1. NAME OF THE MEDICINAL PRODUCT

Zopiclone Actavis 5 mg film-coated tablet
Zopiclone Actavis 7.5 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<Product name> 5 mg film-coated tablet
Each film-coated tablet contains 5 mg zopiclone.

<Product name> 7.5 mg film-coated tablet
Each film-coated tablet contains 7.5 mg zopiclone.

Excipient(s) with known effect:

<Product name> 5 mg film-coated tablet
Each film-coated tablet contains 30.8 mg lactose monohydrate.

<Product name> 7.5 mg film-coated tablet
Each film-coated tablet contains 30.8 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

<Product name> 5 mg film-coated tablet
Yellow, round, biconvex film-coated tablets.
The tablets are debossed with “ZOC 5” on one side.

<Product name> 7.5 mg film-coated tablet
White, round, biconvex film-coated tablets.
The tablets are debossed with "ZOC 7.5" on one side and a division mark on both sides.
The division mark is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adults
The usual initial dose is 5 mg at bedtime. Patients who do not respond to this dose should take 7.5 mg. The lowest possible dose should be chosen when treating elderly patients.

The duration of treatment should be as short as possible and not exceed 4 weeks, including the discontinuation phase. Extending the duration of treatment should only be done after a reassessment of the patient's condition.

Elderly
Treatment of elderly patients should start with a dose of 3.75 mg. The dose can later be increased to 5 mg and up to 7.5 mg if necessary.

Renal impairment
Although no accumulation of zopiclone or its metabolites has been observed in patients with renal impairment, an initial dose of 3.75 mg is recommended in patients with renal impairment.

Hepatic impairment
Treatment should start with a dose of 3.75 mg. The dose can later be increased to 5 mg and up to 7.5 mg if necessary.

Chronic respiratory insufficiency
Treatment should start with a dose of 3.75 mg. The dose can later be increased to 5 mg and up to 7.5 mg if necessary.

For dosages that cannot be achieved with <Product name> (e.g. a dose of 3.75 mg) other medicinal products are available on the market and should be used in these cases.

Paediatric population
<Product name> 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

To be taken immediately before bedtime. The tablets should be taken in an upright position as absorption may otherwise be delayed.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in 6.1.
- Severe hepatic impairment
- Sleep apnoea syndrome
- Myasthenia gravis
- Respiratory impairment.

4.4 Special warnings and precautions for use

Sleep problems can be caused by mental or somatic illness. Prolonged sleeping difficulties should therefore be investigated in this regard.Caution should be exercised in patients with hepatic impairment, respiratory impairment, in treatment of elderly, and patients with impaired general condition. <Product name> should also be used with caution in patients with a history of alcohol or drug abuse. Simultaneous alcohol consumption should be avoided.

Drug dependence
Use of sedative/hypnotic agents, such as zopiclone, may lead to physical or psychological dependence or abuse of these agents. The risk of dependence or abuse increases with the dose and length of treatment. The risk of dependence or abuse is also greater for patients with a history of alcohol or drug abuse and if zopiclone is combined with alcohol or other psychotropic agents. Once physical dependence has developed, abrupt discontinuation of zopiclone will lead to withdrawal symptoms (see section 4.8).

Rebound phenomenon in the form of insomnia
A transient syndrome in which the symptoms that led to the initiation of the sedative/hypnotic agent treatment recur in a more severe form may occur upon discontinuation. The risk of these symptoms occurring is greater in the event of abrupt withdrawal, especially after prolonged treatment with sleeping pills. Therefore, it is recommended that the patient is informed of this and instructed to

gradually reduce the dose (see also section 4.8). Treatment with sleeping pills should be temporary or intermittent to reduce the risk of withdrawal problems.

Anterograde amnesia
Anterograde amnesia may occur, especially if sleep is interrupted or bedtime is delayed after taking <product name>.
To reduce the risk of anterograde amnesia, the patient should:
– take the tablet at bedtime
– make sure to be able to have a full night's sleep

Drug tolerance
The effectiveness of zopiclone may decrease after repeated use.

Somnambulism and associated behaviour
Sleep walking and other associated behaviours such as driving, cooking and eating, or making phone calls while asleep 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 zopiclone at doses exceeding the maximum recommended dose. Discontinuation of zopiclone should be strongly considered for patients who report such behaviours (see section 4.5).

Other psychiatric and paradoxical reactions
See section 4.8 . There is a risk of habituation, which should be taken into account when prescribing this medicinal product.

Risk from concomitant use of opioids
Concomitant use of <product name> 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 <product name> with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe <product name> concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see 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).

Paediatric population
<Product name> 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.

Excipients

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol
Concomitant use of alcohol should be avoided. The sedative effect of <product name> may be enhanced when used in combination with alcohol.

CNS depressants

Combination with other CNS depressants, such as neuroleptics, hypnotics, anxiolytics/sedatives, antidepressants, narcotic analgesics, antiepileptics, anesthetics and sedative antihistamines should be carefully considered as the suppressive effect of zopiclone on the central nervous system may be increased in combination with these agents.

Opioids
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as <product name> 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).*

CYP3A4 inhibitors and inducers
Because zopiclone is metabolized via CYP3A4, plasma levels of zopiclone may increase if co-administered with CYP3A4 inhibitors. Examples of such are macrolide antibiotics, azoles, HIV protease inhibitors and grapefruit juice. A dose reduction of zopiclone may be necessary during concomitant treatment with CYP3A4 inhibitors. Conversely, plasma levels of zopiclone may decrease if co-administered with CYP3A4 inducers. Examples of inducers are phenobarbital, phenytoin, carbamazepine, rifampicin and products containing St. John's wort. A dose increase of zopiclone may then be necessary.

Combinations that may require dose adjustment
The effect of erythromycin on the pharmacokinetics of zopiclone has been studied in healthy volunteers. AUC of zopiclone is increased by 80% in the presence of erythromycin most likely because erythromycin inhibits the metabolism of drugs metabolised by CYP3A4.
If the combination is used, it may lead to a more pronounced hypnotic effect of zopiclone.

If co-administered with itraconazole (which inhibits CYP3A4-mediated metabolism), the bioavailability of zopiclone is increased by about 70%.

Rifampicin potently induces zopiclone metabolism, most likely via CYP3A4. Its plasma concentration is reduced by about 80%, and its effects in psychomotor tests are reduced significantly.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of zopiclone in pregnant women.. Data from animal experiments do not indicate any increased risk of birth defects. During the last trimester, there is a risk of adverse pharmacological effects on the foetus and/or the neonate, such as hypotonia, effects on respiratory function and hypothermia. <Product name> should therefore not be used during pregnancy.

If the product 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.

Breast-feeding

<Product name> passes into breast milk. <Product name> to breast feeding women is not recommended although the concentration in breast milk is low.

4.7 Effects on ability to drive and use machines

<Product name> may impair the ability to react. This should be taken into consideration when alertness is required, e.g. when driving or performing precision work. There is a risk that part of the effect remains the day after intake. The risk increases with simultaneous consumption of alcohol. With insufficient sleep, the risk is even higher. Patients should be advised not to drive or operate machinery until treatment is completed or until it has been determined that ability is not impaired.

4.8 Undesirable effects

About 10% of treated patients experience some form of side effect. The most common side effect is a bitter taste, often transient, which occurs in about 4% of patients in clinical studies, followed by drowsiness, which is dose-dependent.

The undesirable effects are listed below according to MedDRA Organ Class and frequency. The following frequency classification has been used: 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).

	Common (≥1/100 to <1/10)	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1000)**
Immune system disorders			Angiooedema and/or anaphylactic reactions
Psychiatric disorders		Agitation, abnormal dreams	Somnambulism, anxiety irritability, aggressiveness, abnormal behaviour possibly associated with amnesia, hallucinations, confusion, difficulty in concentrating, anterograde amnesia
Nervous system disorders	Drowsiness, dysgeusia (bitter/metallic taste)	Headache, dizziness	
Gastrointestinal disorders	Dry mouth	Nausea	Dyspepsia
Skin and subcutaneous tissue disorders			Exanthema, itching, urticaria
Investigations			Mild to moderate elevations in serum transaminases and/or alkaline phosphatases

Withdrawal symptoms have been reported after stopping treatment with <product name> (see section 4.4). Withdrawal symptoms vary and include difficulty sleeping, restlessness, tremors, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, hallucinations and irritability. In very rare cases, convulsions have also occurred.

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

Toxicity
Great individual variation.
5 mg to a 1½ year old caused mild intoxication.
About 30 mg to a 6 year-old caused moderate intoxication.
22.5-50 mg to adults and 40 mg to an elderly caused mild intoxication.

>50-<100 mg to adults caused mild to moderate intoxication.
100 mg to adults caused deep unconsciousness.
187 mg and alcohol to adults caused severe intoxication.

Symptoms
Fatigue, drowsiness, somnolence, confusion, lethargy, unconsciousness (in the elderly sometimes very long term), sometimes preceded or followed by agitation and hallucinations. Respiratory depression (mainly in combination with alcohol or CNS depressants). Ataxia, muscle weakness, hypotension, sinus tachycardia or bradycardia. Intraventricular block, AV block. Hypokalaemia, hyperglycaemia. Transient prolongation of APTT, slightly increased bilirubin. Gastrointestinal symptoms.
Other risk factors, such as other diseases or the debilitated condition of the patient, may contribute to the severity of the symptoms and may, in very rare cases, lead to a fatal outcome.

Treatment
Treatment is symptomatic and involves monitoring and supporting vital functions, such as heart function and breathing.
If relevant, gastric lavage, charcoal. Flumazenil can reverse CNS and respiratory depression and is mainly indicated in severe poisoning to avoid intubation and respiratory care. Note that the duration of action of flumazenil is shorter than that of zopiclone. Symptomatic treatment. (Hemodialysis is not of value as zopiclone has a large volume of distribution).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and sedatives, benzodiazepine related drugs, ATC code: N05CF01.

The active substance of <product name> is zopiclone which belongs to the group of cyclopyrrolones, which structurally differ from other hypnotic agents.
The pharmacological properties are: hypnotic, sedative, anxiolytic, antispasmodic and muscle relaxant.

Mechanism of action

Like benzodiazepines, zopiclone binds with high affinity to the macromolecular GABA receptor complex and induces specific conformational changes, thus increasing the normal transmission of the signal substance GABA in the central nervous system.

Clinical efficacy and safety

Zopiclone has a rapid onset of action (within about 30 minutes), shortens sleep onset latency, prolongs sleep duration and reduces the number of awakenings during the night. The amount of REM sleep and deep sleep (stages III and IV) remains constant at the recommended dose.

Development of tolerance to the hypnotic effect has not been established.

5.2 Pharmacokinetic properties

Absorption
The bioavailability of zopiclone is about 80%. Peak plasma concentration is reached within 1.5-2 hours and is about 30 and 60 ng/ml after a dose of 3.75 mg, and 7.5 mg respectively. Absorption is the same in women and men and is not affected by simultaneous food intake.
Absorption may be prolonged if zopiclone is not taken in an upright position.

Distribution

Zopiclone is rapidly distributed from the bloodstream. The volume of distribution is 1.3 l/kg and the degree of protein binding is approximately 45% and not saturable. Less than 1% of the dose ingested by the mother can be expected to reach a nursing infant via breast milk.

Biotransformation
No accumulation occurs after repeated dosing and individual differences appear insignificant.
Zopiclone is extensively metabolized in the liver by decarboxylation.
About 11% is converted to N-oxide-zopiclone, which is less active than the parent substance and without clinical significance, and about 15% is converted to inactive N-desmethyl-zopiclone. The respective apparent half-lives are approximately 4.5 and 7.4 hours respectively.

Elimination
The low renal clearance of zopiclone (average 8.4 ml/minute) compared to plasma clearance (232 ml/minute) suggests that zopiclone is mainly eliminated by metabolism.

The half-life is 5 hours, increased to 7 hours in elderly people. No accumulation of zopiclone in plasma in elderly patients after repeated dosing during clinical trials has been detected.
Plasma clearance is reduced by approximately 40% in patients with liver cirrhosis due to the slower methylation process and therefore the dose should be adjusted for these patients. In patients with renal insufficiency, no accumulation of zopiclone, which also crosses dialysis membranes, or its metabolites has been detected after prolonged administration.

Approximately 80% of all zopiclone is excreted in the urine, mainly in the form of unconjugated metabolites (N-oxide and N-desmethyl derivatives). About 16% is excreted in faeces.

5.3 Preclinical safety data

No special data.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Calcium hydrogen phosphate dihydrate
Maize starch
Carmellose sodium
Magnesium stearate
Titanium dioxide (E171)
Hypromellose

5 mg tablets also contain yellow iron oxide (E172) and macrogol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Tablets 5 mg: 4 years
Tablets 7.5 mg: 3 years

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

PVC/PVDC/aluminium blister: 10, 30, 100 and 50x1 tablets (single dose)
HDPE plastic container: 500 tablets (only for dose dispensing and hospital use).

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBERS

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2024-09-19
[To be completed nationally]