PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

Zolpidem 10 Unicorn

Each tablet contains 10 mg Zolpidem (as Zolpidem Tartrate)

Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg Zolpidem Tartrate

Contains sugar (59,000 mg lactose monohydrate per film-coated tablet).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

White to almost white, caplet shaped, biconvex, film coated tablets with

breakline on one side and “10” embossed on other side.

The breakline is to facilitate the division of the tablet into 2 equal halves where

a 5 mg dose is recommended.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ZOLPIDEM 10 UNICORN is indicated for the short-term treatment of insomnia.

ZOLPIDEM 10 UNICORN or a short acting hypnotic, is only indicated when the disorder

is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Treatment should be as short as possible. Generally, the duration of treatment varies from a few days to two weeks with a maximum, including the 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.

ZOLPIDEM 10 UNICORN should be taken immediately before going to bed, or in bed.

ZOLPIDEM 10 UNICORN should be taken in a single intake and not be readministered during the same night.

Posology:

The recommended daily dose for adults is 10 mg immediately before bedtime, or in bed.

The lowest effective daily dose of **ZOLPIDEM 10 UNICORN** should be used and must not exceed 10 mg.

Special populations

Elderly:

Since elderly or debilitated patients may be especially sensitive to the effects of **ZOLPIDEM 10 UNICORN**, in these patients, a dose of 5 mg is recommended. The total **ZOLPIDEM 10 UNICORN** dose should not exceed 10 mg in this population.

Hepatic impairment:

In patients with hepatic insufficiency, the recommended starting dose is 5 mg and particular caution must be exercised in elderly patients.

Paediatric population:

Safety and effectiveness of **ZOLPIDEM 10 UNICORN** in paediatric patients under the age of 18 years have not been established. **ZOLPIDEM 10 UNICORN** should not be prescribed in this population. (see section 4.3).

Method of administration

For oral use

4.3 Contraindications

ZOLPIDEM 10 UNICORN is contraindicated in:

- Patients with a hypersensitivity to zolpidem tartrate or any of the excipients listed in section 6.1.
- Myasthenia gravis.
- Sleep apnoea syndrome.
- Acute and/or severe respiratory insufficiency.
- Severe hepatic insufficiency (see section 4.4).
- Paediatric population under the age of 18.
- Safety in pregnancy and lactation has not been established (see section 4.6).

4.4 Special warnings and precautions for use

The cause of insomnia should be identified wherever possible and the underlying factors treated before **ZOLPIDEM 10 UNICORN** is prescribed. The failure of insomnia to remit after a 7 - 14 days course of treatment may indicate the presence of a primary psychiatric or physical disorder, and the patient should be carefully re-evaluated at regular intervals.

Next-day psychomotor impairment

ZOLPIDEM 10 UNICORN has CNS-depressant effects. The risk of next-day psychomotor impairment, including impaired driving ability, is increased if:

• **ZOLPIDEM 10 UNICORN** is taken within less than 8 hours before performing activities that require mental alertness (see section 4.7);

• a dose higher than the recommended dose is taken;

• **ZOLPIDEM 10 UNICORN** is co-administered with other CNS depressants or with other medicines that increase the blood levels of **ZOLPIDEM 10 UNICORN**, or with alcohol or illicit drugs (see section 4.5).

Respiratory Insufficiency:

Caution should be observed when prescribing **ZOLPIDEM 10 UNICORN** to patients with chronic respiratory insufficiency as respiratory drive may be suppressed.

Severe Hepatic Insufficiency:

ZOLPIDEM 10 UNICORN is contraindicated in patients with severe hepatic insufficiency as it may precipitate encephalopathy (see section 4.3).

Risks from concomitant use with opioids:

Concomitant use of benzodiazepines and other sedative-hypnotic medicines, including **ZOLPIDEM 10 UNICORN**, may result in sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe **ZOLPIDEM 10 UNICORN** concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients to be aware of these symptoms (see section 4.5).

Elderly:

See section 4.2 for dose recommendations.

Psychotic illness:

ZOLPIDEM 10 UNICORN should not be used as the primary treatment of psychotic illness.

Amnesia:

ZOLPIDEM 10 UNICORN may induce anterograde amnesia. The condition occurs most often several hours after ingesting **ZOLPIDEM 10 UNICORN** and therefore, to reduce this risk, patients should ensure that they will be able to have an uninterrupted sleep of 7 to 8 hours (see section 4.8).

Suicidality and depression:

An increased incidence of suicide and suicide attempt in patients with or without depression, treated with benzodiazepines and other hypnotics, including **ZOLPIDEM 10 UNICORN** may occur. A causal relationship has not been established.

ZOLPIDEM 10 UNICORN should not be used as the primary treatment of depressive syndromes.

ZOLPIDEM 10 UNICORN should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present, therefore, the least amount of **ZOLPIDEM 10 UNICORN** that is feasible, should be supplied to these patients because of the possibility of intentional overdosage by the patient.

Pre-existing depression may be unmasked during use of **ZOLPIDEM 10 UNICORN**.

Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

Other psychiatric and "paradoxical" reactions:

Other psychiatric and paradoxical reactions like restlessness, exacerbated insomnia, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, abnormal behaviour and other adverse behavioural effects are known to occur when using **ZOLPIDEM 10 UNICORN**. Should this occur, use of **ZOLPIDEM 10 UNICORN** should be discontinued. These reactions are more likely to occur in the elderly. (See Section 4.8).

Somnambulism and associated behaviours:

Sleep walking and other associated behaviours such as "sleep driving", preparing and eating food, making phone calls or having sex, with amnesia from the event, have occurred in patients who had taken **ZOLPIDEM 10 UNICORN** and were not fully awake. The use of alcohol and other CNS-depressants with **ZOLPIDEM 10 UNICORN** appears to increase the risk of such behaviours, as does the use of **ZOLPIDEM 10 UNICORN** at

doses exceeding the maximum recommended dose. Discontinuation of **ZOLPIDEM 10 UNICORN** should strongly be considered for patients who experience such behaviours.

Psychomotor impairment:

The risk of psychomotor impairment, including impaired driving ability, is increased if: **ZOLPIDEM 10 UNICORN** is taken within less than 7 – 8 hours before performing activities that require mental alertness, a dose higher than the recommended dose is taken, or **ZOLPIDEM 10 UNICORN** is co-administered with other CNS depressants, alcohol, or with other medicines that increase the blood levels of **ZOLPIDEM 10 UNICORN**.

Duration of treatment:

The duration of treatment should be as short as possible and should not exceed 4 weeks, including the tapering off process. Extensions 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.

Tolerance:

Some loss of efficacy of the hypnotic effects of **ZOLPIDEM 10 UNICORN** may develop after repeated use for a few weeks.

Rebound insomnia:

A transient syndrome, whereby the symptoms that led to treatment with sedative/hypnotic medicines recur in an enhanced form, may occur on withdrawal of **ZOLPIDEM 10 UNICORN** treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

The syndrome is more likely to develop if **ZOLPIDEM 10 UNICORN** is discontinued abruptly, and therefore treatment with **ZOLPIDEM 10 UNICORN** should be withdrawn gradually.

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 the **ZOLPIDEM 10 UNICORN** is being discontinued. In the case of hypnotics with a short duration of action, such as **ZOLPIDEM 10 UNICORN**, withdrawal phenomena can become manifest within the dosage interval.

Dependence and abuse:

Use of **ZOLPIDEM 10 UNICORN** may lead to the development of physical and psychological dependence. The risk of dependence increases with the dose and duration of treatment; it is also greater in patients with a history of psychiatric disorders and/or alcohol or drug abuse. Patients with a history of psychiatric disorders should be under careful surveillance when receiving **ZOLPIDEM 10 UNICORN**. Patients with a history of alcohol or drug abuse – see History of alcohol and drug abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches or muscle pain, extreme anxiety and 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.

Sedatives/hypnotics including **ZOLPIDEM 10 UNICORN** have produced withdrawal signs and symptoms following abrupt discontinuation. These symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors and convulsions. The following adverse events have been reported: fatigue, nausea, flushing, light-headedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness and abdominal discomfort.

Adverse events may occur at an incidence of 1 % or less. However, a reliable estimate of the incidence of dependence during treatment at recommended doses cannot be provided. Post-marketing reports of abuse, dependence and withdrawal have been received.

Patients with a history of psychiatric disorders or addiction to, or abuse of, drugs or alcohol are at increased risk of habituation and dependence. Patients with a history of psychiatric disorders should be under careful surveillance when receiving **ZOLPIDEM 10 UNICORN** or any other hypnotic. Patients with a history of addiction to, or abuse of, drugs or alcohol – see History of alcohol and drug abuse.

History of alcohol and drug abuse:

ZOLPIDEM 10 UNICORN should not be used in patients with a history of alcohol or drug abuse.

Severe injuries:

Due to its pharmacological properties, **ZOLPIDEM 10 UNICORN** can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries.

Patients with Long QT syndrome:

ZOLPIDEM 10 UNICORN may reduce the hERG (human ether-a-go-go-related gene) related potassium currents in cardiac electrophysiology using very high concentration and pluripotent stem cells. The potential
consequence in patients with congenital long QT syndrome is unknown. As a precaution, the benefit/risk ratio of **ZOLPIDEM 10 UNICORN** treatment in patients with known congenital long QT syndrome should be carefully considered.

Lactose intolerance:

Since **ZOLPIDEM 10 UNICORN** tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption, should not take **ZOLPIDEM 10 UNICORN**.

Paediatric population:

ZOLPIDEM 10 UNICORN is contraindicated in patients under the age of 18 years due to increased occurrence of adverse effects including dizziness, headache and hallucinations.

4.5 Interaction with other medicines and other forms of interaction

Alcohol:

Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when **ZOLPIDEM 10 UNICORN** is used in combination with alcohol. This affects the ability to drive or use machines.

CNS depressants:

Enhancement of the central depressive effects may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant medicines, narcotic analgesics, antiepileptic medicines, anaesthetics and sedative antihistamines. Concomitant use of **ZOLPIDEM 10 UNICORN** with these medicines may increase drowsiness and psychomotor impairment, including impaired driving ability.
Co-administration of fluvoxamine may increase blood levels of **ZOLPIDEM 10 UNICORN**; concurrent use is not recommended. (see section 4.5: CYP450 inhibitors and inducers (below)).
In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychological dependence.

Opioids:

The concomitant use of benzodiazepines and other sedative-hypnotic medicines, including **ZOLPIDEM 10 UNICORN**, and 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).

CYP450 inhibitors and inducers:

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of some hypnotics like **ZOLPIDEM 10 UNICORN**.

ZOLPIDEM 10 UNICORN is metabolised via several hepatic cytochrome P450 enzymes: the main enzyme being CYP3A4 with the contribution of CYP1A2.

The pharmacodynamic effect of **ZOLPIDEM 10 UNICORN** is decreased when it is administered with a CYP3A4 inducer such as rifampicin and St John's Wort. Co-administration of St. John's Wort may decrease blood levels of **ZOLPIDEM 10 UNICORN**, concurrent use is not recommended.

However, when **ZOLPIDEM 10 UNICORN** was administered with itraconazole (a CYP3A4 inhibitor) its pharmacokinetics and pharmacodynamics were not significantly modified.

Co-administration of **ZOLPIDEM 10 UNICORN** with ketoconazole (200 mg twice daily), a potent CYP3A4 inhibitor, prolongs **ZOLPIDEM 10 UNICORN** elimination half-life, increased total AUC, and decreased apparent total clearance. A routine dosage adjustment is not considered necessary, but patients should be advised that use of **ZOLPIDEM 10 UNICORN** with ketoconazole may enhance the sedative effects.

Fluvoxamine is a strong inhibitor of CYP1A2 and a moderate to weak inhibitor of CYP2C9 and CYP3A4. Co-administration of fluvoxamine may increase blood levels of **ZOLPIDEM 10 UNICORN**, concurrent use is not recommended. Ciprofloxacin has been shown to be a moderate inhibitor of CYP1A2 and CYP3A4. Coadministration of ciprofloxacin may increase blood levels of **ZOLPIDEM 10 UNICORN**, concurrent use is not recommended.

Other medicines:

When **ZOLPIDEM 10 UNICORN** is administered with warfarin, digoxin, ranitidine or cimetidine, no significant pharmacokinetic interactions may occur.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been demonstrated (see section 4.3).

The use of **ZOLPIDEM 10 UNICORN** in pregnancy and breastfeeding should be avoided.

Pregnancy:

If **ZOLPIDEM 10 UNICORN** is administered during the late phase of pregnancy, or during labour, effects on the neonate such as hypothermia, hypotonia and moderate respiratory depression, can be expected due to the pharmacological action of the product.

Infants born to mothers who take **ZOLPIDEM 10 UNICORN** chronically during the latter stages of pregnancy may develop physical dependence and may be at risk of developing withdrawal symptoms in the postnatal period. Appropriate monitoring of the newborn in the postnatal period is recommended.

If **ZOLPIDEM 10 UNICORN** is prescribed to a woman of childbearing potential, she should be warned to contact her doctor about stopping the product if she intends to become or suspects that she is pregnant.

Breastfeeding:

Small quantities of zolpidem appear in breast milk. The use of **ZOLPIDEM 10 UNICORN** in breastfeeding mothers is, therefore not recommended (see section 4.3).

4.7 Effects on ability to drive and use machines

ZOLPIDEM 10 UNICORN has major influence on the ability to drive and use machines. Vehicle drivers and machine operators should be warned that there may be a possible risk of adverse reactions including drowsiness, prolonged reaction time, dizziness and vertigo, sleepiness, blurred/double vision, reduced alertness and impaired driving the morning after therapy.

If insufficient sleep duration occurs, the likelihood of impaired alertness may increase. In order to minimise this risk a full night of sleep (7 – 8 hours) is recommended.

Furthermore, the co-administration of **ZOLPIDEM 10 UNICORN** with alcohol and other CNS depressants increases the risk of such effects. Patients should be warned not to use alcohol or other psychoactive substances when taking **ZOLPIDEM 10 UNICORN**.

4.8 Undesirable effects:

There is evidence of a dose-relationship for adverse effects associated with **ZOLPIDEM 10 UNICORN** use, particularly for certain CNS events. They occur most frequently in elderly patients.

Infections and infestations:

Frequent: upper respiratory tract infection, lower respiratory tract infection

Nervous system disorders:

Frequent: somnolence, headache, dizziness, exacerbated insomnia, cognitive disorders such as anterograde amnesia (amnestic effects may be associated with inappropriate behaviour)

Less frequent: paraesthesia, tremor, disturbance in attention and speech disorder

Frequency unknown: Depressed level of consciousness

Psychiatric disorders:

Frequent: hallucinations, agitation, nightmare, depression (see section 4.4)

Less frequent: confusional state, irritability, libido disorder, restlessness aggression, somnambulism (see Section 4.4: somnambulism and associated behaviours"), dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation), euphoric mood, delusion

Frequency unknown: anger, abnormal behaviour, psychosis

Most of these psychiatric side effects are related to paradoxical reactions.

General disorders and administrative site conditions:

Frequent: fatigue

Less frequent: Gait disturbances, drug tolerance and fall

Eye disorders:

Less frequent diplopia, blurred vision, visual impairment

Respiratory, thoracic and mediastinal disorders:

Less frequent: respiratory depression (see section 4.4)

Gastrointestinal disorders:

Frequent: diarrhoea, nausea, vomiting, abdominal pain

Metabolism and nutrition disorders:

Less frequent: appetite disorder

Musculoskeletal and connective tissue disorders:

Frequent: back pain

Less frequent: arthralgia, myalgia, muscle spasms, neck pain, muscular weakness

Skin and subcutaneous tissue disorders:

Frequency unknown: Rash, angioneurotic oedema, pruritus, urticaria and hyperhidrosis

Hepatobiliary disorders:

Less frequent Elevated liver enzymes, hepatocellular, cholestatic or mixed liver injury

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

Adverse reactions must also be reported to Unicorn Pharmaceuticals (Pty) Ltd: vigilance@unicornpharma.co.za.

By reporting side effects, you can help provide more information on the safety of **ZOLPIDEM 10 UNICORN**.

4.9 Overdose

Signs and symptoms

In cases of overdose involving **ZOLPIDEM 10 UNICORN** alone or with other CNS-depressant agents (including alcohol), impairment of consciousness ranging from somnolence to coma, and more severe symptomatology including fatal outcomes may occur.

Management:

General symptomatic and supportive measures should be used. Sedating medicines should be withheld even if excitation occurs.

The use of benzodiazepine-antagonists (e.g. flumazenil) may be considered where serious symptoms are observed. Flumazenil is reported to have an elimination half-life of about 40 – 80 minutes. Patients should be kept under close observation because of this short duration of action; further doses of flumazenil may be necessary.

However, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).

In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

ZOLPIDEM 10 UNICORN is not dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.2 Sedatives, hypnotics.

ATC code: N05C F02

Zolpidem is an imidazopyridine compound with sedative/hypnotic effects. These effects are related to a specific agonist action at central receptors belonging to GABA-omega benzodiazepine-1 and benzodiazepine-2 macromolecular receptor complex, modulating the opening of the chloride ion channel. Zolpidem acts primarily upon the omega-1 **(**benzodiazepine-1) receptor subtypes. The clinical relevance of this is not known.

Paediatric population

Safety and efficacy of zolpidem tartrate have not been established in children aged less than 18 years. A randomized placebo-controlled study in 201 children aged 6 – 17 years with insomnia associated with attention deficit hyperactivity disorder (ADHD) failed to demonstrate efficacy of zolpidem tartrate 0,25 mg/kg/day (with a maximum of 10

mg/day) as compared to placebo. Psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem tartrate versus placebo and included dizziness (23,5 % versus 1,5 %), headache (12,5 % versus 9,2 %), and hallucinations (7,4 % versus 0 %) (see sections 4.2 and 4.3).

5.2 Pharmacokinetic properties

Absorption:

After oral administration, the bioavailability of zolpidem is about 70 %, reaching peak plasma concentration between 0,5 and 3 hours after dosing.

Distribution:

At therapeutic dose levels, the pharmacokinetics are linear. The degree of plasma protein binding is about 92 %. The plasma elimination half-life is about 2,5 hours (1,4 - 3,8 hours). The distribution volume in adults is 0,54 ± 0,02 l/kg. The distribution volume decreases to 0,34 ± 0,05 l/kg in the very elderly.

Excretion:

Zolpidem is excreted in the form of inactive metabolites (hepatic metabolism), mainly in the urine (56 %) and faeces (37 %). It has no inducing effects on hepatic enzymes. In elderly subjects, clearance is reduced. The peak concentration is increased by about 50 % and elimination half-life by 32 %.

In patients with renal insufficiency, whether dialysed or not, there is a moderate reduction in clearance. The other pharmacokinetic parameters are unaffected.

Bioavailability:

In patients with hepatic insufficiency, the bioavailability of zolpidem is increased.

Clearance is reduced and the elimination half-life prolonged (about 10 hours).

5.3 Preclinical safety data

Not Applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core*:*

Lactose monohydrate,

Magnesium Stearate,

Microcrystalline cellulose,

Pregelatinised starch (Maize starch),

Silica colloidal anhydrous,

Sodium starch glycolate (Type A)

Film Coating*:*

Hypromellose (5 cps),

Macrogol 6000,

Purified Talc,

Titanium dioxide.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C

This medicine does not require any special storage conditions

6.5 Nature and contents of container

Tablets are packed in blisters of 10 tablets. The blisters are then packaged in an outer carton containing 30 tablets.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

4th Floor Offices, Block A, The District Building,

41 Sir Lowry Road, Woodstock, Cape Town,

Western Cape, 7925, Republic of South Africa

8 REGISTRATION NUMBER(S)

56/2.2/0729

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 March 2025