SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE
Z-DORM® (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Z-DORM tablet contains 7,5 mg zopiclone.
Contains sugar (lactose monohydrate 78,5 mg).
For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM
The tablets are white to off-white, oval, biconvex, film-coated and with a break line.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Z-DORM is used in the short-term treatment of insomnia in adults.

Z-DORM is only indicated when the disorder is severe, disabling or subjecting the individual to extreme stress.

Safety in long-term treatment has not been demonstrated.

4.2 Posology and method of administration
Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded. The treatment 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 *Special warnings and precautions for use*).

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

Paediatric dosage:
Not to be used in children.

4.3 Contraindications
Hypersensitivity to zopiclone.

Z-DORM should not be used in children under the age of 18.

The safety in pregnancy and lactation has not been established.

Z-DORM should be avoided in patients with pre-existing central nervous system depression or coma, acute pulmonary insufficiency or sleep apnoea.

4.4 Special warnings and precautions for use
Drowsiness and incoordination on waking can occur.

Z-DORM is not recommended for the primary treatment of psychotic illness. Z-DORM should not be used alone to treat depression or anxiety with depression (suicide may be precipitated in such patients). Z-DORM 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.

Z-DORM should be given with care to elderly or debilitated patients who may be more prone to adverse effects.

Caution is required in patients with muscle weakness, or impaired liver or kidney function.

Severe hepatic insufficiency (serum albumin less than 30 g/l or presence of gross oedema) may significantly interfere with the elimination of Z-DORM and the lower dosage level (half a tablet) is recommended in such patients. The standard single tablet dose may be cautiously prescribed to patients with moderate (compensated) hepatic or renal insufficiency, but higher doses are not recommended in these patients. Z-DORM is removed by dialysis.

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

Z-DORM has less frequently provoked seizures in epileptic patients; seizures may also occur on abrupt withdrawal of therapy.

Rebound effects:
A transient syndrome whereby the symptoms that led to treatment with Z-DORM recur in an enhanced form may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness. Since risk of withdrawal phenomena / rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Dependence:
There is a potential for abuse and the development of physical and psychic dependence, especially with prolonged use and high doses. The risk of dependence is also greater in patients with a history of alcohol or drug abuse. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of 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.

Duration of treatment:
The duration of treatment should be as short as possible (see Section 4.2 *Posology and method of administration*), 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 to 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 minimising anxiety over such symptoms, should they occur while Z-DORM is being discontinued.

Lactose intolerance:
Z-DORM contains lactose. Patients with the rare hereditary conditions of galactose intolerance, e.g., galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take Z-DORM.

Z-DORM contains lactose 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 Z-DORM and prolongs its elimination.

4.6 Fertility, pregnancy and lactation
The safety in pregnancy and lactation has not been established (see Section 4.3 *Contraindications*).

4.7 Effects on the ability to drive and use machines
Patients should be cautioned about driving motor vehicles or operating machinery until it has been established that their performance is not affected.

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 effects include vertigo, headache, confusion, mental depression, slurred speech or dysarthria, changes in libido, 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.

Respiratory depression and hypotension occasionally occur with high dosage.

Rebound insomnia may be the result of tolerance to the effect of zopiclone or part of a withdrawal syndrome (see Section 4.4 *Special warnings and precautions for use*).

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

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. Drowsiness, lethargy and ataxia have been the principal effects reported. Overdose may be life-threatening especially when combined with other central nervous system depressants (including alcohol).

Treatment is symptomatic and supportive.

Flumazenil may be useful as an antidote.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacological classification:
A 2.2 Sedatives, hypnotics
ATC Code: N05CF01 Benzodiazepine-related drugs

Zopiclone 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
Zopiclone is rapidly absorbed. 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.

Zopiclone is rapidly distributed from the vascular compartment.

Plasma protein binding is weak (approximately 45 %) and non-saturable. There is very little risk of drug interactions due to protein binding.

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

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

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

The low renal clearance value of unchanged zopiclone (mean 8,4 ml/min), compared with the plasma clearance (232 ml/min), indicates that zopiclone clearance is mainly metabolic. Zopiclone 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 zopiclone or of 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 with the decrease of the demethylation process. Therefore, dosage will have to be modified in these patients.

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 NF/BGA, titanium dioxide EP 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. Protect from light.

6.5 Nature and contents of container
Sealed aluminium bags of 30 or 100 tablets.
Blister packs, securitainers or amber glass containers containing 30, 100, 300 or 500 tablets.

6.6 Special precautions for disposal
No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION
Kiara Health (Pty) Ltd
72 Steel Road
Spartan
Kempton Park
1619
South Africa

8. REGISTRATION NUMBER
34/2.2/0421

9. DATE OF FIRST AUTHORISATION
1 August 2001

10. DATE OF REVISION OF THE TEXT
18 September 2021

KIARA

SKEDULERINGSTATUS: S5

1. NAAM VAN DIE MEDISYNE
Z-DORM® (filmbedekte tablette)

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
Elke Z-DORM tablet bevat 7,5 mg sopikloon.
Bevat suiker (laktosemonohidraat 78,5 mg).
Vir die volledige lys van eksipiënte, sien Afdeling 6.1.

3. FARMASEUTIESE VORM
Die tablette is wit tot naaswit, ovaal, bikonveks, filmbedek en met 'n breeklyn.

4. KLINIESE BESONDERHEDE
4.1 Terapeutiese indikasies
Z-DORM word gebruik vir die korttermynbehandeling van insomnia in volwassenes. Z-DORM is slegs aangedui wanneer die steuring erg of stremmend is of dit die individu aan uiterste spanning onderwerp. Veiligheid met langtermyngebruik is nog nie gedemonstreer nie.

4.2 Posologie en metode van toediening
Behandeling behoort teen die laagste aanbevole dosis begin te word. Die maksimum dosis moenie oorskry word nie. Behandeling behoort so kort as moontlik te wees. Oor die algemeen wissel die duur van behandeling vanaf 'n aantal dae tot twee weke met 'n maksimum van 4 weke wat die afskaalproses insluit. In sekere gevalle mag verlenging van die maksimum behandelingsperiode nodig wees; indien dit die geval is, moet dit nie geskied sonder herevaluasie van die pasiënt se status nie.

Volwassenes:
Een tablet per mond, kort voor slaaptyd.

Bejaarde pasiënte:
'n Laer dosis van 3,75 mg (halwe tablet) moet aanvanklik gebruik word en, afhangende van die effektiwiteit en toleransie, kan die dosis tot 7,5 mg verhoog word.

Pasiënte met hepatiese ontoereikendheid:
Behandeling moet teen 'n dosis van 3,75 mg (halwe tablet) snags begin word (sien Afdeling 4.4 *Spesiale waarskuwings en voorsorgmaatreëls vir gebruik*).

Renale ontoereikendheid:
Dit word aanbeveel dat pasiënte met ingekorte renale funksie behandeling met 3,75 mg moet begin.

Pediatriese dosis:
Moenie in kinders gebruik word nie.

4.3 Kontra-indikasies
Hipersensitiwiteit vir sopikloon.

Z-DORM moenie in kinders onder die ouderdom van 18 gebruik word nie.

Veiligheid in swangerskap en laktasie is nog nie vasgestel nie.

Z-DORM behoort in pasiënte met voorafbestaande sentrale senuweesisteemonderdrukking of koma, akute pulmonêre ontoereikendheid of slaapapnee vermy te word.

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

Slaperigheid en inkoördinasie kan met opstaantyd voorkom.

Z-DORM word nie vir die primêre behandeling van psigotiese siektes aanbeveel nie. Z-DORM moenie alleen gebruik word om depressie of angs met depressie te behandel nie (selfdood mag in sulke pasiënte geprespiteer word). Z-DORM moet met die uiterste omsigtigheid in pasiënte met 'n geskiedenis van alkohol- of dwelmmisbruik gebruik word.

Gebruik met sorg in pasiënte met chroniese pulmonêre ontoereikendheid.

Z-DORM moet met sorg aan bejaarde of verswakte pasiënte, wat meer vatbaar vir ongunstige effekte mag wees, gegee word.

Omsigtigheid is nodig in pasiënte met spierswakheid of ingekorte lewer- of nierfunksie.

Erge hepatiese ontoereikendheid (serumalbumien minder as 30 g/l of die teenwoordigheid van uitgesproke edeem) mag beduidend met die eliminasie van Z-DORM inmeng en die laer dosismaat (halwe tablet) word vir sulke pasiënte aanbeveel. Die standaarddosis van 'n enkele tablet mag met omsigtigheid vir pasiënte met matige (gekompenseerde) hepatiese of renale ontoereikendheid voorgeskryf word, maar hoër dosisse word nie vir hierdie pasiënte aanbeveel nie. Z-DORM word deur dialise verwyder.

Omsigtigheid is nodig in pasiënte met organiese breinveranderinge, veral arteriosklerose.

Z-DORM het minder dikwels stuipe in epileptiese pasiënte ontlok; stuipe mag ook met skielike onttrekking van terapie voorkom.

Terugslageffekte:
'n Kortstondige sindroom waartydens die simptome wat tot behandeling met Z-DORM gelei het in 'n erger vorm mag herverskyn, kan met onttrekking van behandeling voorkom. Dit mag deur ander reaksies, insluitende gemoedsveranderinge, angs en rusteloosheid, vergesel word. Aangesien die risiko vir onttrekkingsverskynsels / terugslagverskynsels groter na skielike staking van behandeling is, word dit aanbeveel dat die dosis geleidelik verminder word.

Afhanklikheid:
Daar is 'n potensiaal vir misbruik en die ontwikkeling van fisiese en psigiese afhanklikheid, veral met verlengde gebruik en hoë dosisse. Die risiko vir afhanklikheid is ook groter in pasiënte met 'n geskiedenis van alkohol- of dwelmmisbruik. Sodra fisiese afhanklikheid ontwikkel het, sal skielike beëindiging van behandeling met onttrekkingsimptome gepaardgaan. Hierdie mag uit hoofpyne, spierpyn, erge angs, spanning, rusteloosheid, verwarring en irriteerbaarheid bestaan. In erge gevalle kan die volgende simptome voorkom: derealisasie, depersonalisasie, hiperakoesie, gevoelloosheid en tinteling van die ekstremiteite, hipersensitiwiteit vir lig, geraas en fisiese kontak, hallusinasies of epileptiese aanvalle.

Duur van behandeling:
Die duur van behandeling moet so kort as moontlik wees (sien Afdeling 4.2 *Posologie en metode van toediening*), maar moenie 4 weke, wat die afskaalproses insluit, vir insomnia oorskry nie. Verlenging buite hierdie tydperke moenie geskied sonder herevaluasie van die situasie nie. Dit mag van waarde wees om, wanneer behandeling begin word, die pasiënt in te lig dat dit van beperkte duur sal wees en om presies te verduidelik hoe die dosis geleidelik verminder sal word. Bowendien is dit belangrik dat die pasiënt bewus van die moontlikheid van terugslagverskynsels moet wees om sodoende angs oor sulke simptome, sou hulle voorkom wanneer Z-DORM gestaak word, tot 'n minimum te beperk.

Laktose-intoleransie:
Z-DORM bevat laktose. Pasiënte met die raar oorerflike toestande van galaktose-intoleransie, bv. galaktosemie, Lapp-laktasetekort, glukose-galaktose-wanabsorpsie of fruktose-intoleransie, moenie Z-DORM neem nie.

Z-DORM bevat laktose wat 'n effek op die glisemiese kontrole van pasiënte met diabetes mellitus mag hê.

4.5 Interaksie met ander medisyne en ander vorms van interaksie
Sedasie of respiratoriese en kardiovaskulêre onderdrukking mag deur ander geneesmiddels met sentrale senuweesisteemonderdrukkende eienskappe versterk word; hierdie sluit alkohol, antidepressante, antihistamiene, antipsigotika, algemene narkosemiddels, ander hipnotika of sedeermiddels en opioïede analgetika in.

Eritromisien verhoog die tempo van absorpsie van Z-DORM en verleng die eliminasie daarvan.

4.6 Fertiliteit, swangerskap en laktasie
Veiligheid in swangerskap en laktasie is nog nie vasgestel nie (sien Afdeling 4.3 *Kontra-indikasies*).

4.7 Effekte op die vermoë om te bestuur en masjiene te gebruik
Pasiënte moet gewaarsku word oor die bestuur van motorvoertuie en die bedryf van masjinerie totdat dit vasgestel is dat hulle vermoë nie aangetas is nie.

4.8 Ongewenste effekte
Die newe-effek wat mees dikwels aangeteken word, is bitter of metaalagtige nasmaak.

Slaperigheid, sedasie en ataksie is ook algemene newe-effekte. Oor die algemeen verminder dit met volgehoue toediening en dit is die gevolg van sentrale senuweesisteemonderdrukking.

Minder algemene newe-effekte sluit vertigo, hoofpyn, verwarring, geestesonderdrukking, slepende spraak of disartrie, veranderinge in libido, tremor, visuele steurings, urinêre retensie of inkontinensie, gastro-intestinale steurings, veranderinge in speekselproduksie en amnesie in.

Sommige pasiënte mag paradoksale opwekking ervaar en dit mag tot vyandigheid, aggressie en disinhibisie lei.

Geelsug, bloedafwykings en hipersensitiwiteitsreaksies is seldsaam gerapporteer.

Respiratoriese onderdrukking en hipotensie kom soms met hoër dosisse voor.

Terugslaginsomnia mag die resultaat van toleransie vir die effek van sopikloon of deel van 'n onttrekkingsindroom wees (sien Afdeling 4.4 *Spesiale waarskuwings en voorsorgmaatreëls vir gebruik*).

Aanmelding van vermoedelike nadelige reaksies

Dit is belangrik om vermoedelike nadelige reaksies na goedkeuring van die medisyne aan te meld. Dit laat voortgesette monitering van die voordeel/risiko-balans van die medisyne toe. Gesondheidsorgverskaffers word versoek om enige vermoedelike nadelige reaksies aan die SARGP via die "**6.04 Nadelige Middel-reaksie-Aanmeldingsvorm**" te rapporteer; dit kan aanlyn onder die SARGP se publikasies by https://www.sahpra.org.za/Publications/Index/8 gevind word.

4.9 Oordosis
Oordosis word gewoonlik gemanifesteer deur wisselende grade van sentrale senuweesisteemonderdrukking wat strek van slaperigheid tot koma na gelang van die hoeveelheid ingeneem. Slaperigheid, letargie en ataksie is die vernaamste effekte wat gerapporteer is. Oordosis kan lewensdreigend wees, veral wanneer met ander sentrale senuweesisteemonderdrukkers (insluitende alkohol) gekombineer.

Behandeling is simptomaties en ondersteunend.

Flumaseniel mag van waarde as teenmiddel wees.

5. FARMAKOLOGIESE EIENSKAPPE
5.1 Farmakodinamiese eienskappe
Farmakologiese klassifikasie:
A 2.2 Sedeermiddels, hipnotika
ATC-Kode: N05CF01 Bensodiasepien-verwante middels

Sopikloon is 'n hipnotiese middel, 'n lid van die siklopirroloon groep van verbindings wat gerapporteer is om hipnotiese, sederende, angsiolitiese, spierverslappende en antikonvulsante eienskappe te besit.

Hierdie effekte is verwant aan 'n spesifieke agonisaksie op sentrale reseptore wat aan die $GABA_A$- makromolekulêre kompleks, wat die opening van die chloriedio-onkanaal moduleer, behoort.

5.2 Farmakokinetiese eienskappe
Sopikloon word vinnig geabsorbeer. Piekkonsentrasies word binne 1,5 tot 2 ure bereik en dit is ongeveer 30 tot 60 ng/ml na toediening van 3,75 mg en 7,5 mg, onderskeidelik. Absorpsie word nie deur voedsel gewysig nie.

Sopikloon word vinnig vanaf die vaskulêre kompartement versprei.

Plasmaproteïenbinding is swak (ongeveer 45 %) en nie-versadigbaar. Daar is 'n baie klein risiko vir middelinteraksies vanweë proteïenbinding.

Die volume van distribusie is 91,8 tot 104,6 liter.

Na herhaalde toediening is daar geen akkumulasie van sopikloon en sy metaboliete nie. Interindividuele variasies blyk om laag te wees.

Teen aanbevole dosisse is die eliminasie-halflewe van onveranderde sopikloon ongeveer 5 uur.

Die lae renale opruimingswaarde van onveranderde sopikloon (gemiddeld 8,4 ml/min), vergeleke met plasma-opruiming (232 ml/min), dui daarop dat sopikloonopruiming hoofsaaklik metabolies is. Sopikloon word deur die urinêre roete (ongeveer 80 %) geëlimineer, hoofsaaklik in die vorm van vry metaboliete (N-oksied en N-demetielderivate) asook in die feses (ongeveer 16 %).

In bejaarde pasiënte, desnieteenstaande 'n geringe afname in hepatiese metabolisme en verlenging van die eliminasie-halflewe na ongeveer 7 uur, het verskeie studies nie plasma-ophoping van die substans met herhaalde dosisse getoon nie.

Met renale ontoereikendheid is geen ophoping van sopikloon of sy metaboliete bespeur na verlengde toediening nie. Sopikloon word deur hemodialise verwyder.

In pasiënte met sirrose is die plasma-opruiming van sopikloon met ongeveer 40 % verminder in verhouding met die afname in die demetilasieproses. Derhalwe moet die dosis in hierdie pasiënte aangepas word.

6. FARMASEUTIESE BESONDERHEDE
6.1 Lys van eksipiënte
Die eksipiënte is kalsiumwaterstoffosfaat, kolloïdale anhidriese silika, laktose-monohidraat, magnesiumstearaat, mieliestysel, Opadry-wit Y-1-700 (metielsellulose E5 Premium EP, poliëtileenglikol 400 NF/BGA, titaandioksied EP C.I. 77891), povidoon K30 en natriumstyselglikolaat.

6.2 Onverenigbaarhede
Nie van toepassing nie.

6.3 Raklewe
24 maande.

6.4 Spesiale voorsorgmaatreëls vir berging
Berg teen of benede 25 °C in diggeslote houers. Beskerm teen lig.

6.5 Aard en inhoud van die houer
Geseëlde aluminiumsakkies van 30 of 100 tablette.
Stulpverpakkings, sekuriteitsbewaarders of amber glashouers wat 30, 100, 300 of 500 tablette bevat.

6.6 Spesiale voorsorgmaatreëls vir wegdoening
Geen spesiale vereistes nie.

7. HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE
Kiara Health (Pty) Ltd
72 Steel Road
Spartan
Kempton Park
1619
South Africa

8. REGISTRASIENOMMER
34/2.2/0421

9. DATUM VAN EERSTE MAGTIGING
1 Augustus 2001

10. DATUM VAN HERSIENING VAN DIE TEKS
18 September 2021

KIARA

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