Adults:

One tablet orally, shortly before retiring.

Elderly patients:

A lower dose of 3,75 mg (half a tablet) should be employed initially and depending on the effectiveness and tolerance, the dose can be increased to 7,5 mg.

Patients with hepatic insufficiency:

Treatment should be initiated with a dose of 3,75 mg (half a tablet) at night (see section 4.4).

Renal insufficiency:

It is recommended that patients with impaired renal function should start treatment with 3,75 mg.

Paediatric population:

SANDOZ ZOPICLONE 7,5 should not be used in children.

4.3 Contraindications

- Hypersensitivity to SANDOZ ZOPICLONE 7,5 or any of the inactive ingredients of SANDOZ ZOPICLONE 7,5 (see section 6.1).
- Myasthenia gravis.
- Respiratory failure.
- Severe sleep apnoea syndrome.
- Severe hepatic insufficiency.
- Who have previously experienced complex sleep behaviours after taking SANDOZ ZOPICLONE 7,5 (see section 4.4).

- SANDOZ ZOPICLONE 7,5 should not be used in children under the age of 18.
- The safety in pregnancy and lactation has not been established.
- SANDOZ ZOPICLONE 7,5 should be avoided in patients with pre-existing central nervous system depression or coma, acute pulmonary insufficiency or sleep apnoea.

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4.4 Special warnings and precautions for use

Drowsiness and incoordination on waking can occur.

SANDOZ ZOPICLONE 7,5 is not recommended for the primary treatment of psychotic illness. SANDOZ ZOPICLONE 7,5 should not be used alone to treat depression or anxiety with depression (suicide may be precipitated in such patients). SANDOZ ZOPICLONE 7,5 should be used with extreme caution in patients with a history of alcohol or drug abuse.

Use with care in patients with chronic pulmonary insufficiency.

SANDOZ ZOPICLONE 7,5 should be given with care to elderly or debilitated patients who may be more prone to adverse effects.

Caution is required in patients with impaired kidney function.

Severe hepatic insufficiency (serum albumin less than 30 g/l or presence of gross oedema) may significantly interfere with the elimination of SANDOZ ZOPICLONE 7,5.

The standard one tablet dose may be cautiously prescribed to patients with moderate (compensated) renal insufficiency, but higher doses are not recommended in these patients. SANDOZ ZOPICLONE 7,5 is removed by dialysis.

Caution is required in patients with organic brain changes, particularly arteriosclerosis.

SANDOZ ZOPICLONE 7,5 has less frequently provoked seizures in epileptic patients; seizures may also occur on abrupt withdrawal of therapy.

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

The lack of relief from insomnia after 7 - 10 days of treatment possibly indicates the presence of a primary psychiatric and / or medical pathology or the presence of an erroneous perception of the state of sleep.

Specific patient groups

Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy (see section 4.3).

Use in Paediatric population

SANDOZ ZOPICLONE 7,5 should not be used children and adolescents less than 18 years. The safety and efficacy of SANDOZ ZOPICLONE 7,5 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). Due to the muscle relaxant effect of SANDOZ ZOPICLONE 7,5, there is a risk of fall, especially in the elderly if they get up during the night.

Rebound insomnia:

A transient syndrome whereby the symptoms that led to treatment with SANDOZ ZOPICLONE 7,5, a benzodiazepine or benzodiazepine-like agent, recur in an enhanced form on discontinuation of therapy. It may be accompanied by other reactions including mood changes, anxiety and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after prolonged treatment, or abrupt discontinuation of treatment, it is, therefore recommended that the dosage is decreased gradually and to advise the patient accordingly.

A course of treatment should employ the lowest effective dose for the minimum length of time necessary for effective treatment. For guidance on a possible treatment regimen, see section 4.2. A course of treatment should not continue for longer than 4 weeks including any tapering off (see section 4.8).

Risk of dependence:

Clinical experience to date with SANDOZ ZOPICLONE 7,5 suggests that the risk of dependence is minimal when the duration of treatment is limited to not more than 4 weeks.

The use of benzodiazepines and benzodiazepine-like substances (even at therapeutic doses) can lead to the development of physical and psychological dependence as well as a potential for abuse especially with prolonged use and high doses. The risk of dependence or abuse is also greater in patients with a history of alcohol or other psychotropics or drug abuse or those who have marked personality disorders. This should be considered when taking the decision to use a hypnotic in such patients. If physical dependence occurs, sudden discontinuation of the treatment will be accompanied by withdrawal symptoms (see section 4.4). These may be expressed as headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability.

In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. Rare cases of abuse have been reported.

Duration of treatment

The duration of treatment should be as short as possible (see section 4.2), but should not exceed 4 weeks for insomnia, including tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation. It may be useful to inform the patient when treatment is started that it will be of limited duration and explain precisely how the dosage will be progressively decreased. Moreover, it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimizing anxiety over such symptoms, should they occur while SANDOZ ZOPICLONE 7,5 is being discontinued.

Withdrawal

The termination of treatment with SANDOZ ZOPICLONE 7,5 is unlikely to be associated with withdrawal effects when duration of treatment is limited to 4 weeks. Patients may benefit from tapering of the dose before discontinuation (see section 4.8).

Depression

As with other hypnotics, SANDOZ ZOPICLONE 7,5 does not constitute a treatment for depression and may even unmask its symptoms (suicide may be precipitated in such patients). Any underlying cause of insomnia should be addressed carefully before symptomatic treatment to avoid under treating potentially serious effects of depression. Suicidal tendencies may be present, therefore the least amount of SANDOZ ZOPICLONE 7,5 that is feasible should be supplied to these patients to avoid the possibility of intentional overdose by the patient. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

Suicidality

Some epidemiological studies indicate an increased incidence of suicide and suicide attempts in patients with or without depression, and treated with benzodiazepines or hypnotics, including SANDOZ ZOPICLONE 7,5. However, a causal association has not been demonstrated.

Tolerance

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

However, with SANDOZ ZOPICLONE 7,5 there is an absence of any marked tolerance during treatment periods of up to 4 weeks.

Amnesia

Anterograde amnesia may occur, especially when sleep is interrupted or when retiring to bed is delayed after taking the tablet. Therefore, to reduce the possibility of anterograde amnesia, patients should ensure that they take the tablet when certain of retiring for the night and they are able to have a full night's sleep (uninterrupted sleep of about 8 hours).

Psychomotor impairment

Like other sedative/hypnotic drugs, SANDOZ ZOPICLONE 7,5 has CNS-depressant effects. The risk of psychomotor impairment, including impaired driving ability, is increased if: SANDOZ ZOPICLONE 7,5 is taken within 12 hours of performing activities that require mental alertness, a dose higher than the recommended dose is taken, or SANDOZ ZOPICLONE 7,5 is co-administered with other CNS-depressants, alcohol or with other drugs that increase the blood levels of SANDOZ ZOPICLONE 7,5 (see section 4.5). Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle following administration of SANDOZ ZOPICLONE 7,5 and in particular during the 12 hours following that administration.

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 agents like SANDOZ ZOPICLONE 7,5. Should this occur, use of SANDOZ ZOPICLONE 7,5 should be discontinued. These reactions are more likely to occur in the elderly.

Somnambulism and associated behaviours

Complex sleep behaviour, including sleep walking and other associated behaviours such as “sleep driving”, preparing and eating food, or making phone calls, with amnesia of the event, have been

reported in patients who have taken SANDOZ ZOPICLONE 7,5 and were not fully awake. These events may occur following the first or any subsequent use of SANDOZ ZOPICLONE 7,5. The use of alcohol and other CNS-depressants with SANDOZ ZOPICLONE 7,5 appears to increase the risk of such behaviours, as does the use of SANDOZ ZOPICLONE 7,5 at doses exceeding the maximum recommended dose. Discontinuation of SANDOZ ZOPICLONE 7,5 should be strongly considered for patients who report such behaviours (see section 4.3).

Risk from concomitant use of opioids

Concomitant use of SANDOZ ZOPICLONE 7,5 and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as SANDOZ ZOPICLONE 7,5 with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe SANDOZ ZOPICLONE 7,5 concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see section 4.2).

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

Precautions relating to excipients

SANDOZ ZOPICLONE 7,5 contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take SANDOZ ZOPICLONE 7,5.

SANDOZ ZOPICLONE 7,5 contains lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Sedation or respiratory and cardiovascular depression may be enhanced by other medicines with central nervous system depressant properties; these include alcohol, antidepressants, antihistamines, antipsychotics, general anaesthetics, other hypnotics or sedatives and opioid analgesics. Erythromycin increases the rate of absorption of SANDOZ ZOPICLONE 7,5 and prolongs its elimination.

Association not recommended:

Concomitant use with alcohol is not recommended because the sedative effect of SANDOZ ZOPICLONE 7,5 may be intensified when used in combination with alcohol. This may affect the ability to drive or operate machines.

Associations to be taken into account:

In combination with CNS depressants an enhancement of the central depressive effect may occur. The therapeutic benefit of co-administration with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines should therefore be carefully weighed. 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 agents.

Since SANDOZ ZOPICLONE 7,5 is metabolised by P450 (CYP)3A4 isoenzyme (see section 5.2), the plasma levels of SANDOZ ZOPICLONE 7,5 and thus the effect of SANDOZ ZOPICLONE 7,5 may be increased when used in combination with drugs which inhibit CYP3A4, such as erythromycin, clarithromycin, azole antimycotics such as ketoconazole, itraconazole and ritonavir. Dose reduction should be considered if SANDOZ ZOPICLONE 7,5 is co-administered with CYP3A4 inhibitors.

Co-administration with medicines which induce CYP3A4, like phenobarbital, phenytoin, carbamazepine, rifampicin and products containing St John's wort, may reduce SANDOZ ZOPICLONE

7,5 plasma levels and thus the effect of SANDOZ ZOPICLONE 7,5. A dose increase for SANDOZ ZOPICLONE 7,5 may be required when it is co-administered with CYP3A4 inducers.

The effect of erythromycin on the pharmacokinetics of SANDOZ ZOPICLONE 7,5 has been studied in 10 healthy subjects. The AUC of SANDOZ ZOPICLONE 7,5 is increased by 80 % in presence of erythromycin which indicates that erythromycin can inhibit the metabolism of medicines metabolised by CYP 3A4. As a consequence, the hypnotic effect of SANDOZ ZOPICLONE 7,5 may be enhanced.

Opioids:

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as SANDOZ ZOPICLONE 7,5 with 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

SANDOZ ZOPICLONE 7,5 should not be used during pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. SANDOZ ZOPICLONE 7,5 crosses the placenta.

Cases of reduced foetal movement and foetal heart rate variability have been described after administration of benzodiazepines or benzodiazepine-like substances during the second and/or third trimester of pregnancy.

Moreover, if SANDOZ ZOPICLONE 7,5 is prescribed during the last three months of pregnancy or during labour, due to the pharmacological action of the product, effects on the neonate, such as hypothermia, hypotonia, feeding difficulties (floppy infant syndrome) and respiratory depression can be expected due to the pharmacological action of the product. Cases of severe neonatal respiratory depression have been reported.

Infants born to mothers who took benzodiazepines or benzodiazepine-like agents chronically during the latter stages of pregnancy, may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period. Appropriate monitoring of the newborn in the postnatal period is recommended.

If the product is prescribed to a woman of childbearing potential, she should be advised to contact her physician about stopping the product if she intends to become pregnant, or suspects that she is pregnant.

Breastfeeding

SANDOZ ZOPICLONE 7,5 is excreted in breast milk, although the concentration of SANDOZ ZOPICLONE 7,5 in the breast milk is low; use in nursing mothers must be avoided.

Fertility

In a double-blind long-term study in healthy male volunteers, no negative changes in sperm volume, sperm concentration, sperm motility and cell morphology were found in spermatograms at doses of 7,5 mg zopiclone over a period of 84 days.

4.7 Effects on ability to drive and use machines

Because of its pharmacological properties and its effect on central nervous system, SANDOZ ZOPICLONE 7,5 may adversely affect the ability to drive or to use machines. The risk of psychomotor impairment, including impaired driving ability, is increased if:

• SANDOZ ZOPICLONE 7,5 is taken within 12 hours of performing activities that require mental alertness,

• a dose higher than the recommended dose is taken, or

• SANDOZ ZOPICLONE 7,5 is co-administered with other CNS depressants, alcohol, or with other drugs that increase the blood levels of SANDOZ ZOPICLONE 7,5.

Patients should be cautioned against engaging in hazardous occupations requiring complete mental

alertness or motor coordination such as operating machinery or driving a motor vehicle following administration of SANDOZ ZOPICLONE 7,5 and in particular during the 12 hours following that administration.

4.8 Undesirable effects

The side effect most commonly recorded is bitter or metallic aftertaste.

Drowsiness, sedation and ataxia are also frequent side effects. They generally decrease on continued administration and are a consequence of central nervous system depression.

Less frequent side effects include vertigo, slurred speech or dysarthria, tremor, visual disturbances, urinary retention or incontinence, gastrointestinal disturbances, changes in salivation and amnesia.

Some patients may experience a paradoxical excitation which may lead to hostility, aggression and disinhibition.

Jaundice, blood disorders and hypersensitivity reactions have been reported rarely.

Hypotension occasionally occurs with high dosage.

Rebound insomnia may be the result of tolerance to the effect of SANDOZ ZOPICLONE 7,5 or part of a withdrawal syndrome (see section 4.4).

Immune system disorders:

Less frequent: Angioedema, anaphylactic reaction, Stevens-Johnson syndrome, toxic epidermal necrosis, erythema multiforme.

Psychiatric disorders:

Less frequent: Nightmare, agitation, confusional state, libido disorder, irritability, aggression, hallucination.

Not known: Restlessness, delusion, anger, depressed mood, abnormal behaviour (possibly associated with amnesia) and complex sleep behaviour including somnambulism (see section 4.4), dependence (see section 4.4), withdrawal syndrome (see below).

Nervous system disorders:

Frequent: Dysgeusia (bitter taste), somnolence (residual)

Less frequent: Dizziness, headache, anterograde amnesia

Not known: Ataxia, paraesthesia, cognitive disorders such as memory impairment, disturbance in attention, speech disorders.

Eye disorders:

***Not known*:** Diplopia

Respiratory, thoracic and mediastinal disorders:

***Less frequent*:** Dyspnoea (see section 4.4)

***Not known*:** Respiratory depression (see section 4.4)

Gastrointestinal disorders:

***Frequent*:** Dry mouth

***Less frequent*:** Nausea, vomiting

***Rare*:** Diarrhoea

***Not known*:** Dyspepsia

Hepatobiliary disorders:

***Less frequent*:** Transaminases increased and/or blood alkaline phosphatase increased (mild to moderate)

Skin and subcutaneous tissue disorders:

***Less frequent*:** Urticaria or rash, pruritus

Musculoskeletal and connective tissue disorders:

***Not known*:** Muscular weakness

General disorders and administration site conditions:

***Less frequent*:** Fatigue

***Not known*:** Light headedness, incoordination injury, poisoning and procedural complications

***Rare*:** Fall (predominantly in elderly patients)

Injury, poisoning and procedural complications:

***Less frequent*:** Fall (predominantly in elderly patients)

Withdrawal syndrome has been reported upon discontinuation of SANDOZ ZOPICLONE 7,5 (see section 4.4). Withdrawal symptoms vary and may include rebound insomnia, muscle pain, 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,

numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations. In very rare cases, seizures may occur.

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

Suspected adverse reactions can also be reported directly to the holder of the certificate of registration (HCR) via the link: https://pvi1j.solutions.iqvia.com, or the e-mail address, adverse.event.sac@sandoz.com.

4.9 Overdose

Overdose is usually manifested by 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 severe cases, symptoms may include ataxia, hypotonia, hypotension, methaemoglobinaemia, respiratory depression, and coma. Overdose should not be life threatening unless 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 symptoms and very rarely can result in fatal outcome. Treatment is symptomatic and supportive. Flumazenil may be useful as an antidote.

Fatal dose not known.

Management

Symptomatic and supportive treatment in adequate clinical environment is recommended; attention should be paid to respiratory and cardiovascular functions.

Consider activated charcoal if an adult has ingested more than 150 mg or a child more than 1,5 mg/kg within one hour.

Alternatively, consider gastric lavage in adults within one hour of a potentially life-threatening overdose. Haemodialysis is not effective because it is high zopiclone distribution volume, if CNS depression is severe, consider the use of flumazenil. It has a short half-life (about an hour). NOT TO BE USED IN MIXED OVERDOSE OR AS A “DIAGNOSTIC” TEST. Management should include general symptomatic and supportive measures including a clear airway and monitoring cardiac and vital signs until stable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 2.2 Sedatives, hypnotics

5.1 Pharmacodynamic properties

SANDOZ ZOPICLONE 7,5 is a hypnotic agent, a member of the cyclopyrrolone group of compounds which is reported to have hypnotic, sedative, anxiolytic, muscle relaxant and anticonvulsant properties.

These effects are related to a specific agonist action at central receptors belonging to the $GABA_A$ macromolecular complex, modulating the opening of the chloride ion channel.

5.2 Pharmacokinetic properties

Absorption

SANDOZ ZOPICLONE 7,5 is absorbed rapidly. Peak concentrations are reached within 1,5 to 2 hours and they are approximately 30 to 60 ng/ml after administration of 3,75 mg and 7,5 mg respectively. Absorption is not modified by food.

Distribution

SANDOZ ZOPICLONE 7,5 is rapidly distributed from the vascular compartment. Plasma protein binding is weak (approximately 45 %) and is non-saturable. There is very little risk of medicine interactions due to protein binding.

The distribution volume is 91,8 to 104,6 litres.

Biotransformation

After repeated administration there is no accumulation of SANDOZ ZOPICLONE 7,5 and its metabolites. Inter-individual variations appear to be low.

The most important metabolites are the N-oxide derivative (pharmacologically active in animals) and the N-desmethyl metabolite (pharmacologically inactive in animals). An *in-vitro* study indicates that cytochrome P450 (CYP) 3A4 is the major isoenzyme involved in the metabolism of SANDOZ ZOPICLONE 7,5 to both metabolites, and that CYP2C8 is also involved with N-desmethyl SANDOZ ZOPICLONE 7,5 formation. Their apparent half-life times are approximately 4.5 hours and 1.5 hours respectively. No significant accumulation of the compound is seen following repeat dosing, (15mg) for 14 days. In animals, no enzyme induction has been observed even at high doses.

Elimination

At recommended doses, the elimination half-life of the unchanged SANDOZ ZOPICLONE 7,5 is approximately 5 hours.

The low renal clearance value of unchanged SANDOZ ZOPICLONE 7,5 (mean 8,4 ml/min) compared with the plasma clearance (232 ml/min) indicates that SANDOZ ZOPICLONE 7,5 clearance is mainly metabolic. SANDOZ ZOPICLONE 7,5 is eliminated by the urinary route (approximately 80 %) mainly in the form of free metabolites (N-oxide and N demethyl derivates) and in the faeces (approximately 16 %).

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

In renal insufficiency, no accumulation of SANDOZ ZOPICLONE 7,5 or of its metabolites has been detected after prolonged administration.

SANDOZ ZOPICLONE 7,5 is removed by haemodialysis.

In cirrhotic patients, the plasma clearance of SANDOZ ZOPICLONE 7,5 is reduced by approximately 40 % in relation with the decrease of the demethylation process.

Therefore, dosage will have to be modified in these patients.

Special patient groups

In various trials with elderly patients, no accumulation of SANDOZ ZOPICLONE 7,5 was observed in the plasma after repeated doses, in spite of a slight reduction in the renal function and extension of the elimination half-life to approximately 7 hours.
In renal insufficiency, no accumulation of SANDOZ ZOPICLONE 7,5 or its metabolites have been detected after prolonged administration. SANDOZ ZOPICLONE 7,5 crosses the dialysing membrane. However, in the event of an overdose, haemodialysis is not effective in the event of an overdose due to the large volume of distribution of SANDOZ ZOPICLONE 7,5 and the low molecular weight (see section 4.9).

In patients with cirrhosis of the liver, the plasma clearance of SANDOZ ZOPICLONE 7,5 is reduced by approximately 40 % due to a decrease of the demethylation process and an extended half-life of about 8 hours is observed. For this reason, the initial dosage should be reduced for these patients.

5.3 Preclinical safety data

Chronic toxicity

Hepatotoxic effects were elicited in repeated dose toxicity studies conducted in rats and dogs. In dogs, anaemia was evident in some studies.

Mutagenicity and carcinogenicity

SANDOZ ZOPICLONE 7,5 did not show a mutagenic potential *in vitro* and *in vivo*. An increased incidence of mammary carcinomas in female rats at high multiples of the maximum plasma concentration of therapeutic doses in humans have been attributed to elevated serum levels of 17-beta-estradiol.
An increased incidence of thyroid tumours in rats has been attributed to elevated TSH serum levels. In humans, SANDOZ ZOPICLONE 7,5 has no effects on thyroid hormones.

Reproduction toxicity

Fertility was reduced in two rat studies, while SANDOZ ZOPICLONE 7,5 did not adversely affect fertility in rabbits. Foetal developmental retardations and foetotoxic effects in rats and rabbits were observed

only at doses well above the maximum human dosage. There was no evidence of a teratogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The excipients are calcium hydrogen phosphate, colloidal anhydrous silica, lactose monohydrate, magnesium stearate, maize starch, Opadry White Y-1-7000 (methocel E5 Premium EP, polyethylene glycol 400, titanium dioxide C.I. 77891), povidone K30 and sodium starch glycolate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C in well closed containers, protected from light.

6.5 Nature and contents of container

Sealed aluminium bags of 30 or 100 tablets.

Blister packs, securitainers or amber glass bottles containing 30, 100, 300 or 500 tablets.

Not all packs may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand, 2090

8. REGISTRATION NUMBER

32/2.2/0487

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 February 1999

10. DATE OF REVISION OF THE TEXT

26 August 2022

Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Botswana	Sandoz Zopiclone 7.5	S2	BOT0200511
Namibia	Sandoz Zopiclone 7.5	NS3	04/2.2/1576

Name and address of manufacturer:

Kiara Health (Pty.) Ltd.
72 Steel Road, Spartan
Kempton Park
1619
South Africa

[1]Company Reg. No.: 1990/001979/07