SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zopiclone Orion 3.75 mg film-coated tablets
Zopiclone Orion 7.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

3.75 mg
Each film-coated tablet contains 3.75 mg of zopiclone.

Excipient with known effect
Each tablet also contains 16 mg of lactose monohydrate.

7.5 mg
Each film-coated tablet contains 7.5 mg of zopiclone.

Excipient with known effect
Each tablet also contains 32 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

3.75 mg
White to off white, round, diameter 6 mm, biconvex film-coated tablets.

7.5 mg
White to off white, oval (10 mm x 5 mm), biconvex film-coated tablets with breakline on one side. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Transient and short-term treatment of insomnia in adults. Supportive therapy, for a limited time, for treatment of chronic insomnia in adults.

Benzodiazepines and benzodiazepine-like substances are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

The treatment duration should be as short as possible. Lowest effective dose should be used.

Usually the treatment duration varies from a few days to 2 weeks, but no longer than 4 weeks, including tapering off. In some cases it may be necessary to extend treatment beyond the maximum treatment period; however, this should not take place without re-evaluation of the patient's status.

Posology

There is no marketing authorisation for Zopiclone Orion 5 mg tablets, in cases a patient needs a dose of 5 mg this presentation may be available from other zopiclone products.

Adults
The usual initial dose is 5–7.5 mg at bedtime. Treatment duration should be as short as possible and not exceed 4 weeks.

Elderly
In the elderly, treatment should be started at a dosage of 3.75 mg. The dose may later be increased to 5 mg and if necessary up to 7.5 mg.

Hepatic impairment
As elimination of zopiclone may be reduced in patients with hepatic dysfunction, the treatment should be started at a dosage of 3.75 mg. The dose may later be increased to 5 mg and if necessary up to 7.5 mg. Severe hepatic impairment is contraindicated (see section 4.3).

Renal impairment
Although no accumulation of zopiclone or its metabolites have been found in patients with renal insufficiency, it is advisable to begin treatment of patients with reduced renal function at 3.75 mg.

Chronic respiratory insufficiency
The treatment should be started at a dosage of 3.75 mg. The dose may later be increased to 5 mg and if necessary up to 7.5 mg.

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.

Method of administration

The product should be taken just before retiring for the night. The tablets should not be taken in the lying position as the absorption might be delayed.
For oral use only.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Myasthenia gravis
- Respiratory insufficiency
- Severe sleep apnoea
- Severe hepatic insufficiency
- Previously experienced complex sleep behaviours after taking zopiclone (see section 4.4).

4.4 Special warnings and precautions for use

Before starting treatment with zopiclone any underlying cause of insomnia should be addressed carefully.

As hypnotics have the capacity to cause respiratory depression, precautions should be observed if zopiclone is prescribed to patients with compromised respiratory function (see section 4.8).

Dependence
The use of benzodiazepines and benzodiazepine-like substances can lead to physical and psychological dependence on these agents. Clinical experience to date suggests that the risk of dependence is minimal when the duration of treatment is limited to not more than 4 weeks.
The risk of dependence or abuse increases with:

- Dose and duration of treatment
- Use with alcohol or other psychotropics
- It is also greater in patients with a history of alcohol and or drug abuse
- Those patients who have marked personality disorders.

If physical dependence occurs, sudden discontinuation of the treatment will be accompanied by withdrawal symptoms. These may be expressed as headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise or physical contact, hallucinations or epileptic seizures.

Rebound insomnia
After discontinuation of treatment with a benzodiazepine or a benzodiazepine-like substance, a temporary syndrome may occur in which the symptoms which led to the treatment with the benzodiazepine or a benzodiazepine-like substance return in a more severe form. This syndrome may be accompanied by other reactions, including mood changes, anxiety and restlessness. Since the risk of withdrawal symptoms or rebound symptoms is greater after abrupt interruption of the treatment, it is advisable to reduce the dosage gradually (see section 4.8).

Treatment duration
The duration of treatment should be as short as possible (see section 4.2) but not longer than 4 weeks including the tapering off process. This period should only be exceeded after re-evaluation of the patient's status. It may be of benefit to inform the patient at the beginning of treatment that the treatment will be of short duration, and to explain precisely how to reduce the dose gradually.
It is also important to draw attention to the possibility of a rebound effect, so the patient does not worry unduly about these symptoms during the treatment withdrawal. For short-acting benzodiazepines and benzodiazepine-like substances there are indications that withdrawal symptoms may occur within the dosage interval, especially when the dose is high.

Tolerance
The hypnotic effect of short-acting benzodiazepines and benzodiazepine-like substances may diminish after repeated use for a few weeks. For zopiclone however, no pronounced tolerance has occurred during a treatment period of up to 4 weeks.

Anterograde amnesia
Benzodiazepines and benzodiazepine-like substances may cause anterograde amnesia, in particular a few hours after taking the product especially 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 will be able to have an uninterrupted sleep of 7–8 hours (see section 4.8).

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.

Psychiatric and paradoxical reactions
Reactions like restlessness, agitation, irritability, aggressiveness, delusions, outbursts of anger, nightmares, hallucinations, psychoses, inappropriate behaviour and other behavioural disturbances may occur during treatment with benzodiazepines and benzodiazepine-like substances. In this case, the medicinal product must be discontinued. These reactions occur more often in children and the elderly (see section 4.8).

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

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

Somnambulism and associated behaviours
Complex sleep behaviour, including sleep walking and other associated behaviours such as “sleep driving”, preparing and eating food, making phone calls or having sex, with amnesia for the event have been reported in patients who had taken zopiclone and were not fully awake. These events may occur following the first or any subsequent use of zopiclone. Discontinue treatment immediately if a patient experiences a complex sleep behaviour, due to the risk to the patient and others (see section 4.3). The use of alcohol and other CNS depressants with zopiclone appears to increase the risk of such behaviours, as does the use of zopiclone at doses exceeding the maximum recommended dose.

Suicidal ideation/suicide attempt/suicide depression
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.

As with other hypnotics, zopiclone does not constitute a treatment for depression and may even mask its symptoms (suicide may be precipitated in such patients).

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.

<u>Special populations</u>

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.

Respiratory insufficiency
A lower dose is recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

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.

Elderly
Elderly should be given a reduced dose (see section 4.2). There is a risk of fall, particularly in the elderly when they get up during the night due to the muscle relaxing effect of zopiclone.

Benzodiazepines and benzodiazepine-like substances are not recommended as the primary treatment of psychoses. Benzodiazepines and benzodiazepine-like substances should not be used as the sole

treatment of depression or anxiety linked with depression (suicide may be triggered in such patients). Benzodiazepines and benzodiazepine-like substances should be administered with extreme caution to patients with a previous history of alcohol or drug abuse.

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use is not recommended:
Concomitant intake with alcohol is not recommended. The sedative effect of zopiclone may be enhanced when used in combination with alcohol. This could affect the patient's ability to drive or use machines.

Interaction has to be taken into account and may require dose adjustment:
Combination with other central depressive agents, such as antipsychotic agents (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressants, narcotic analgesics, antiepileptics, anaesthetics and sedative antihistamines may increase the suppressive effect of zopiclone on the central nervous system and should therefore be carefully weighed.
In the case of narcotic analgesics potentiation of euphoria may also occur, which can lead to increased psychological dependence.

Opioids: The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Zopiclone Orion with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

Combination of zopiclone and muscle relaxants may increase the muscle relaxing effect.

Since zopiclone is metabolised by CYP3A4, plasma levels of zopiclone may be increased when co-administered with CYP3A4 inhibitors such as macrolides, azoles, HIV protease inhibitors and grapefruit juice. Dose reduction should be considered if zopiclone is administered with CYP3A4 inhibitors.

The effect of erythromycin on the pharmacokinetics of zopiclone has been studied in healthy volunteers. The AUC of zopiclone is increased by 80% in presence of erythromycin which indicates that erythromycin can inhibit the metabolism of drugs metabolized by CYP 3A4. As a consequence, the hypnotic effect of zopiclone may be enhanced.

Concomitant administration of itraconazole (that inhibits CYP 3A4-mediated metabolism) increases the biological availability of zopiclone by approximately 70%.

CYP3A4 inducers such as phenobarbital, phenytoin, carbamazepine, rifampicin and products containing St. John's wort may reduce plasma levels of zopiclone. An increased dose of zopiclone may then be needed.

Rifampicine strongly induces the metabolism of zopiclone most likely via CYP3A4. The plasma concentration of zopiclone decreases with about 80% and its effects in psychomotoric tests are reduced significantly. An increased dose of zopiclone may be needed under these conditions.

4.6 Fertility, pregnancy and lactation

Insufficient data are available on zopiclone to assess its safety during human 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 1 000 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 and palate associated with use of benzodiazepines during pregnancy.

Cases of reduced fetal movement and fetal 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 regarding discontinuance of the product if she intends to become or suspects that she is pregnant.

Breastfeeding
Zopiclone is excreted in breast milk, although the concentration of zopiclone in the breast milk is low, use in nursing mothers must be avoided.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscular function may reduce the capability to drive or operate machines. See also section 4.4, psychomotor impairment. The risk is increased with concomitant alcohol intake. The risk is even higher when sleep duration is insufficient. Patients should be warned not to drive or operate machines until treatment has finished or it has been established that performance is unimpaired. Due to residual effects this warning should also be considered the morning after administration of zopiclone.

4.8 Undesirable effects

In this section frequencies of undesirable effects are defined as follows:
Very common (≥ 1/10)
Common (≥ 1/100, < 1/10)
Uncommon (≥ 1/1 000, < 1/100)
Rare (≥ 1/10 000, < 1/1 000)
Very rare (< 1/10 000)
Not known (cannot be estimated from the available data)

System organ class	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders				Angioedema, anaphylactic	

				reactions	
Psychiatric disorders		Agitation, nightmares	Confusion, libido disorders, irritability, aggression, hallucinations, depression[I]		Restlessness, delusions, anger, abnormal behaviour (possibly associated with amnesia), complex sleep behaviours including somnambulism (see section 4.4), dependence, withdrawal syndrome[II]
Nervous system disorders	Dysgeusia (bitter taste), drowsiness	Decreased alertness, headache, dizziness	Anterograde amnesia		Ataxia, paraesthesia, cognitive disorders such as memory impairment, disturbance in attention, speech disorder
Eye disorders					Diplopia
Respiratory, thoracic and mediastinal disorders			Dyspnoea (see section 4.4)		Respiratory depression (see section 4.4)
Gastrointestinal disorders	Dry mouth	Nausea, malaise, abdominal pain	Vomiting		Dyspepsia
Hepatobiliary disorders				Increases in serum transaminases and/or blood alkaline phosphatase (mild or moderate)	
Skin and subcutaneous tissue disorders			Allergic skin reactions (including rash, pruritus, urticaria)		
Musculo-skeletal and connective tissue disorders					Muscular weakness
General disorders and administration site conditions		Difficulty getting up in the morning, fatigue			
Injury, poisoning and			Fall (mainly in elderly		

procedural complications			patients) (see section 4.2)		

[I] Existing depression may manifest itself during use of benzodiazepines and benzodiazepine-like substances.
[II] Use of zopiclone may lead to physical dependence even at therapeutic doses, and discontinuation of treatment may cause withdrawal symptoms or rebound effect (see section 4.4). Psychological dependence may also occur. Abuse has occurred.

There are reports of withdrawal symptoms during withdrawal of zopiclone (see section 4.4).

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 the national reporting system listed in Appendix V

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 the presence of concomitant illness and debilitated state of the patient, may contribute to the severity of symptoms and can, very rarely, result in a fatal outcome.
In the treatment of an overdose of any medicinal product the possibility that multiple agents may have been taken should be taken into consideration.

Symptoms
Overdose with benzodiazepines and benzodiazepine-like substances is usually manifested by varying degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy; in more serious cases, symptoms include ataxia, hypotonia, hypotension, methemoglobinemia, difficulty breathing, coma (rarely) and death (very rarely).

Treatment
Following overdose with oral benzodiazepines and benzodiazepine-like substances, vomiting should be induced (within 1 hour) if the patient is conscious. Gastric lavage should be carried out with protection of the airways if the patient is unconscious. If it is not advisable to empty the stomach, activated charcoal should be administered to reduce the absorption. Gastric lavage or administration of activated charcoal is only useful when performed soon after taking zopiclone. During intensive care, special attention should be paid to respiratory and cardiac functions. Haemodialysis is not useful in treating overdose due to the large volume of distribution.

Flumazenil may be useful as an antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, benzodiazepine related drugs, ATC code: N05CF01

Zopiclone is a benzodiazepine-like hypnotic agent which belongs to the group of cyclopyrrolones. The pharmacological properties are: sedation, anxiolysis, anticonvulsion, muscle relaxation. These are related to its high affinity and specific agonist action at central receptors belonging to the “GABA” macromolecular receptor complex modulating the opening of the chloride ion channel. However, it has been shown that zopiclone and other cyclopyrrolones act on a different site to those of benzodiazepines including different conformational changes in the receptor complex.

5.2 Pharmacokinetic properties

Absorption
The bioavailability of zopiclone is about 80%. Maximum plasma concentrations are achieved within 1.5–2 hours and are approximately 30 ng/ml and 60 ng/ml after administration of 3.75 mg and 7.5 mg respectively. Absorption is the same in men and women and is not affected by simultaneous ingestion of food. The absorption might be delayed if zopiclone is administrated in a lying position.

Distribution
Zopiclone is swiftly distributed from the vascular compartment. The volume of distribution is 1.3 l/kg and the protein binding levels is about 45% and is not saturable. Less than 1.0% of the dose ingested by the mother is eliminated in breast milk.

Biotransformation
There is no accumulation after repeated administration and inter-individual variations appear to be minor. Zopiclone is to a great extent metabolized in the liver by decarboxylation. About 11% are transformed into N-oxide-zopiclone which is less active than the parent compound and of no clinical importance. About 15% are transformed into the inactive N-desmetyl-zopiclone. Their apparent half-life is approximately 4.5 hours and 7.4 hours respectively.

Elimination
The half-life of zopiclone is approximately 5 hours.
The low renal clearance of zopiclone (on average 8.4 ml/min) compared to the plasma clearance (232 ml/min) shows that zopiclone is cleared chiefly 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%).

Pharmacokinetic in special populations

Elderly
The half-life of zopiclone is increased to 7 hours in the elderly. In various trials with elderly patients, no accumulation of zopiclone was observed in the plasma after repeated doses.

Renal impairment
In renal insufficiency, no accumulation of zopiclone or its metabolites have been detected after prolonged administration. Zopiclone crosses the dialysing membrane.

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

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Calcium hydrogen phosphate dihydrate
Maize Starch
Lactose Monohydrate

Pregelatinised starch
Hydroxypropyl cellulose
Magnesium Stearate

Tablet coating:
Hypromellose
Titanium dioxide (E171)
Macrogol

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 storage conditions.

6.5 Nature and contents of container

Aluminium/PVC blister: 10, 14, 20, 28, 30, 56, 60 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

08/2022