Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zileze 3.75 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Zopiclone 3.75 mg.

Excipients: Each tablet contains 30.8mg of lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet. (Short term: tablets)

Orange, round, biconvex, film-coated tablets embossed with “Zoc 3.75” on one side.

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

Method of administration

Oral

Treatment should be as short as possible. The duration of treatment, including a tapering off period, should not exceed 4 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. Long-term continuous use is not recommended.

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.

Posology

Adults:
The usual dose of zopiclone in healthy adults is 7.5 mg, taken orally 30 to 60 minutes before retiring.

The Elderly:
An initial dose of 3.75 mg is recommended. This can be increased, if necessary, to 7.5 mg per day.

Use in patients with renal & hepatic impairment:
In general, in patients who have a decrease in renal and/or hepatic function, the dose should be kept to a minimum. In patients with mild hepatic and mild to moderate renal insufficiency, a daily dose of 3.75 mg should be used with caution. In patients with severe hepatic and renal insufficiency a daily dose of 3.75 mg should not be exceeded.

Chronic respiratory insufficiency:
In patients with chronic respiratory insufficiency, a starting dose of 3.75 mg zopiclone is recommended initially. The dosage subsequently may be increased 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.

4.3 Contraindications

- Hypersensitivity to zopiclone or any other excipient in the tablet (listed in section 6.1)
- Myasthenia gravis
- Severe sleep apnoea
- Severe respiratory insufficiency
- Severe hepatic insufficiency

4.4 Special warnings and precautions for use

Tolerance:
Development of tolerance with zopiclone is unlikely with treatment periods of up to 4 weeks.

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.

Risk of Dependence:
Use of benzodiazepines and benzodiazepine – like agents (even at therapeutic doses) may lead to the development of physical and psychic dependence or abuse upon these products. 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 or drug abuse and those patients who have marked personality disorders.

The decision to use a hypnotic in such patients should be taken only with this clearly in mind.
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: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rare cases of abuse have been reported.

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 therefore, recommended that the dosage is decreased gradually.

A course of treatment should employ the lowest effective dose for the minimum length of time necessary for effective treatment. See Posology for guidance on possible treatment regimen. A course of treatment should not continue for longer than 4 weeks including any tapering off (see section 4.8).

Duration of treatment:
A course of treatment should employ the lowest effective dose for the minimum length of time necessary for effective treatment. See Posology for guidance on possible treatment regimen. A course of treatment should not continue for longer than 4 weeks including any tapering off (see section 4.8). 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:
Amnesia is rare, but anterograde amnesia may occur, especially when sleep is interrupted or when retiring to bed is delayed after taking the tablet. Therefore to reduce the possibility of anterograde amnesia, patients should ensure that they take the tablet when certain of retiring for the night and they are able to have a full night's sleep (uninterrupted sleep of about 7 to 8 hours).

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:
Other psychiatric and paradoxical reactions have been reported (see section 4.8), 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 most 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 Interactions with other medicinal products and other forms of interactions).

Specific patient groups:

Use in hepatic insufficiency
A reduced dosage is recommended, see Posology. Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy (see section 4.3)

Use in renal insufficiency
A reduced dosage is recommended, see Posology.

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 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.

Use in Elderly patients
Elderly should be given a reduced dose (see section 4.2)

Benzodiazepines and benzodiazepine - like agents are not recommended for the primary treatment of psychotic illness. Benzodiazepines and benzodiazepines - 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, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Withdrawal
The termination of treatment with Zileze is unlikely to be associated with withdrawal effects when duration of treatment is limited to 4 weeks. Patients may benefit from tapering off the dose before discontinuation (see section 4.8.).

Depression
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). Any underlying cause of the insomnia should also be addressed before symptomatic treatment to avoid under treating potentially serious effects of depression.

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 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 analgesic, 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 indicates that erythromycin can inhibit the metabolism of drugs metabolised by CYP 3A4. Quinupristin/dalfopristin may also inhibit the metabolism of zopiclone. 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
Use of zopiclone in pregnancy is not recommended since insufficient data exist on the use of zopiclone during pregnancy in humans. Animal studies have shown that zopiclone only partially crosses the placenta and does not cause any teratogenic effects.

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.

Administration of zopiclone during the last three months of pregnancy is only allowed on strict medical indication as due to the pharmacological action of the product, effects on the neonate, such as hypothermia, hypnotic 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.

Lactation
Zopiclone and its metabolites are excreted in breast milk. Although calculations have shown that the dose that would be received by the neonate corresponds to 1.4% of the maternal dose, 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. Patients should be advised not to drive or operate machinery until it is established that their performance is not impaired.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

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).

System organ class	Frequency	Adverse reaction
Immune system disorders	Very rare	angiooedema, anaphylactic reaction
Psychiatric disorders	Uncommon	nightmare, agitation
	Rare	confusional state, libido disorder, irritability, aggression, hallucination
	Not known	restlessness, delusion, anger, depressed mood, abnormal behaviour (possibly associated with amnesia) and somnambulism (see section 4.4: somnambulism and associated behaviour), dependence (see section 4.4), withdrawal syndrome (see below), affective blunting, psychosis

Nervous system disorders	Common	dysgeusia (Bitter taste), somnolence (residual)
	Uncommon	dizziness, headache
	Rare	anterograde amnesia
	Not known	ataxia, paraesthesia, cognitive disorders such as memory impairment, disturbance in attention, speech disorder, double vision
Eye disorders	Not known	diplopia
Respiratory, thoracic and mediastinal disorders	Rare	dyspnoea (see section 4.4)
	Not known	respiratory depression (see section 4.4)
Gastrointestinal disorders	Common	dry mouth
	Uncommon	nausea, vomiting
	Not known	dyspepsia
Hepatobiliary disorders	Very rare	transaminases increased and/or blood alkaline phosphatase increased (mild to moderate)
Skin and subcutaneous tissue disorders	Rare	urticaria or rash, pruritus
Musculoskeletal and connective tissue disorders	Not known	muscular weakness
General disorders and administration site conditions	Uncommon	fatigue
	Not known	light headedness, incoordination
Injury, poisoning and procedural complications	Rare	fall (predominantly in elderly patients)

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 Special warnings and precautions for use).*

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 4.4, Special warnings and precautions for use)*.

Withdrawal symptoms vary and may include rebound insomnia, muscle pain, anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, hallucinations, panic attacks, muscle aches/cramps, gastrointestinal disturbances and irritability.

In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations. 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.

The fatal dose of zopiclone is not known.

Symptoms

In the cases of overdosage reported the main effects are drowsiness, lethargy and ataxia. Rarely, A-V block has occurred.

Management

Consider activated charcoal if an adult has ingested more than 150mg or a child more than 1.5 mg/kg within 1 hour. Alternatively consider gastric lavage in adults within 1 hour of a potentially life-threatening overdose. If CNS depression is severe consider the use of flumazenil. It has a short half-life (about an hour). It should not be used in mixed overdose or as a “diagnostic” test. Management should include general symptomatic and supportive measures including a clear airway and monitoring cardiac and vital signs until stable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: hypnotics and sedatives; ATC code: N05C F01

Zopiclone is a cyclopyrrolone which possesses similar sedative, anxiolytic, muscle relaxant and anticonvulsant properties as the benzodiazepines. Zopiclone recognises specifically and with high affinity the central receptors of the $GABA_A$-benzodiazepine chloride channel macromolecular receptor complex in the central nervous system. After binding of zopiclone to this receptor complex (at a site distinct from, but closely related to the benzodiazepine binding site), the affinity of the receptor complex for GABA increases. Binding of GABA to the complex induces opening of the chloride channels, through which hyperpolarisation of the cell membrane and inhibition of the neurons takes place.

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 and 60 ng/ml after administration of 3.75mg and 7.5mg respectively. Absorption is not modified by gender, food 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. The volume of distribution is 91.8 - 104.6 litres.

At doses between 3.75 - 15mg, 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.

Metabolism: Zopiclone is exensively 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 (15mg) for 14 days. In animals, no enzyme induction has been observed even at high doses.

Excretion: 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 patient groups: 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. 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 preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Calcium hydrogen phosphate
Maize starch
Croscarmellose sodium
Magnesium stearate
Titanium dioxide (E171)
Hypromellose (E464)
Iron oxide yellow (E172)
Iron oxide red (E172)
Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/PVDC/A1 - 2 years

6.4 Special precautions for storage

Do not store above 25°C. Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

PVC/PVDC/Al blister strips.

Each pack contains 28, 30, 56 or 60 Tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Chiesi Limited
333 Styal Road
Manchester
M22 5LG
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0743/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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