SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zopiclone 7.5 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Zopiclone 7.5 mg film coated tablet contains 7.5 mg zopiclone.

Excipient with known effect:
Each tablet contains 36 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

7.5 mg: Zopiclone, film-coated tablets are white, oval shaped, biconvex film-coated tablets with “ZOPICLONE" embossed above and “7.5 mg” embossed below a break line on one side.
Length 10 mm, width 8 mm and thickness 3 mm. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Benzodiazepines or benzodiazepine-like agents is only indicated in cases where the insomnia is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Use the lowest effective dose. Zopiclone should be taken in a single intake and not be re-administered during the same night.

As with all hypnotics, long term use of zopiclone is not recommended. Treatment should be as short as possible (few days to two weeks) and should not exceed four weeks including the period of tapering off. Extension beyond the maximum treatment period 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).

Posology

Paediatric population

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

Adults

The recommended dose is 7.5 mg zopiclone by oral route and this dose should not be exceeded.

Elderly patients

In elderly, a lower dose of 3.75 mg zopiclone should be employed to start treatment. Depending on effectiveness and acceptability, the dosage subsequently may be increased if clinically necessary.

Patients with Hepatic impairment

In Patients with hepatic insufficiency elimination of zopiclone may be reduced, a lower dose of 3.75 mg Zopiclone is recommended to start treatment. The dosage subsequently may be increased to 7.5 mg if clinically necessary.

Patients with Renal impairment

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.

Chronic respiratory insufficiency

Patients with chronic respiratory insufficiency should start with, a dose of 3.75 mg zopiclone. The dosage subsequently may be increased to 7.5 mg if clinically necessary.

Method of administration

For oral use only. Zopiclone should be taken immediately before bedtime. Each tablet should be swallowed whole without sucking, chewing or breaking.

4.3 Contraindications

Zopiclone is contraindicated in the following cases:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Myasthenia gravis
- Severe respiratory failure
- Severe sleep apnoea syndrome
- Children and adolescents less than 18 years.
- Severe hepatic insufficiency
- Previously experienced complex sleep behaviours after taking zopiclone (see section 4.4).

4.4 Special warnings and precautions for use

Use in Respiratory insufficiency
As hypnotics have the capacity to depress respiratory drive, precautions should be observed if zopiclone is prescribed to patients with compromised respiratory function (see section 4.8). A lower dose is recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Use in Psychomotor impairment
Like other sedative/hypnotic drugs, zopiclone has CNS-depressant effects. The risk of psychomotor impairment, including impaired driving ability, is increased if:
zopiclone 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.

Tolerance
Some loss of the hypnotic effects of short-acting benzodiazepines and benzodiazepine-like agents may develop after repeated use for a few weeks.

However, with Zopiclone there is an absence of any marked tolerance during treatment periods of up to 4 weeks.

Risk of dependence

Use of zopiclone may lead to the development of abuse and/or physical and psychological dependence, a sudden discontinuation of treatment will be accompanied by withdrawal symptoms (see section 4.8).

Cases of dependence have been reported more frequently in patients treated with zopiclone for longer than 4 weeks. The risk of dependence increases with dose and duration of treatment. The risk of abuse and dependence is also greater in patients with a history of psychiatric disorders and/or alcohol, substance or drug abuse. Zopiclone should be used with extreme caution in patients with current or a history of alcohol, substance or drug abuse or dependence.

Rebound effect

A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine or benzodiazepine-like agent recur in an enhanced form may occur on withdrawal of hypnotic treatment.

It may be accompanied by other reactions including mood changes, anxiety and restlessness.

As the risk of withdrawal symptoms/rebound phenomena are most likely to develop after abrupt discontinuation of treatment, especially when the treatment is of longer duration, it is recommended to decrease the dose gradually.

Duration of treatment

A course of treatment should employ the lowest effective dose and the duration should be as short as possible (se section 4.2), but should not exceed four weeks including the tapering off process.
Extension beyond the maximum treatment period should not take place without re-evaluation of the patient's status.

It may be useful to inform the patients, when treatment is started, that it will be of limited duration and explain precisely how the dosage can be gradual reduced.

It is also important to make the patient aware of the possibility of rebound effect, so the patient dose not unnecessary worry about these types of symptoms when tapering off the treatment.
For short-acting benzodiazepines or benzodiazepine-like substances, signs of withdrawal symptoms may occur within the dose range, especially if the dosage is high.

Risks from concomitant use with opioids

Concomitant use of opioids with benzodiazepines or other sedative-hypnotic drugs, including zopiclone may result in sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of

opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.
If a decision is made to prescribe zopiclone concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation (see section 4.5).

Anterograde amnesia
Benzodiazepines or benzodiazepine-like agents may induce anterograde amnesia, especially a few hours after ingesting of the preparation. Anterograde amnesia usually happens when sleep is interrupted or when retiring to bed is delayed after taking the tablet. In order to reduce the risk, patients should ensure that they take the tablet when certain of retiring for the night and they will be able to have an uninterrupted sleep of 7 to 8 hours (see section 4.8).

Psychiatric and paradoxical reactions
Reactions like restlessness, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, delirium, inappropriate behaviour and other adverse behavioural effects are known to occur when using sedative/hypnotic agents like zopiclone. Should this occur, use of zopiclone should be discontinued. These reactions are more likely to occur in the elderly.

Somnambulism and associated behaviours
Sleep walking and other associated behaviours such as “sleep driving”, preparing and eating food, or making phone calls, with amnesia for the event, have been reported in patients who have taken zopiclone and were not fully awake. These events may occur following the first or any subsequent use of zopiclone.
The use of alcohol and other CNS-depressants with zopiclone appears to increase the risk of such behaviour, as does the use of zopiclone at doses exceeding the maximum recommended dose.
Discontinuation of zopiclone should be strongly considered for patients who report such behaviours due to the risk to the patient and others. (see section 4.5).

Suicidal ideation/suicide attempt/suicide and depression
As with other hypnotics, zopiclone does not constitute a treatment for depression but can in some cases mask it (suicide may be precipitated in such patients).
Some epidemiological studies show an increased incidence of suicidal ideation, suicide attempt and suicide in patients with or without depression, and treated with benzodiazepines and other hypnotics, including zopiclone. However, a causal relationship has not been established.

Zopiclone should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present therefore the least amount of zopiclone that is feasible should be supplied to these patients to avoid the possibility of intentional overdose by the patient. Pre-existing depression may be unmasked during use of zopiclone. Since insomnia may be

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

Special populations:

Paediatric population
Zopiclone should not be used in children and adolescents less than 18 years. Safety and efficacy of zopiclone have not been established in patients below the age of 18 years.

Elderly
A reduced dose is recommended, see section 4.2.
There is a risk of falling, especially in older people when they get up during the night, due to the muscle relaxing effect of zopiclone.

Chronic respiratory insufficiency
A lower dose is recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression, see section 4.2.

Hepatic impairment
A reduced dosage is recommended, see section 4.2.

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

Renal impairment
A reduced dosage is recommended, see section 4.2.

Other warnings

Benzodiazepines and benzodiazepine-like agents are not recommended for the primary treatment of psychosis.

Benzodiazepines and benzodiazepine-like agents should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

Benzodiazepines and benzodiazepine-like agents should be used with caution in patients with a history of alcohol and substance/drug abuse.

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

Zopiclone contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium free”.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended

Concomitant intake with alcohol:
The sedative effect may be enhanced when Zopiclone is used in combination with alcohol. This affects the ability to drive or use machines.

Take into account

Combination with CNS depressants:
Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative antihistamines.
For centrally acting analgesics (opioids), increased euphoria may also occur leading to an increase in psychological dependence.

Combination of Zopiclone and muscle relaxants can increase the muscle relaxant effect.

Since zopiclone is metabolised by CYP3A4, the plasma levels of zopiclone and therefor the effect of zopiclone can be increased when co-administered with CYP3A4 inhibiting drugs like macrolides, azoles and HIV protease inhibitors and grapefruit juice.
A dose reduction for zopiclone may be required when it is co-administered with CYP3A4 inhibitors.
A dose increase for zopiclone may be required when it is co-administered with CYP3A4 inducers.

Plasma levels of zopiclone may be decreased when co-administered with CYP3A4 inducers such as phenobarbital, phenytoin, carbamazepine, rifampicin, and products containing St. John's wort.

The effect of erythromycin on the pharmacokinetics of zopiclone has been studied in 10 healthy subjects. The AUC of zopiclone is increased by 80% in presence of erythromycin which indicates that erythromycin can inhibit the metabolism of drugs metabolised by CYP 3A4. This might may enhance the hypnotic effects of Zopiclone.

Opioids

The concomitant use of benzodiazepines and other sedative-hypnotic drugs, including zopiclone, and opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of zopiclone is not recommended during pregnancy.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Zopiclone crosses the placenta.

A large amount of data on pregnant women (more than 1000 pregnancy outcomes) collected from cohort studies has not demonstrated evidence of the occurrence of malformations following exposure to benzodiazepines or benzodiazepine-like substances during the first trimester of pregnancy. However, certain case-control studies reported an increased incidence of cleft lip with use of benzodiazepines during pregnancy.

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.

Administration of benzodiazepines or benzodiazepine-like substances, including zopiclone, during the late phase of pregnancy or during labour have been associated with effects on the neonate, such as hypothermia, hypotonia, feeding difficulties (*'floppy infant syndrome'*), and respiratory depression, due to the pharmacological action of the product. Cases of severe neonatal respiratory depression have been reported.

Moreover, infants born to mothers who took sedative/hypnotics agents chronically during the latter stages of pregnancy may have developed 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 Zopiclone is prescribed to a woman of childbearing potential, she should be warned to contact her physician about stopping the product if she intends to become or suspects that she is pregnant.

Breastfeeding
Because benzodiazepine or benzodiazepine-like substances is excreted in the breast milk, use of Zopiclone in nursing mothers must be avoided.

4.7 Effects on ability to drive and use machines

Because of zopiclones pharmacological properties and its effect on central nervous system, zopiclone may adversely affect the ability to drive or to use machines.

Due to side effects (sedation, amnesia, decreased concentration and muscle function), Zopiclone can significantly affect the ability to drive or use machines.

The risk of psychomotor impairment, including impaired driving ability, is increased if:

- zopiclone is taken within 12 hours of performing activities that require mental alertness
- a dose higher than the recommended dose is taken
- 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. The risk increases further when sleep deprived. Patients must be warned about operating machinery or driving a motor vehicle, before the treatment is over or it is settled, that it does not affect the patient. Because of the residual effects this warning does also apply the morning after the administration of Zopiclone.

4.8 Undesirable effects

Most side effects are due to high doses and regular use every night. Around 10% of the treated patients experiences side effects.
Side effects such as drowsiness in the daytime, reduced emotional state, reduced attention, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or double vision occur mainly at the start of the treatment and usually disappears during continued treatment. The most common side effects are taste changes (about 4 % of those treated), dry mouth and morning tiredness.

The adverse drug reactions are stated in the table below using the following convention:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Immune system disorders Very rare (<1/10,000)	Angioedema, anaphylactic reaction
Psychiatric disorders Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000) Not known (cannot be estimated from the available data).	Agitation, nightmare. Confusional state, libido disorder, irritability, aggression, hallucination and depression [I]. Restlessness, delirium, delusion, anger, agitation, abnormal behaviour (possibly associated with amnesia), complex sleep behaviours including somnambulism (see section 4.4), dependence and withdrawal syndrome [II].
Nervous system disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000) Not known (cannot be estimated from the available data).	Dysgeusia (bitter taste or metallic aftertaste), somnolence (residual). Reduced alertness, headache, dizziness. Anterograde amnesia. Ataxia, paraesthesia, cognitive disorders such as memory impairment, disturbance in attention, speech disorder.
Eye disorders Not known (cannot be estimated from the available data).	Diplopia
Respiratory, thoracic and mediastinal disorders Rare (≥1/10,000 to <1/1,000) Not known (cannot be estimated from the available data).	Dyspnoea (see section 4.4) Respiratory depression (see section 4.4)
Gastrointestinal disorders Common (≥1/100 to	Dry mouth

<1/10) Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000) Not known (cannot be estimated from the available data).	 Nausea, malaise, abdominal pain. Vomiting Dyspepsia
Hepatobiliary disorders Very rare (<1/10,000)	Mild to moderate increase in transaminases and/or blood alkaline phosphatase.
Skin and subcutaneous tissue disorders Rare (≥1/10,000 to <1/1,000)	Allergic skin reaction (inclusive rash, pruritus, urticaria).
Musculoskeletal and connective tissue disorders Not known (cannot be estimated from the available data).	Muscular weakness
General disorders and administration site conditions Uncommon (≥1/1,000 to <1/100) Not known (cannot be estimated from the available data).	Difficulty getting up in the morning, fatigue. light headedness, incoordination
Injury, poisoning and procedural complications Rare (≥1/10,000 to <1/1,000)	Fall (predominantly in elderly patients) **(**see section 4.2)

[I] Pre-existing depression may become manifest during use of benzodiazepines or benzodiazepine-like agents (see section 4.4).
[II] Use (even at therapeutic dosages) may lead to physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see section 4.4). Psychic dependence may occur. Abuse has been reported.

Withdrawal has been reported with discontinuation of Zopiclone (see section 4.4).

Withdrawal symptoms vary and can take the form of insomnia, muscle aches, anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, panic attacks, muscle aches/cramps, gastrointestinal disturbances and irritability. In severe cases, the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling in the extremities, hypersensitivity to light, noise and physical contact, hallucinations and epileptic seizures.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

As with other benzodiazepines and benzodiazepine-like substances, overdose should not be life-threatening unless combined with other CNS depressants (including alcohol). Other risk factors, such as concomitant illness and debilitating condition of the patient, can contribute to the severity of the symptoms and very rarely result in a fatal outcome.
When treating overdose with any drug, one should be aware that several drugs may be ingested.

Symptoms
Overdose with benzodiazepines and benzodiazepine-like substances usually manifests itself in varying degrees of depression of the central nervous system, which can range from lethargy to coma. In mild cases the symptoms include lethargy, mental confusion and drowsiness, in more severe cases the symptoms include ataxia, hypotonia, hypotension, methemoglobinemia, difficulty breathing, rarely coma and very rarely death.

Management:
Following overdose with oral benzodiazepines and benzodiazepine-like substances, vomiting should be induced (within 1 hour) if the patient is conscious or flushing of the stomach under respiratory protection if the patient is unconscious. If it is not appropriate to empty the stomach, activated charcoal should be given to reduce absorption if an adult has ingested more than 150 mg or a child more than 1.5 mg/kg within one hour. Rinsing the stomach or administering activated charcoal is only beneficial when done soon after taking zopiclone. During intensive monitoring, special attention should be paid to respiratory and cardiac functions. Haemodialysis is not useful for the treatment of overdose due to the large volume of distribution of the drug. Flumazenil may be useful as an antidote; it has a short half-life (about an

hour). NOT TO BE USED IN MIXED OVERDOSE OR AS A "DIAGNOSTIC" TEST.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine related drugs, ATC code: N 05 CF 01.
Zopiclone is a benzodiazepine-like hypnotic agent and belongs to the group of cyclopyrrolone compounds. Its pharmacological properties include anxiolytic, sedative, hypnotic, anticonvulsant and muscle-relaxant effects.

These effects are related to a specific agonist action at central receptors belonging to the 'GABA-omega (BZ1 and BZ2) macromolecular receptor"- complex modulating the opening of the chloride ion channel.

5.2 Pharmacokinetic properties

Absorption
Zopiclone is absorbed rapidly. Peak concentrations are reached within 1.5 - 2 hours and they are approximately 30 ng/ml, 60 ng/ml and 115 ng/ml after administration of 3.75 mg, 7.5 mg and 15 mg respectively. Absorption is not modified by gender, food, time of intake or repetition of doses.

Distribution
The product 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.
Decrease in plasma concentration: At doses between 3.75 - 15 mg, plasma clearance does not depend on dose. The elimination half-life is approximately 5 hours.

After repeated administration, there is no accumulation, and inter-individual variations appear to be very small. During lactation, the kinetic profiles of zopiclone in breast milk and in plasma are similar. It is estimated that the portion of the dose a breast-feeding baby will be exposed to will not exceed 0.2% of the dose taken by the mother within 24 hours.

Biotransformation
Zopiclone is extensively metabolised in humans to two major metabolites, N-oxide zopiclone (pharmacologically active in animals) and N- desmethyl zopiclone (pharmacologically inactive in animals).

An in-vitro study indicates that cytochrome P450 (CYP) 3A4 is the major isoenzyme involved in the metabolism of zopiclone to both metabolites, and that CYP2C8 is also involved with N-desmethyl zopiclone formation.

Their apparent half-lives (evaluated from the urinary data) are approximately 4.5 hours and 1.5 hours respectively. No significant accumulation is seen on repeated dosing (15 mg) for 14 days. In animals, no enzyme induction has been observed even at high doses.

Elimination

The low renal clearance value of unchanged zopiclone (mean 8.4ml/min) compared with the plasma clearance (232ml/min) indicates that zopiclone clearance is mainly metabolic. The product is eliminated by the urinary route (approximately 80%) in the form of free metabolites (n-oxide and n-desmethyl derivatives) and in the faeces (approximately 16%).

Special populations

In elderly patients, notwithstanding a slight decrease in hepatic metabolism and lengthening of elimination half-life to approximately 7 hours, various studies have shown no plasma accumulation of drug substance on repeated dosing.

In renal insufficiency, no accumulation of zopiclone or of its metabolites has been detected after prolonged administration. Zopiclone crosses dialysis membranes. However, haemodialysis is not useful for the treatment of overdose due to the large volume of distribution of the substance (see section 4.9. Overdose).

In cirrhotic patients, the plasma clearance of zopiclone is clearly reduced by the slowing of the desmethylation process: dosage will therefore have to be modified in these patients.

5.3 Preclinical safety data

There are no additional preclinical data of relevance to healthcare professionals than those already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate

Maize starch
Calcium hydrogen phosphate, anhydrous
Sodium starch glycolate
Magnesium stearate

Film-coating
Titanium dioxide (E 171)
Macrogol
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Cartons of 14 and 28 tablets containing PVC-Aluminium foil blisters of 7 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 15764/0185

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/03/2025

10 DATE OF REVISION OF THE TEXT

25/03/2025