SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zopitan 3.75 mg Film-coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains zopiclone 3.75 mg.

Excipient with known effect
Contains lactose monohydrate 30.8 mg.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet.

Orange, round, biconvex, film-coated tablets with a diameter of approximately 7.0 mm and a height of 3.5-4.0 mm. Embossed with "Zoc 3.75" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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.

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

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

Treatment of the elderly and patients with impaired liver function or chronic respiratory insufficiency should be initiated on a dose of 3.75 mg. Although in case of renal insufficiency no accumulation of zopiclone or of its metabolites has been detected, it is recommended that patients with impaired renal function should start treatment with 3.75 mg.

Method of administration

Oral.

4.3 Contraindications

Hypersensitivity to zopiclone to the active substance 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.

4.4 Special warnings and precautions for use

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 psychic 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 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
Rebound insomnia is 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 abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Duration of treatment
The duration of treatment should be as short as possible (see Posology) 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 revaluation 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. 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 Undesirable Effects).

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. Should this occur, use of the drug 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. 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).

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 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).

Specific patient groups:

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

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

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.

Excipients
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 dosage unit, 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 psychic dependence.

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 indicated 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 metabolised by the cytochrome P450 (CYP) 3A4 isoenzyme (see section 5.2 pharmacokinetics), plasma levels may be increased when co-administered with CYP 3A4 inhibitors, such as erythromycin, clarithromycin, ketoconazole, itraconazole and ritonavir. A dose reduction for zopiclone may be required when it is administered with CYP 3A4 inhibitors. Conversely, plasma levels of zopiclone may be decreased when co-administered with CYP 3A4 inducers, such as rifampicin, carbamazepine, phenobarbital, phenytoin and St. John's wort. A dose increase for zopiclone may be required when it is co-administered with CYP 3A4 inducers.

Opioids:
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).

4.6 Fertility, pregnancy and lactation

Insufficient data are available on zopiclone to assess its safety during pregnancy and lactation, therefore its use is not recommended.

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.

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, effects on the neonate, such as hypothermia, hypotonia and moderate 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.

4.7 Effects on 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. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see also Interactions). Patients should be advised not to drive or operate machinery until it is established that their performance is not impaired.

4.8 Undesirable effects

For this product no modern clinical documentation is available to determine frequency of adverse effects.

Bitter taste is the most common side effect observed with zopiclone.

	Frequency	
MedDRA SOC	**Very rare (<1/10,000)**	**Not known**
Investigations	Transaminases increased, alkaline phosphatase increased (changes in liver function detected by a blood test)	
Nervous system disorders		Taste bitter, drowsiness, alertness decreased, confusion, headache, dizziness, muscle weakness, ataxia, double vision, anterograde amnesia
Gastrointestinal disorders		Gastrointestinal disorder, dyspepsia, nausea, dry mouth
General disorders and administration site conditions		Fatigue
Musculoskeletal and connective tissue disorders		Muscle weakeness*
Immune system disorders	Angioedema (rapid swelling of face, tongue or throat which can cause breathing and swallowing problems) anaphylactic reaction (a life-threatening type of allergic reaction	Allergic reactions (such as pruritus or rash)
Psychiatric disorders		Affective blunting, libido disorder, restlessness, agitation, irritability, aggressiveness, delusion, rage, nightmare, hallucination, psychosis, abnormal behaviour, drug dependence physical, drug dependence psychic, sleep walking

* Due to the myrolexant effect there is a risk of falls and consequently fractures in the elderly.

Drowsiness, affective blunting, alertness decreased, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or double vision occur predominantly at the start of the therapy and usually disappear with repeated administration.

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour (see Section 4.4).

Pre-existing depression may be unmasked during benzodiazepines and benzodiazepine-like agents use.

Reactions like restlessness agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychosis and abnormal behaviour are more likely to occur in children and the elderly.

Dependence
Use (even at therapeutic doses) may lead to the development of physical dependence. Psychic dependence may occur.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@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.

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

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 the debilitated state of the patient may contribute to the severity of symptoms and very rarely can result in fatal outcome.

Methaemoglobinaemia has been reported to occur in a number of cases of zopiclone overdose.

Symptomatic and supportive treatment in an adequate clinical environment is recommended, attention should be paid to the respiratory and cardiovascular functions. Gastric lavage is only useful when performed soon after ingestion. Haemodialysis is of no value due to the large volume of distribution of zopiclone. Flumazenil may be useful as an antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotic and sedatives; benzodiazepine related drugs,
ATC code: N05CF01

Zopiclone is a benzodiazepine-like hypnotic agent, a member of the cyclopyrrolone group of compounds. Its pharmacological properties are: anxiolytic, sedative, hypnotic, anticonvulsant, 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 and 60 ng/ml after administration of 3.75 mg and 7.5 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/min) compared with the plasma clearance (232 ml/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-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 after prolonged administration. Zopiclone crosses the dialysing membrane.

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

No information submitted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose (monohydrate)
Calcium hydrogen phosphate (dihydrate)
Maize starch
Carmellose sodium
Magnesium stearate

Film-coating:
Titanium dioxide (E171)
Hypromellose
Iron oxide yellow (E172)
Iron oxide red (E172)
Macrogol

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 to protect from moisture.

6.5 Nature and contents of container

Lithographed carton boxes containing 1, 3 or 6 PVC/PVDC/Al blister strips of 10 tablets, and lithographed carton boxes containing 1, 2 or 4 PVC/PVDC/Al blister strips of 14 tablets. Each box contains a patient insert.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd

Clonmel
Co. Tipperary

8. MARKETING AUTHORISATION NUMBER

PA 126/104/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 25th June 1999
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