

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zorclone 7.5 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 7.5mg zopiclone.

Excipients with known effect:

Each film coated tablet contains 30.8mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

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 tablets can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

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

4.2 Posology and method of administration

Posology

Treatment should be as short as possible. Generally the duration of treatment varies from a few days to two weeks with a maximum, including tapering off 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. The product should be taken just before retiring for the night.

Dose:

The recommended dose is 7.5 mg. This dose should not be exceeded.

Elderly:

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

Patients with hepatic insufficiency:

As elimination of zopiclone may be reduced in patients with hepatic dysfunction, a lower dose of 3.75 mg zopiclone is recommended.

Patients with renal insufficiency:

Although in cases of renal insufficiency no accumulation of zopiclone or its metabolites has been detected, it is recommended that patients with impaired renal function should start treatment with 3.75 mg.

Patients with chronic respiratory insufficiency:

Treatment should be initiated on a dose of 3.75 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.

4.3 Contraindications

- Hypersensitivity to zopiclone or to any of the excipients listed in section 6.1.
- Myasthenia gravis.
- Severe respiratory insufficiency.
- Sleep apnoea syndrome.
- Severe hepatic insufficiency.
- Use in children aged less than 18 years.

4.4 Special warnings and precautions for use

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

Tolerance

Some loss of efficacy to the hypnotic effects of 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 for treatment periods of up to 4 weeks.

Dependence

Use of benzodiazepines and benzodiazepine-like agents may lead to the development of physical and psychological dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion, insomnia and irritability. In severe cases the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound insomnia

A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine and benzodiazepine-like agents recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness.

Since the risk of withdrawal phenomena/rebound phenomena is greater after prolonged treatment, or abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Duration of treatment

The duration of treatment should employ the lowest effective dose and should be as short as possible (see section 4.2) depending on the indication, but should not exceed 4 weeks for insomnia including tapering off process. Extension 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. Moreover 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 medicinal product is being discontinued.

There are indications that, in the case of benzodiazepines and benzodiazepine-like agents with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

Amnesia

Benzodiazepines and benzodiazepine-like agents may induce anterograde amnesia especially when sleep is interrupted or when retiring to bed is delayed after taking the tablet. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see also Section 4.8).

Psychiatric and 'paradoxical' reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines and benzodiazepine-like agents (see also Section 4.8). Should this occur, use of the drug should be discontinued.

These reactions are more likely to occur in children and the elderly.

Risk from concomitant use of opioids

Concomitant use of zopiclone 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 with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe zopiclone 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 "Posology and method of administration"). 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 "Interaction with other medicinal products and other forms of interaction").

Somnambulism and associated behaviour

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. 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 "Interactions with other medicinal products and other forms of interactions").

Specific patient groups

Elderly should be given a reduced dose (see section 4.2). A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Due to the myorelaxant effects there is a risk of falls and consequently of hip fractures in the elderly.

Benzodiazepines and benzodiazepine-like agents are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.

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

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 extreme caution in patients with a history of alcohol or drug abuse.

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.

Excipient(s)

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

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 interactions

Not recommended

Concomitant intake with alcohol

The sedative effect may be enhanced when the product 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, anti-epileptic drugs, anaesthetics and sedative antihistamines.

In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychological dependence.

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as zopiclone 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 "Special warnings and precautions for use").

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

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450), may enhance the activity of benzodiazepines and benzodiazepine-like agents. To a lesser degree this also applies to benzodiazepines and benzodiazepine-like agents that are metabolised only by conjugation."

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 the presence of erythromycin which indicates that erythromycin can inhibit the metabolism of drugs metabolised by CYP 3A4. As a consequence, the hypnotic effect of zopiclone may be enhanced.

Since zopiclone is mainly metabolised by CYP3 A4, the plasma levels of zopiclone and thus the effect of zopiclone may be increased when used in combination with drugs which inhibit CYP 3A4, such as macrolide antibiotics,azole antimycotics and HIV protease inhibitors, as well as grape fruit juice. Dose reduction should be considered if zopiclone is co-administered with CYP 3A4 inhibitors. Drugs which induce CYP 3A4, like phenobarbital, phenytoin, carbamazepine, rifampicin and products containing St. John's wort, may reduce zopiclone plasma levels and thus the effect of zopiclone.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of use in pregnant women and during lactation has not been established. Studies in animals have shown reproductive toxicity (see section 5.3).

Use in pregnancy is not recommended.

If the product is prescribed to a woman of child bearing potential, she should be advised to contact her physician about stopping the product if she intends to become pregnant, or suspects that she is pregnant.

Administration of the medicinal product during the last three months of pregnancy or during labour is only allowed on strict medical indication as, due to the pharmacological action of the product, with effects on the neonate, such as hypothermia, hypotonia, feeding difficulties ('floppy infant syndrome'), and respiratory depression can be expected.

Moreover infants born to mothers who took benzodiazepines or benzodiazepine-like agents chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

Breast-feeding

Since benzodiazepine and benzodiazepine-like agents are found in the breast milk, zopiclone should not be administered to breast-feeding mothers.

Fertility

Impaired fertility has been observed in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Zorclon has major influence on the ability to drive and use machines.

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. The likelihood of impaired alertness may be increased with concomitant alcohol intake or after insufficient sleep duration, (see also Interactions, section 4.5). Patients should be advised not to drive or operate machinery until it is established that their performance is not impaired.

The patient should be careful as these above effects can remain until the following morning.

4.8 Undesirable effects

Undesirable effects reported are listed according to the following frequency: very common ($\geq 1/10$); common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1000$); very rare ($\leq 1/10,000$), not known (cannot be estimated from the available data).

Immune system disorders

Very rare: anaphylactic reactions

Psychiatric disorders

Rare: confusion*, depression, restlessness, agitation, irritability, aggression, delusions, rages, nightmares, hallucinations, psychoses, inappropriate behaviour, other behavioural disturbances and somnambulism(see section 4.4 "Special warnings and precautions for use")

Very rare: change in libido.

Not known: Physical and psychological dependence, numbed emotions*

See also below under "Depression", "Psychiatric and paradoxical reactions" and "Dependence".

Nervous system disorders

Common: Sleepiness during the following day, reduced alertness, a bitter taste or metallic after-taste is the most common adverse reaction of zopiclone

Uncommon: Headache, dizziness

Rare: Amnesia, light headedness

Not known: Incoordination, ataxia *

See also below under "Amnesia"

Eye disorders

Rare: double vision*.

Gastrointestinal disorders

Rare: Dry mouth, dyspepsia, gastrointestinal problems, including nausea and vomiting

Skin and subcutaneous tissue disorders

Rare: skin reactions, including urticaria.

Very rare: Angioedema

Musculoskeletal and connective tissue disorders

Rare: muscle weakness*.

General disorders and administration site conditions

Rare: tiredness.

Investigations

Very rare: mild to moderate increases in serum transaminases and/or alkaline phosphatase.

Injury and poisoning

Rare: fall (predominantly in older people).

*These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration.

Amnesia

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. This undesirable effect has been observed rarely. Amnesic effects may be associated with inappropriate behaviour (see section 4.4 "Special warnings and special precautions for use").

Depression

Pre-existing depression may be unmasked during benzodiazepines and benzodiazepine-like agents use.(see section 4.4 "Special warnings and special precautions for use").

Psychiatric and 'paradoxical' reactions

Reactions like restlessness agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines and benzodiazepine-like agents. They may be quite severe with this product but long experience is still lacking. They are more likely to occur in children and the elderly.

Dependence

Use (even at therapeutic doses) may lead to the development of physical dependence. Psychological dependence may occur. Misuse has been reported. Abuse of benzodiazepines and benzodiazepine-like agents has been reported. Discontinuation of the therapy may result in withdrawal or rebound phenomena. Withdrawal syndrome has been reported upon discontinuation of zopiclone (see section 4.4). Withdrawal symptoms vary and may include rebound insomnia, anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, hallucinations, and irritability. In very rare cases seizures may occur.

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 HPRC Pharmacovigilance website: www.hpra.ie.

4.9 Overdose

As with other benzodiazepines and benzodiazepine-like agents, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol).

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

Following overdose with any medicinal product, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption.

Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Overdose of benzodiazepines and benzodiazepine-like agents is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma, depending on the amount ingested

In mild cases, symptoms include drowsiness, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, methaemoglobinaemia, respiratory depression, rarely coma and very rarely death.

Treatment should be aimed at supporting vital functions and is chiefly symptomatic (e.g. monitor the heart function and respiration). Gastric lavage or activated charcoal is only useful shortly after ingestion.

Haemodialysis is not useful because of the high distribution volume of zopiclone. Flumazenil may be useful as an antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-code: N05C F01

Zopiclone is a benzodiazepine - like hypnotic agent, a member of the cyclopyrrolone group of compounds. Its pharmacological properties are: anxiolytic, sedative, hypnotic, anticonvulsant, and muscle-relaxant.

These effects are related to a specific agonist action at central receptors belonging to the GABA-omega (BZ1 + 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 1h30 to 2h and they are approximately 30, 60 and 115 ng/ml after administration of 3.75 mg and 15 mg respectively. Absorption is not modified by sex, 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 a very little risk of drug interactions due to protein binding.

Plasma level decrease: between 3.75 and 15mg, the decrease in plasma level does not depend on the dose. The elimination half life is approximately 5 h.

After repeated administration, there is no accumulation and inter individual variations appeared to be very low.

During lactation, the kinetic profiles of zopiclone in breast milk and in plasma are similar. The estimated percentage of the dose ingested by a nursing child would not exceed 0.2% of the dose administered to the mother over 24 h.

Biotransformation

Among the metabolites, the main ones are the N-oxide derivative (pharmacologically active in animals) and the N-Desmethyl metabolite (pharmacologically inactive in animals).

Their apparent half-lives evaluated from the urinary data are approximately 4h30 and 1h30 respectively, in accord with the fact that they do not significantly accumulate on repeated dosing (15mg) 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 8.4 ml/mn) compared with the plasma clearance (232 ml/mn) 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-demethyl derivatives) and in the faeces (Approximately 16%).

Physio-pathological variations

In elderly patients, notwithstanding a slight decrease in hepatic metabolism and a lengthening of elimination half-life to approximately 7 hours, various studies have failed to show plasma accumulation of zopiclone or of its metabolites has been detected after prolonged administration. Zopiclone crosses the dialysing membrane.

In patients with liver cirrhosis, 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

Hepatotoxic effects were elicited in repeated dose toxicity studies conducted in rats and dogs. In dogs anaemia were evident in some studies.

Mutagenicity and carcinogenicity

Zopiclone did not show a mutagenic potential *in vitro* and *in vivo*. Increased incidence of mammary carcinomas in female rats, at high multiples of the maximum plasma concentrations from therapeutic doses in human, has been attributed to increased 17-beta-estradiol serum levels. Increased incidence in thyroid tumours in rats were associated with increased TSH levels. In humans, zopiclone has no effects on thyroid hormones and therefore this finding is not considered clinically relevant.

Reproductive toxicity

Fertility was impaired in two rat studies, whereas zopiclone had no adverse effects on fertility in rabbits.

Foetal developmental retardations and foetotoxic effects in rats and rabbits were observed only at doses well above the maximum human dosage. There was no evidence of a teratogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The following active ingredients are used in Zorclone 7.5mg Film-Coated tablets:

Core:

Lactose monohydrate
Calcium hydrogen phosphate dihydrate
Maize starch
Croscarmellose sodium
Magnesium stearate

Film Coat

Titanium dioxide (E171)
Hypromellose (E464)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package.

6.5 Nature and contents of container

Lithographed carton boxes containing 1, 3 or 6 PVC/PVDC/A1 blister strips of 10 tablets, and lithographed carton boxes containing 1, 2 or 4 PVC/PVDC/A1 blister strips of 14 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/080/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th June 1999

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10 DATE OF REVISION OF THE TEXT

July 2022