PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINAL PRODUCT
ZOPEAZE 3,75 (film coated tablets)
ZOPEAZE 7,5 (film coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
ZOPEAZE 3,75: Each film coated tablet contains 3,75 mg zopiclone
ZOPEAZE 7,5: Each film coated tablet contains 7,5 mg zopiclone

Excipient(s) with known effect:
Contains sugar: lactose monohydrate
ZOPEAZE 3,75 contains 15,75 mg of lactose monohydrate
ZOPEAZE 7,5 contains 31,50 mg of lactose monohydrate

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Film coated tablets.
ZOPEAZE 3,75: White to off white, round, biconvex film coated tablets.
ZOPEAZE 7,5: White to off white, oval, biconvex film coated tablets with breakline on one side.
The tablets can be divided into equal halves.

4. CLINICAL PARTICULARS
5. Therapeutic indications
ZOPEAZE is indicated in adults for the short-term treatment of insomnia (see sections 4.2, 4.4 and 5.1).
ZOPEAZE is only indicated when the disorder is severe, disabling or subjecting the individual to extreme stress.

6. Posology and method of administration
Posology
Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded. ZOPEAZE should be taken in a single intake and not be re-administered during the same night

Long-term use of ZOPEAZE is not recommended. 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, since the risk of abuse and dependence increases with the duration of treatment (see section 4.4).

Adults:
One tablet (ZOPEAZE 7,5) orally, shortly before retiring. This dose should not be exceeded.

Special populations:
Elderly patients, Patients with impaired liver function, and Chronic respiratory insufficiency:
A lower dose of ZOPEAZE 3,75 should be employed to start treatment in these patients, and if necessary, the dose may be increased to 7,5 mg.

Renal insufficiency:
Accumulation of zopiclone or its metabolites has not been seen during treatment of insomnia in patients with renal insufficiency. However, it is recommended that patients with impaired renal function should start treatment with 3,75 mg.

Paediatric population
No data are available.

Method of administration
ZOPEAZE is for oral use. The tablet should be swallowed whole.

7. Contraindications
ZOPEAZE is contraindicated in:
- Hypersensitivity to zopiclone or to any of the excipients listed in section 6.1.
- Myasthenia gravis
- respiratory failure
- severe sleep apnoea syndrome
- severe hepatic insufficiency

ZOPEAZE should not be used in children and young adults under the age of 18.
Safety in pregnancy and lactation has not been established (see section 4.6).

8. Special warnings and precautions for use
ZOPEAZE should be used with caution in patients with:
- hepatic insufficiency, a reduced dosage is recommended. Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy (see section 4.3)
- renal insufficiency, a reduced dosage is recommended (see section 5.1)
- respiratory insufficiency, hypnotics have the capacity to depress respiratory drive. Zopiclone should be used with caution in patients with compromised respiratory function. A lower dose is recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Paediatric Population
ZOPEAZE should not be used in children and adolescents less than 18 years (see section 4.3). The safety and efficacy of zopiclone in children and adolescents aged less than 18 years have not been established.

Elderly
Elderly should be given a reduced dose.

Psychomotor Impairment
Like other sedative/hypnotic medicine, ZOPEAZE has CNS-depressant effects. The risk of psychomotor impairment, including impaired driving ability, is increased if: ZOPEAZE is taken within 12 hours of performing activities that require mental alertness, a dose higher than the recommended dose is taken, or zopiclone is co-administered with other CNS depressants, alcohol or with other drugs that increase the blood levels of zopiclone (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 zopiclone and in particular during the 12 hours following that administration (see section 4.7).

Psychotic Illness
ZOPEAZE is not recommended for the primary treatment of psychotic illness.

Risk of suicide in patients with depression
ZOPEAZE should not be used alone to treat depression, or anxiety with depression, as suicide may be precipitated in such patients. ZOPEAZE may also mask the symptoms of depression. Therefore any underlying cause of insomnia must be addressed prior to initiation of treatment with ZOPEAZE.

Concomitant use with Opioids
If a decision is made to prescribe ZOPEAZE concomitantly with opioids, prescribe the lowest effective dosages and minimum duration of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Concomitant use of benzodiazepines and other sedative-hypnotic medicines may result in sedation, respiratory depression, coma, and death. Therefore, concomitant prescribing of opioids and benzodiazepines must be reserved for use in patients for whom alternative treatment options are inadequate.

Other psychiatric and paradoxical reactions
Psychiatric and paradoxical reactions such as 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 zopiclone as found in ZOPEAZE (see section 4.8). Should this occur the use of zopiclone should be discontinued. These reactions are more likely to occur in the elderly.

Amnesia
Amnesia is rare, but anterograde amnesia may occur, especially when retiring to bed is delayed after taking the tablet or sleep is interrupted. Therefore, to reduce the possibility of anterograde amnesia, patients should ensure that they are able to have a full night's sleep (uninterrupted sleep of about 7 to 8 hours) and to take ZOPEAZE when certain of retiring for the night.

Tolerance
Some loss of efficacy to the hypnotic effect of benzodiazepines and benzodiazepine-like agents such as ZOPEAZE may develop after repeated use.

Rebound Insomia
A transient syndrome, which may occur in withdrawal of treatment, whereby the symptoms that led to treatment with ZOPEAZE recur in an enhanced form. It may be accompanied by other reactions including mood changes, anxiety and restlessness. Since the risk of withdrawal or rebound phenomena, is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually (see section 4.2).
The duration of treatment should be as short as possible (see section 4.2) but should not exceed four weeks, including the tapering-off process.
Extension beyond these periods should not take place without re-evaluation of the patient. 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 is aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while ZOPEAZE is being discontinued.

Risk of Dependence
There is a potential for abuse and the development of physical and psychological dependence, especially with prolonged use and high doses. Cases of dependence have been reported more frequently in patients treated with zopiclone for longer than 4 weeks. The risk of dependence is also greater in patients with psychiatric disorders and/or a history of alcohol or drug abuse. ZOPEAZE should be used with extreme caution in such patients.
If physical dependence has however 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 the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures (see section 4.8).

Somnambulism and associated behaviours
Sleepwalking 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 and were not fully awake. The use of alcohol and other CNS-depressants with zopiclone appears to increase the risk of such behaviours as does the use of increased doses exceeding the maximum recommended dose. Discontinuation of ZOPEAZE should be strongly considered for patients who report such behaviours (see section 4.5 and 4.8).

Withdrawal syndrome
The termination of treatment with ZOPEAZE 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 4.2).

Lactose intolerance:
ZOPEAZE contains lactose monohydrate. The use of ZOPEAZE is therefore not recommended in patients with rare hereditary problems of galactose intolerance, the Lapp deficiency or glucose-galactose malabsorption

9. Interaction with other medicines and other forms of interaction
CNS depressants
In combination with central nervous system depressants an enhancement of the central depressive effect may occur. The therapeutic benefit of co-administration with anxiolytics/sedatives, antipsychotics (neuroleptics), narcotic analgesics, antidepressant agents, antiepileptic drugs, hypnotics, anaesthetics and sedative antihistamines should therefore be considered and weighed carefully. In the case of narcotic analgesics enhancement of euphoria may also occur, this might lead to an increase in psychic dependence.

Cytochrome P450 (CYP34A) inhibitors and inducers
In presence of erythromycin the AUC of zopiclone is increased by 80 %. This indicates that erythromycin can inhibit the metabolism of drugs metabolised by CYP 3A4. As a result the hypnotic effect of zopiclone may be enhanced.
ZOPEAZE is metabolised by the cytochrome P450 (CYP) 3A4 isoenzyme, and this may increase plasma levels of ZOPEAZE when co-administered with CYP3A4 inhibitors such as erythromycin, clarithromycin, itraconazole, ketoconazole and ritonavir. When ZOPEAZE is co-administered with CYP3A4 inhibitors a dose reduction for ZOPEAZE may be required. Conversely, when co-administered with CYP3A4 inducers, such as rifampicin, carbamazepine, phenobarbital, phenytoin and St. John's wort, plasma levels of ZOPEAZE may be decreased. A dose increase for ZOPEAZE may be required when it's co-administered with CYP3A4 inducers.

Alcohol
The sedative effect of ZOPEAZE may be enhanced when used in combination with alcohol, concomitant use is therefore not recommended. It is not recommended to drive or operate machinery while taking ZOPEAZE and alcohol simultaneously (see section 4.4).

Opioids
Concomitant use with opioids increases the risk of sedation, respiratory depression, coma and death due to additive CNS depressant effects (see section 4.4).

10. Fertility, pregnancy and lactation
Safety in pregnancy and lactation has not been established.

Women of childbearing potential / Contraception in males and females
If a woman of childbearing potential is prescribed ZOPEAZE, she should be warned to contact her physician medical practitioner about stopping her treatment if she intends to become pregnant or suspects that she is pregnant.

Pregnancy
ZOPEAZE is not recommended for use during pregnancy (see section 4.3).
If ZOPEAZE is used 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, and respiratory depression can be expected. (see section 4.4 and 4.8).

Infants born to mothers who took sedative/hypnotic medicines during the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms during the postnatal period. Appropriate monitoring of the newborn is recommended.

Breastfeeding
Zopiclone is excreted in breast milk. ZOPEAZE should not be used during lactation (see section 4.3).

Fertility
No fertility data is available.

11. Effects on ability to drive and use machines
ZOPEAZE has central nervous system depressant effects and may lead to drowsiness and impaired concentration. The risk of impairment may be aggravated by exceeding the recommended dose, the simultaneous intake of alcohol or other central nervous system depressants. ZOPEAZE should not be taken within 12 hours of performing activities that require mental alertness. Patients should be cautioned against driving motor vehicles or operating machinery or performing potentially hazardous tasks where loss of concentration may lead to accidents.

12. Undesirable effects
a. Tabulated summary of adverse reactions

System Organ Class	Frequency	Undesirable effect
Immune system disorders	*Less frequent*	Angio-oedema, anaphylactic reaction
Psychiatric disorders	*Less frequent*	Nightmare, agitation, confusional state, libido disorder, irritability, aggression, hallucination
	Frequency unknown	Restlessness, delusion, anger, depressed mood, abnormal behaviour (possibly associated with amnesia) and somnambulism, dependence, withdrawal syndrome
Nervous system disorders	*Frequent*	Dysgeusia, somnolence
	Less frequent	Dizziness, headache, anterograde amnesia
	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*	Dysphonia
	Frequency unknown	Respiratory depression
Gastrointestinal disorders	*Frequent*	Dry mouth
	Less frequent	Nausea, vomiting
	Frequency unknown	Dyspepsia
Hepato-biliary 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	*Frequency unknown*	Muscular weakness
General disorders and administrative site conditions	*Less frequent*	Fatigue
	Frequency unknown	Light headedness, incoordination
Injury, poisoning and procedural complications	*Less frequent*	Fall (predominantly in elderly patients)
	Frequency unknown	Incoordination

b. Description of selected adverse reactions
Withdrawal symptoms may vary and include rebound insomnia, muscle pain/cramps, extreme anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, panic attacks, GI 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 and hallucinations. In 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. 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

13. Overdose
Symptoms:
Depending on the quantity ingested overdose is usually manifested by varying degrees of central nervous system depression, ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, confusion, and lethargy; in more severe cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, and coma. Overdose could be life threatening especially if 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 can result in fatal outcome.

Treatment:
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. If CNS depression is severe consider the use of flumazenil.

14. PHARMACOLOGICAL PROPERTIES
15. Pharmacodynamic properties
ATC Code: N05C F01
Zopiclone is a hypnotic agent belonging to the cyclopyrrolone class of psychotherapeutic agents. Its pharmacological properties include anxiolytic, sedative, hypnotic, anticonvulsant and muscular relaxant actions. These pharmacological actions are related to zopiclone's high affinity and specific agonist action at central receptors belonging to the 'GABA' macromolecular receptor complex. However, it has been shown that zopiclone and other cyclopyrrolones act on a different site to those of benzodiazepines.

16. Pharmacokinetic properties
Absorption
Zopiclone is rapidly absorbed and widely distributed. Peak plasma concentrations are reached within 1,5 – 2 hours and they are approximately 30 ng/ml and 60 ng/ml after administration of 3,75 mg and 7,5 mg respectively. Absorption is not affected by food.
Distribution
The product is rapidly distributed from the vascular compartment. Plasma protein binding is approximately 45 % and non-saturable. There is very little risk of drug interactions due to protein binding. The volume of distribution is 91,8 – 104,6 litres.
After repeated administration, there is no accumulation, and inter-individual variations appear to be very small.
Biotransformation
Zopiclone is extensively metabolised. The 2 most important metabolites are the N-oxide derivative and the N-desmethyl metabolite. Cytochrome P450 (CYP) 3A4 is the major isoenzyme involved in the metabolism of zopiclone to both metabolites, and CYP2C8 is involved with N-desmethyl zopiclone formation.
Elimination
The low renal clearance of unchanged zopiclone (on average 8,4 ml/min) compared with the plasma clearance (232 ml/min) shows that zopiclone is cleared mainly by metabolism. Zopiclone is eliminated in the urine (approximately 80 %) in the form of unconjugated metabolites (N-oxide and N-desmethyl derivatives) and in the faeces (approximately 16 %). The elimination half-life of unchanged zopiclone is approximately 5 hours.

Special populations:
Elderly patients
Notwithstanding a slight decrease in hepatic metabolism and lengthening of elimination half-life to approximately 7 hours, no plasma accumulation of zopiclone occurs with repeated dosing.

Renal insufficiency
No accumulation of zopiclone or of its metabolites has been detected after prolonged administration. Zopiclone crosses dialysis membranes.

Hepatic insufficiency
In patients with cirrhosis of the liver, the slow demethylating process causes the plasma clearance of zopiclone to be delayed by approximately 40 %. For this reason the dosage should be adjusted for these patients.

17. PHARMACEUTICAL PARTICULARS
18. List of excipients
Calcium hydrogen phosphate dihydrate
Hydroxy propyl cellulose
Lactose monohydrate
Magnesium stearate
Maize starch
Opadry white (hypromellose, titanium dioxide, macrogol) Pregelatinised starch

19. Incompatibilities
Not applicable.

20. Shelf life
3 years

21. Special precautions for storage
Store at or below 30 °C.

22. Nature and contents of container
ZOPEAZE film coated tablets are packed in PVC/Alu blisters, with 10 tablets per blister strip, placed in a carton box as pack sizes of 30's.

23. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product
No special requirements

24. HOLDER OF CERTIFICATE OF REGISTRATION
TRINITY PHARMA (PTY) LTD
106 16th Road,
Midrand,
1686
South Africa

25. REGISTRATION NUMBER(S)
ZOPEAZE 3,75: 52/2.2/0541
ZOPEAZE 7,5: 52/2.2/0542

26. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18 May 2022

27. DATE OF REVISION OF TEXT
N.A

TRINITY PHARMA

Tel: 010 594 5610. Email: PV@kahmagroup.co.za

PROFESSIONELE INLIGTING

SKEDULERINGSTATUS:

S5

1. NAAM VAN DIE MEDISYNE
ZOPEAZE 3,75 (film-bedekte tablette)
ZOPEAZE 7,5 (film-bedekte tablette)

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
ZOPEAZE 3,75: Elke film-bedekte tablet bevat 3,75 mg sopikloon
ZOPEAZE 7,5: Elke film-bedekte tablet bevat 7,5 mg sopikloon

Hulpstof met bekende effekte:
Bevat suiker: laktosemonohidraat
ZOPEAZE 3,75 bevat 15,75 mg laktosemonohidraat
ZOPEAZE 7,5 bevat 31,50 mg laktosemonohidraat

Vir 'n volledige lys van hulpstowwe, sien afdeling 6.1.

3. FARMASEUTIESE VORM
Film-bedekte tablette.
ZOPEAZE 3,75: Wit tot naaswit, ronde, bikonvekse film-bedekte tablette.
ZOPEAZE 7,5: Wit tot naaswit, ovaal, bikonvekse film-bedekte tablette met 'n breeklyn aan een kant.
Die tablette kan verdeel word in twee gelyke halftes.

4. KLINIESE BESONDERHEDE
5. Terapeutiese indikasies
ZOPEAZE word by volwassenes aangedui vir die korttermynbehandeling van slaaploosheid (sien afdelings 4.2, 4.4 en 5.1).

ZOPEAZE word slegs aangedui wanneer die versteuring ernstig, ontwrigtend is, óf wanneer dit die individu aan buitensporige spanning plaas.

6. Posologie en metode van toediening
Posologie
Behandeling moet met die laagste aanbevole dosis begin word. Die maksimum dosis moet nie oorskry word nie.
ZOPEAZE moet in 'n enkele inname geneem word en nie weer toegedien word gedurende dieselfde nag nie.

Langtermyngebruik van ZOPEAZE word nie aanbeveel nie. Behandeling moet so kort as moontlik wees. Gewoonlik wissel die duurte van behandeling van 'n paar dae tot twee weke, met 'n maksimum, insluitend die afskaalproses, van vier weke. In sekere gevalle kan langer periodes as die maksimum behandelingsperiode nodig wees. Indien wel, moet dit nie plaasvind sonder om die status van die pasiënt te herevalueer nie, aangesien die risiko van misbruik en afhanklikheid met die duurte van die behandeling toeneem (sien afdeling 4.4).

Volwassenes:
Een tablet (ZOPEAZE 7,5) oraal, kort voor slapenstyd. Die dosis moet nie oorskry word nie.

Spesiale populasies
Bejaarde pasiënte, Pasiënte met ingekorte lewerfunksie en chroniese respiratoriese ontoereikendheid:
'n Laer dosis van ZOPEAZE 3,75 moet gebruik word om behandeling by hierdie pasiënte te begin, en indien nodig, kan die dosis verhoog word tot 7,5 mg.

Renale ontoereikendheid:
Akkumulasie van sopikloon of die metaboliete daarvan is nie waargeneem tydens die behandeling van slaaploosheid by pasiënte met renale ontoereikendheid nie. Dit word egter aanbeveel dat pasiënte met ingekorte nierfunksie behandeling moet begin met 3,75 mg.

Pediatriese populasie
Geen data is beskikbaar.

Metode van toediening
ZOPEAZE is vir orale gebruik. Die tablet moet heel ingesluk word.

7. Kontraïndikasies
ZOPEAZE is gekontraïndikeerd in:
- Hipersensitiwiteit teenoor sopikloon of enige van die hulpstowwe gelys in afdeling 6.1.
- Myasthenia gravis
- Respiratoriese versaking
- Ernstige slaapapnee-sindroom
- Ernstige hepatiese ontoereikendheid

ZOPEAZE moet nie gebruik word by kinders en adolessente onder die ouderdom van 18 jaar nie.
Veiligheid tydens swangerskap en laktasie is nie vasgestel nie (sien afdeling 4.6).

8. Spesiale waarskuwings en voorsorgmaatreëls vir gebruik
ZOPEAZE moet met omsigtigheid gebruik word by pasiënte met:
- hepatiese ontoereikendheid, 'n verminderde dosis word aanbeveel. Bensodiasepiene is nie geïndikeerd om pasiënte met ernstige hepatiese ontoereikendheid te behandel nie, aangesien dit enkefalopatie kan meebring (sien afdeling 4.3)
- renale ontoereikendheid, 'n verminderde dosis word aanbeveel (sien afdeling 5.1)
- respiratoriese ontoereikendheid, hipnotika het die vermoë om respiratoriese dryf te onderdruk. Sopikloon moet met omsigtigheid gebruik word by pasiënte met gekompromitteerde respiratoriese funksie. 'n Laer dosis word aanbeveel vir pasiënte met chroniese respiratoriese ontoereikendheid as gevolg van die risiko van respiratoriese onderdrukking.

Pediatriese Populasie
ZOPEAZE moet nie gebruik word by kinders en adolessente jonger as 18 jaar nie (sien afdeling 4.3). Die veiligheid en effektiwiteit van sopikloon by kinders en adolessente jonger as 18 jaar is nie vasgestel nie.

Bejaardes
Bejaardes moet 'n verlaagde dosis gegee word.

Psigomotoriese verswakking
Soos ander kalmerende/hipnotiese medisyne, het ZOPEAZE SSS-depressiewe effekte. Die risiko van psigomotoriese verswakking, insluitend verswakte bestuursvermoë, word verhoog as ZOPEAZE geneem word binne 12 uur van uitvoering van aktiwiteite wat verstandelike waaksaamheid verg, as 'n dosis hoër as die aanbevole dosis geneem word, **ó**f as sopikloon saam met ander SSS-depressante, alkohol of ander medisyne wat die bloedvlakke van sopikloon verhoog, toegedien word (sien afdeling 4.5). Pasiënte moet gewaarsku word teen beoefening van gevaarlike beroepe wat volledige verstandelike waaksaamheid of motoriese koördinasie vereis, soos die hantering van masjinerie of die bestuur van 'n motorvoertuig na toediening van sopikloon en veral gedurende die 12 uur n**á** toediening (sien afdeling 4.7).

Psigotiese siektes
ZOPEAZE word nie aanbeveel vir die primêre behandeling van psigotiese siektes nie.

Risiko van selfmoord in pasiënte met depressie
ZOPEAZE moet nie alleen gebruik word om depressie of angs met depressie te behandel nie, aangesien selfmoord by sulke pasiënte kan voorkom. ZOPEAZE kan ook die simptome van depressie maskeer. Daarom moet enige onderliggende oorsaak van slaaploosheid aangespreek word voor die behandeling met ZOPEAZE geïnisieer word.

Gelyktydige gebruik met Opioïede
Indien 'n besluit geneem word om ZOPEAZE saam met opioïede voor te skryf, skryf die laagste effektiewe dosisse en minimum duur van gelyktydige gebruik voor, en volg pasiënte noukeurig op vir tekens en simptome van respiratoriese depressie en sedasie. Gelyktydige gebruik van bensodiasepiene en ander kalmerende-hipnotiese medisyne kan lei tot sedasie, respiratoriese depressie, koma en dood. Dus, moet die gelyktydige voorskryf van opioïede en bensodiasepiene gereserveer word vir gebruik by pasiënte vir wie alternatiewe behandelingsopsies onvoldoende is.

Ander psigiatriese en paradoksale reaksies
Psigiatriese en paradoksale reaksies soos rusteloosheid, agitasie, prikkelbaarheid, aggressie, delusie, woede, nagmerries, hallusinasies, onvanpaste gedrag en ander negatiewe gedragseffekte is bekend om voorkom te kom wanneer kalmerende/hipnotiese middels soos sopikloon, soos gevind in ZOPEAZE, gebruik word (sien afdeling 4.8). Indien dit gebeur, moet die gebruik van sopikloon gestaak word. Hierdie reaksies is meer geneig om by bejaardes te voorkom.

Amnesie
Amnesie is skaars, maar anterograde amnesie kan voorkom, veral wanneer slapenstyd vertraag word nadat die tablet geneem is of slaap onderbreek word. Daarom, om die moontlikheid van anterograde amnesie te verminder, moet pasiënte verseker dat hulle 'n volle nag kan slaap (ononderbroke slaap van ongeveer 7 tot 8 uur) en om ZOPEAZE te neem wanneer hulle seker is van slapenstyd.

Toleransie
Na herhaalde gebruik kan 'n sekere mate van verlies aan doeltreffendheid van die hipnotiese effek van bensodiasepiene en bensodiasepienagtige middels soos ZOPEAZE ontwikkel.

Terugslag Slaaploosheid
'n Verbygaande sindroom wat kan voorkom by die onttrekking van die behandeling, waarin die simptome wat gelei het tot behandeling met ZOPEAZE, in 'n erger vorm terugkeer. Dit kan gepaard gaan met ander reaksies, insluitend gemoedsveranderinge, angs en rusteloosheid. Aangesien die risiko van onttrekkings- of terugslagverskynsels groter is na die skielike staking van die behandeling, word aanbeveel dat die dosis geleidelik verminder word (sien afdeling 4.2).
Die duurte van die behandeling moet so kort as moontlik wees (sien afdeling 4.2), maar moet nie langer as vier weke duur nie, insluitend die afskaalproses.
Verlenging van hierdie periodes moet nie plaasvind sonder die herbeoordeling van die pasiënt nie. Dit kan handig wees om die pasiënt met aanvang van die behandeling in te lig dat dit van beperkte duur sal wees, en om presies te verduidelik hoe die dosis geleidelik verminder sal word. Verder is dit belangrik dat die pasiënt bewus is van die moontlikheid van terugslagverskynsels, en sodoende die angs oor sulke simptome verminder, indien dit voorkom wanneer ZOPEAZE gestaak word.

Risiko van Afhanklikheid
Daar is 'n potensiaal vir misbruik en die ontwikkeling van fisiese en sielkundige afhanklikheid, veral met langdurige gebruik en hoë dosisse. Gevalle van afhanklikheid word meer gereeld aangemeld by pasiënte wat met sopikloon behandel word vir langer as vier weke. Die risiko van afhanklikheid is ook groter by pasiënte met psigiatriese versteurings en/óf 'n geskiedenis van alkohol- of dwelmmisbruik. ZOPEAZE moet met uiterse omsigtigheid gebruik word by sulke pasiënte.
Indien fisiese afhanklikheid egter ontwikkel het, sal die skielike staking van die behandeling gepaard gaan met onttrekkingsimptome. Dit kan bestaan uit hoofpyn, spierpyn, uitermatige angs, spanning, rusteloosheid, verwardheid en geïrriteerdheid. In erge gevalle kan die volgende simptome voorkom: derealisering, depersonalisering, hiperakoesie, gevoelloosheid en prikkeling van die ledemate, hipersensitiwiteit teenoor lig, geraas en fisieke kontak, hallusinasies of epileptiese konvulsies (sien afdeling 4.8).

Somnambulisme en verwante gedrag
Slaapwandeling en ander verwante gedrag soos 'slaap ry', voorbereiding en eet van voedsel, of maak van telefoonoproepe, met amnesie van die gebeurtenis, is aangemeld by pasiënte wat sopikloon geneem het en nie heeltemal wakker was nie. Die gebruik van alkohol en ander SSS-depressante met sopikloon blyk die risiko van sulke gedrag te verhoog, asook die gebruik van verhoogde dosisse wat die maksimum aanbevole dosis oorskry. Staking van ZOPEAZE moet sterk oorweeg word vir pasiënte wat sulke gedrag aanmeld (sien afdeling 4.5 en 4.8).

Onttrekkingsindroom
Die beëindiging van die behandeling met ZOPEAZE is onwaarskynlik om geassosieer te word met onttrekkingseffekte wanneer die duur van die behandeling beperk is tot 4 weke. Pasiënte kan baat vind by die geleidelike vermindering van die dosis voor staking (sien afdeling 4.2).

Laktose intoleransie:
ZOPEAZE bevat laktosemonohidraat. Die gebruik van ZOPEAZE word dus nie aanbeveel by pasiënte met seldsame oorerflike probleme van galaktose-onverdraagsaamheid, die Lapp-tekort of glukose-galaktose wanabsorpsie nie.

9. Interaksie met ander medisyne en ander vorms van interaksie
SSS-depressante
In kombinasie met sentrale senuweestelsel depressante kan 'n versterking van die sentrale depressiewe effek voorkom. Die terapeutiese voordeel van gelyktydige toediening met angsiolitikums/sedeermiddels, antipsigotika (neuroleptika), narkotiese pynstillers, antidepressante, anti-epileptiese middels, hipnotika, narkosemiddels en sederende antihistamiene moet dus oorweeg en noukeurig opgeweeg word. In die geval van narkotiese pynstillers kan versterking van die euforie ook voorkom, kan dit lei tot 'n toename in sielkundige afhanklikheid.

Sitochroom P450 (CYP34A) inhibeerders en induseerders
In die teenwoordigheid van eritromisien word die AOK van sopikloon met 80 % verhoog. Dit dui daarop dat eritromisien die metabolisme van medisyne wat deur CYP 3A4 gemetaboliseer word, kan inhibeer. As gevolg hiervan kan die hipnotiese effek van sopikloon versterk word.
ZOPEAZE word gemetaboliseer deur die sitochroom P450 (CYP) 3A4 iso-ensiem, en dit kan die plasmavlakke van ZOPEAZE verhoog wanneer dit saam met CYP3A4-inhibeerders soos eritromisien, klaritromisien, itrakonasool, ketokonasool en ritonavir toegedien word. Wanneer ZOPEAZE saam met CYP3A4-inhibeerders toegedien word, mag 'n dosisvermindering vir ZOPEAZE noodsaaklik wees. Aan die ander kant, wanneer dit saam met CYP3A4-induseerders toegedien word, soos rifampisien, karbamasepien, fenobarbitaal, fenitoïen en Sint-janskruid, kan plasmavlakke van ZOPEAZE verlaag word. 'n Dosisverhoging vir ZOPEAZE mag noodsaaklik wees wanneer dit saam met CYP3A4-induseerders toegedien word.

Alkohol
Die sederende effek van ZOPEAZE mag versterk word wanneer dit in kombinasie met alkohol gebruik word, gesamentlike gebruik word dus nie aanbeveel nie. Dit word nie aanbeveel om te bestuur of masjinerie te hanteer met die gelyktydige gebruik van ZOPEAZE en alkohol nie (sien afdeling 4.4).

Opioïede
Gelyktydige gebruik saam met opioïede verhoog die risiko van sedasie, respiratoriese depressie, koma en dood as gevolg van addisionele SSS-depressiewe effekte (sien afdeling 4.4).

10. Vrugbaarheid, swangerskap en laktasie
Veiligheid tydens swangerskap en laktasie is nie vasgestel nie.

Vroue van kinderbarende potensiaal / Voorbehoeding by mans en vrouens
Indien daar vir 'n vrou van kinderbarende potensiaal ZOPEAZE voorgeskryf word, moet sy gewaarsku word om haar mediese praktisyn te kontak ten opsigte van die staking van haar behandeling indien sy van plan is om swanger te raak of vermoed dat sy swanger is.

Swangerskap
ZOPEAZE word nie aanbeveel vir gebruik tydens swangerskap nie (sien afdeling 4.3).
Indien ZOPEAZE gedurende die laaste drie maande van swangerskap of tydens geboorte gebruik word, as gevolg van die farmakologiese werking van die produk, kan effekte op die neonaat, soos hipotermie, hipotonie en respiratoriese depressie verwag word (sien afdeling 4.4 en 4.8).

Babas gebore van moeders wat sedatiewe/hipnotiese medisyne gedurende die laaste fase van swangerskap gebruik, kan fisiese afhanklikheid ontwikkel en 'n risiko loop om onttrekkingsimptome in die post-natale periode te ontwikkel. Gepaste monitering van die pasgeborene word aanbeveel.

Borsvoeding
Sopikloon word in borsmelk uitgeskei. ZOPEAZE moet nie tydens laktasie gebruik word nie (sien afdeling 4.3).

Vrugbaarheid
Geen vrugbaarheidsdata is beskikbaar nie.

11. Uitwerking op die vermoë om te bestuur en masjiene te gebruik
ZOPEAZE het sentrale senuweestelsel depressiewe effekte en kan lei tot lomerigheid en verswakte konsentrasie. Die risiko van gebrek kan vererger word deur die aanbevole dosis te oorskry, die gelyktydige inname van alkohol of ander sentrale senuweestelsel depressante. ZOPEAZE moet nie binne 12 uur van die uitvoering van aktiwiteite wat verstandelike waaksaamheid benodig, geneem word nie. Pasiënte moet gewaarsku word teen die bestuur van motorvoertuie of die hantering van masjinerie of die uitvoering van potensieel gevaarlike take waar verlies aan konsentrasie tot ongelukke kan lei.

12. Newe-effekte
a. Getabuleerde opsomming van newe-effekte

Sisteem-orgaanklas	Frekwensie	Nadelige effekte
Immuunstelselversteurings	*Minder gereeld*	Angioedeem, anafilaktiese reaksie
Psigiatriese versteurings	*Minder gereeld*	Nagmerries, agitasie, verwarde toestand, libido versteuring, geïrriteerdheid, aggressie, hallusinasie
	Frekwensie onbekend	Rusteloosheid, delusie, woede, depressiewe gemoed, abnormale gedrag (moontlike assosiasie met amnesie) en somnambulisme, afhanklikheid, onttrekkingsindroom
Senusisteemversteurings	*Gereeld*	Disgeusie, somnolensie
	Minder gereeld	Duiseligheid, hoofpyn, anterograde amnesie
	Frekwensie onbekend	Ataksie, para-estesie, kognitiewe versteurings soos geheueversteuring, aandagversteurings, spraakversteurings
Oor- en doolhofversteurings	*Frekwensie onbekend*	Diplopie
Respiratories-, torakale- en mediastinale versteurings	*Minder gereeld*	Disfonie
	Frekwensie onbekend	Respiratoriese depressie
Gastroïntestinale versteurings	*Gereeld*	Droë mond
	Minder gereeld	Naarheid, braking
	Frekwensie onbekend	Dispepsie
Hepato-biliêre versteurings	*Minder gereeld*	Verhoogde transaminase en/of verhoogde bloedalkalienfosfatase (lig tot matig)
Vel- en Onderhuidse weefselversteurings	*Minder gereeld*	Urtikarie of uitslag, pruritus
Muskuloskeletale bindweefselversteurings	*Frekwensie onbekend*	Spierswakheid
Algemene siektes en toedieningsarea toestande	*Minder gereeld*	Uitputting
	Frekwensie onbekend	Lighoofdigheid, wankoördinasie
Beserings, vergiftiging en prosedurele komplikasies	*Minder gereeld*	Val (hoofsaaklik by bejaarde pasiënte)
	Frekwensie onbekend	Wankoördinasie

b. Beskrywing van geselekteerde newe-effekte
Onttrekkingsimptome kan wissel en sluit in terugslag slapeloosheid, spierpyn/krampe, uiterste angs, tremor, sweet, agitasie, verwarring, hoofpyn, palpitasies, tagikardie, delirium, nagmerries, paniekaanvalle, GI-versteurings en geïrriteerdheid. In erge gevalle kan die volgende simptome voorkom: derealisering, depersonalisering, hiperaku**ïteit**, gevoelloosheid en prikkeling van die ledemate, hipersensitiwiteit teenoor lig, geraas en fisiese kontak en hallusinasies. In seldsame gevalle kan epileptiese konvulsies voorkom.

Rapportering van vermoedelike newe-effekte:
Dit is belangrik om vermoedelike newe-effekte wat waargeneem word nadat die medisyne goedgekeur is, te rapporteer. Dit laat volgehoue observering van die voordeel/risiko-balans van die medisyne toe. Gesondheidsorgverskaffers word versoek om enige vermoedelike newe-effekte aan SAHPRA te rapporteer via die "6.04 Adverse Drug Reactions Reporting Form", wat aanlyn by SAHPRA se publikasies gevind kan word: https://www.sahpra.org.za/Publications/Index/8

13. Oordosering
Simptome:
Afhangend van die hoeveelheid wat ingeneem is, word oordosis gewoonlik gemanifesteer deur verskillende grade van sentrale senusisteemdepressie, wat wissel van lomerigheid tot koma. In ligte gevalle, sluit simptome lomerigheid, verwarring en lusteloosheid in; in meer ernstige gevalle, mag simptome ataksie, hipotonie, hipotensie, respiratoriese depressie en koma insluit. Oordosering kan lewensgevaarlik wees, veral as dit gekombineer word met ander SSS-depressante, insluitend alkohol.
Ander risikofaktore, soos die teenwoordigheid van gepaardgaande siektes en die verswakte toestand van die pasiënt, mag bydra tot die erns van simptome en kan lei tot 'n noodlottige uitkoms.

Behandeling**:**
Simptomatiese en ondersteunende behandeling in voldoende kliniese omgewing word aanbeveel en daar moet aandag geskenk word aan respiratoriese en kardiovaskulêre funksies.
Oorweeg geaktiveerde houtskool indien 'n volwassene meer as 150 mg of 'n kind meer as 1,5 mg/kg binne een uur ingeneem het. Indien SSS-depressiewe effekte ernstig is, moet die gebruik van flumaseniel oorweeg.

14. FARMAKOLOGIESE EIENSKAPPE
15. Farmakodinamiese eienskappe
ATK Kode: N05C F01
Sopikloon is 'n hipnotiese middel wat tot die siklopirroloonklas van psigoterapeutiese middels behoort. Die farmakologiese eienskappe daarvan sluit in angswerende-, sedatiewe-, hipnotiese-, antikonvulsante- en spierverslappende effekte. Hierdie farmakologiese effekte hou verband met sopikloon se hoë affiniteit en spesifieke agonistiese werking by sentrale reseptore wat aan die 'GABA' makromolekulêre reseptorkompleks behoort. Daar is egter aangetoon dat sopikloon en ander siklopirrolone op 'n ander plekke optree as dié van bensodiasepiene.

16. Farmakokinetiese eienskappe
Absorpsie
Sopikloon word vinnig opgeneem en wyd versprei. Piekplasmakonsentrasies word binne 1,5 - 2 uur bereik en dit is ongeveer 30 ng/ml en 60 ng/ml na toediening van onderskeidelik 3,75 mg en 7,5 mg. Absorpsie word nie deur voedsel beïnvloed nie.

Verspreiding
Die produk word vinnig uit die vaskulêre kompartement versprei. Plasmaproteïenbinding is ongeveer 45 % en nie-versadigbaar. Daar is 'n baie klein risiko van medisyne interaksies as gevolg van proteïenbinding. Die volume van verspreiding is 91,8 - 104,6 liter.
Na herhaalde toediening is daar geen akkumulasie nie, en inter-individuele variasies blyk baie klein te wees.

Biotransformasie
Sopikloon word ekstensief gemetaboliseer. Die 2 belangrikste metaboliete is die N-oksiedderivaat en die N-desmetielmetaboliet. Sitochroom P450 (CYP) 3A4 is die hoof iso-ensiem wat betrokke is by die metabolisme van sopikloon vir beide metaboliete, en CYP2C8 is betrokke by die vorming van N-desmetielsopikloon.

Eliminasie
Die lae renale opruiming van onveranderde sopikloon (gemiddeld 8,4 ml/min) in vergelyking met die plasmaopruiming (232 ml/min) toon dat sopikloon hoofsaaklik deur metabolisme opgeruim word. Sopikloon word in die urine (ongeveer 80 %) geëlimineer in die vorm van ongekonjugeerde metaboliete (N-oksied en N-desmetielderivate) en in die feses (ongeveer 16 %). Die eliminasiehalfleeftyd van onveranderde sopikloon is ongeveer 5 uur.

Spesiale populasies:
Bejaarde pasiënte
Ten spyte van 'n geringe afname in hepatiese metabolisme en verlenging van die eliminasiehalfleeftyd tot ongeveer 7 uur, kom geen plasma akkumulasie van sopikloon voor met herhaalde dosering nie.

Renale ontoereikendheid
Geen akkumulasie van sopikloon of van die metaboliete daarvan word waargeneem na langdurige toediening nie. Sopikloon kruis dialise membrane.

Hepatiese ontoereikendheid
By pasiënte met sirrose van die lewer, veroorsaak die stadige demetieleringsproses dat die plasmaopruiming van sopikloon met ongeveer 40 % vertraag word. Om hierdie rede moet die dosis vir hierdie pasiënte aangepas word.

17. FARMSEUTIESE BESONDERHEDE
18. Lys van hulpstowwe
Gepregelatiniseerde stysel
Hidroksipropielsellulose
Kalsiumwaterstoffosfaatdihidraat
Laktosemonohidraat
Magnesiumstearaat
Mieliestysel
Opadry wit (hipromellose, titaandioksied, makrogol)

19. Onverenigbaarheid
Nie van toepassing nie.

20. Rakleeftyd
3 jaar.

21. Spesiale voorsorgmaatreëls tydens berging
Stoor teen of benede 30 °C.

22. Aard en inhoud van die houer
ZOPEAZE film-bedekte tablette word verpak in PVC/Alu stolpverpakkings, met 10 tablette per stolpverpakkingstrook, geplaas in 'n kartondoos as verpakkingsgroottes van 30's.

23. Spesiale voorsorgmaatreëls vir die wegdoen van 'n gebruikte medisyne of afvalstowwe afkomstig van sodanige medisyne en ander hantering van die produk
Geen spesiale vereistes.

24. HOUER VAN REGISTRASIESERTIFIKAAT
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25. REGISTRASIENOMMER(S)
ZOPEAZE 3,75: 52/2.2/0541
ZOPEAZE 7,5: 52/2.2/0542

26. DATUM VAN EERSTE MAGTIGING / HERNUWING VAN DIE MAGTIGING
18 Mei 2022

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N.V.T