Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zimoclone 7.5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 7.5 mg of the active ingredient zopiclone.

Excipient with known effect
Each film-coated tablet contains 30.8 mg lactose.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White, film-coated, oval tablet with a breakline, marked with "ZZ" on one side and "7.5" on the other.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zimoclone 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. Long term continuous use is not recommended. A course of treatment should employ the lowest effective dose.

4.2 Posology and method of administration

The lowest effective dose should be used.

Zopiclone should be taken in a single dose and not re-administered during the same night.

Treatment duration
Treatment with zopiclone should be as short as possible. Generally the duration of treatment varies from a few days to two weeks with a maximum, including the tapering off, of four weeks.

In certain cases an extension beyond the maximum treatment period may be necessary; if so it should take place after re-evaluation of the patient's status (see section 4.4).

Posology
Adults:
The recommended dose for adults is 1 tablet (7.5 mg zopiclone). This dose should not be exceeded. The tablet should be taken just before retiring.

Impaired renal function:
Although accumulation of zopiclone and/or its metabolites has not been shown in patients with impaired renal function, a starting dose of 3.75 mg is recommended in these patients.

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

The standard dose of 7.5 mg zopiclone may be used with caution in some cases depending on effectiveness and acceptability.

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.

Elderly:
A starting dose of 3.75 mg is recommended, this dose may consequently be increased to 7.5 mg if considered clinically necessary depending on patient effectiveness and acceptability (see section 4.4).

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
Zopiclone is for oral use only.

4.3 Contraindications

Zimoclone is contraindicated in patients with any of the following:

- Hypersensitivity to zopiclone or to any of the excipients listed in section 6.1
- Myasthenia gravis
- Severe hepatic impairment
- Sleep apnoea syndrome
- Respiratory failure

Zopiclone should not be given to children or adolescents younger than 18 years of age.

4.4 Special warnings and precautions for use

The cause of insomnia should be identified wherever possible the underlying factors treated before a hypnotic is prescribed.

Risk of dependence:
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, however, as with the benzodiazepines and other benzodiazepine-like drugs (even at therapeutic doses), there is a risk of physical and psychological dependence or abuse. This risk increases with dose and length of treatment and use with alcohol or other psychotropics. Patients with a history of alcohol and/or drug abuse or those with personality disorders are more at risk of dependence and this should be considered when prescribing zopiclone. If a patient does become dependent, abrupt cessation of treatment may result in withdrawal symptoms including: extreme anxiety, headaches, muscle pain, tension, confusion and restlessness and irritability. In severe cases symptoms may also include depersonalisation, derealisation, numbness and tingling of the extremities, hypersensitivity to noise, light and physical contact, hallucinations or epileptic seizures.

Rare cases of abuse have been reported.

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

Depression:
Benzodiazepines and benzodiazepine-like substances, such as zopiclone, are not recommended as the primary treatment of psychoses.

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 overdosage 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.

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

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 no marked tolerance occurred during treatment periods of up to four weeks.

Rebound insomnia:
A transient syndrome where the symptoms which led to treatment with a benzodiazepine or benzodiazepine-like agent recur in an enhanced form on discontinuation of therapy. It may be accompanied by other reactions including mood changes, anxiety and restlessness. Since the risk of withdrawal/rebound phenomena may be increased after prolonged treatment, or abrupt discontinuation of therapy, it is therefore, recommended to decrease the dosage gradually and to advise the patient accordingly.

A course of treatment should employ the lowest effective dose for the minimum length of time necessary for the effective treatment. See section 4.2 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).

Amnesia:
Amnesia is rare, but anterograde amnesia may occur, especially if sleep is interrupted or when retiring to bed is delayed after taking the tablet. Situations when this might occur should therefore be avoided and the patient should ensure that 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.

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).

Psychiatric and 'paradoxical' reactions:
It is known that reactions such as restlessness, agitation, irritability, aggression, delusion, outbursts of rage, nightmares, hallucinations, psychoses, unsuitable behaviour and other behavioural disturbances may occur during the use of

benzodiazepines and benzodiazepine-like substances. If this is the case administration of the medicinal product should be discontinued. These reactions are more likely to occur in the elderly.

Somnambulism and associated behaviours:
Sleepwalking 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. It appears that there is an increased risk of such behaviour with the concomitant use of alcohol, other CNS depressants or the use of zopiclone at doses exceeding the maximum recommended dose. If such behaviours are reported, administration of zopiclone should be discontinued (see section 4.5).

Specific patient groups:
Zopiclone should be used with extreme caution in patients with a history of alcohol or drug abuse.

Use in elderly
Hypnotics should be avoided in the elderly who are at risk of becoming ataxic and confused and so liable to fall and injure themselves. If, based on clinical need, a decision to treat is nevertheless taken, treatment should be initiated at a lower dose (see section 4.2) and co-administration of zopiclone with CYP3A4 inhibitors should be avoided (see section 4.5).

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 advised for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Use in hepatic insufficiency
A reduced dosage is recommended, (see section 4.2). Benzodiazepines and benzodiazepine-like substances are not suitable for the treatment of patients with severe hepatic insufficiency, since they may promote the occurrence of encephalopathy (see section 4.3).

Use in renal insufficiency
A reduced dosage is recommended (see section 4.2).

Period of treatment:
The period 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 condition. 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 point out to the patient the possibility of the occurrence of rebound phenomena in order to keep to a minimum any worries about the occurrence of such symptoms during the tapering off period of the treatment. In the case of benzodiazepines and benzodiazepine-like substances with a short period of action, there are indications that withdrawal symptoms may occur within the dosage interval, especially if the dose is high.

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.

Excipients:
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol may enhance the sedative effect of zopiclone, this may persist to the following morning and could affect the patient's ability to drive or use machinery. Concurrent use is therefore not recommended.

Central depressive effects may be enhanced when zopiclone is used in combination with CNS depressants. Therefore, the therapeutic benefit of co-administration with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative antihistamines should therefore be carefully considered.

Use of benzodiazepine-like drugs in combination with narcotic analgesics may enhance their euphoric effects, which may in turn increase the risk of dependency.

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).

The activity of zopiclone may be increased when used in combination with drugs which inhibit hepatic enzymes (in particular cytochrome P_{450})

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 presence of erythromycin which indicates that erythromycin can inhibit the metabolism of drugs metabolised by CYP3A4. 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), plasma levels of zopiclone may be increased when co-administered with CYP3A4 inhibitors such as erythromycin, clarithromycin, ketoconazole, itraconazole, fluconazole, tacrolimus and ritonavir. Co-administration of zopiclone with CYP3A4 inhibitors should be avoided in the elderly (see section 4.4). For all other patients, a dose reduction for zopiclone may be required when it is co-administered with CYP3A4 inhibitors.

Conversely, plasma levels of zopiclone may be decreased when co-administered with CYP3A4 inducers such as rifampicin, nefazodone, phenobarbital, phenytoin and St John's wort. A dose increase for zopiclone may be required when it is co-administered with CYP3A4 inducers.

A single dose study has indicated that when zopiclone and carbamazepine are taken in combination, their sedative effects are additive. However, as carbamazepine is a potent inducer of CYP3A4, it is predicted that long term use of carbamazepine could result in a reduction of zopiclone plasma levels and reduce its hypnotic effects accordingly.

Metoclopramide increases and atropine decreases concentration of zopiclone in plasma.

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

4.6 Fertility, pregnancy and lactation

Insufficient data are available on zopiclone to assess its safety during pregnancy and lactation in humans.

Pregnancy

Zopiclone should not be used during pregnancy unless clearly necessary.

To date zopiclone has not produced injurious effects in animal studies except at very high maternally toxic doses.

Any woman of child-bearing potential prescribed zopiclone, should be advised to consult her physician about discontinuing use of zopiclone in the event that she wishes to, or suspects that she has, become pregnant.

If zopiclone is administered during the last three months of pregnancy or during labour, effects on the neonate such as hypothermia, hypotonia, moderate respiratory depression, decreased muscle tone and suckling reflex (“floppy infant syndrome”) can be expected. Infants born to mothers who took benzodiazepines or benzodiazepine-like agents chronically during the later stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Breast-feeding
Zopiclone is excreted in breast milk, although the concentration of zopiclone in the breast milk is low, use in nursing mothers must be avoided

Fertility

Double-blind long-term studies (7.5 mg zopiclone for 84 days) in healthy volunteers revealed no changes in ejaculate volume, sperm concentration, sperm motility or morphology. In several studies infertility was seen in male animals (see section 5.3).

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. Therefore, patients should not drive or use machinery after taking a dose.

Patients should be advised not to drive or operate machinery the day after treatment until it is established that their performance is unimpaired.

It has been reported that the risk that zopiclone adversely affects driving ability is increased by the concomitant intake of alcohol. Therefore, it is recommended not to drive while taking zopiclone and alcohol concomitantly. This may also affect the patient's ability to drive and use machinery the following morning.

4.8 Undesirable effects

The following undesirable effects have been reported at the approximate frequencies shown: 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)

Immune system disorders

Rare: Allergic reactions including skin reactions

Very rare: Anaphylactic reactions and/or angioedema

Psychiatric disorders

Uncommon: Nightmares, agitation

Rare: Confusional state, numbed emotions, irritability, aggressiveness, hallucinations, psychoses, libido disorder

Not known: Dependency, restlessness, delusion, anger, depressed mood, somnambulism and other abnormal behaviour (possibly associated with amnesia)

See below under 'Depression', 'Psychiatric and paradoxical reactions', 'withdrawal syndrome', 'Somnambulism and associated behaviours' and 'Dependency'.

Nervous system disorders

Common: Somnolence (residual) during the following day, reduced alertness, dysguesia (bitter taste)

Uncommon: Headaches, dizziness

Rare: Anterograde amnesia

See below under 'Amnesia'.

Very rare: Seizures.

Not known: Ataxia (predominantly at the start of therapy and usually disappears with repeated administration), paraesthesia cognitive disorders such as memory impairment, disturbance in attention, speech disorder

Eye disorders

Not known: Diplopia (predominantly at the start of therapy and usually disappears with repeated administration)

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

Rare: Diarrhoea.

Not known: Dyspepsia

Skin and subcutaneous tissue disorders

Rare: Urticaria or rash, pruritis, sweating

Musculoskeletal and connective tissue disorders

Not known: Muscle weakness

General disorders and administration site conditions

Uncommon: Fatigue

Not known: Light headedness, incoordination, unsteadiness

Investigations

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

Injury, poisoning and procedural complications

Rare: Fall (There is a risk of fall and consequently fractures predominantly in elderly patients). (See section 4.4). Withdrawal syndrome has been reported upon discontinuation of zopiclone (see section 4.4). Withdrawal symptoms vary and may include rebound insomnia, muscle pain, anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, hallucinations, tension, restlessness, 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.

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

Depression:
Pre-existing depression may be unmasked during use of benzodiazepines or benzodiazepine-like agents.

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 or benzodiazepine-like products. They are more likely to occur in the elderly.

Somnambulism and associated behaviours:
There is an increased risk of sleepwalking and other associated behaviours with amnesia for the event in patients who have taken zopiclone and were not fully awake (see section 4.4). It appears that there is an increased risk of such behaviour with the concomitant use of alcohol, other CNS depressants and the use of zopiclone at doses exceeding the maximum recommended dose (see section 4.4).

Dependence:
Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see section 4.4). Psychological dependence may occur. Abuse has been reported.

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, Website: www.hpra.ie.

4.9 Overdose

Fatal dose not known.

Symptoms
Symptoms of central nervous system depression which can range from drowsiness to coma according to the quantity ingested. In mild cases, symptoms include drowsiness, confusion and lethargy; in more severe cases, symptoms may include ataxia, hypotonia, hypotension, methaemoglobinaemia, respiratory depression and coma. The effects of overdose may be magnified if combined with alcohol or any other CNS depressants and in severe cases may be life-threatening. 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.

Management
Treatment of overdose should be symptomatic and supportive paying particular attention to respiratory and cardiac functions. Consider activated charcoal if an adult has ingested more than 150 mg or a child more than 1.5 mg/kg within an hour. Alternatively, consider gastric lavage in adults within one 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). NOT TO BE USED IN MIXED OVERDOSE OR AS A 'DIAGNOSTIC' TEST. Haemodialysis does not have any therapeutic effect in cases of zopiclone overdose.

For current practice, refer to local poison centre (or equivalent information sources) regarding management of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotic and sedatives; benzodiazepine related drugs, ATC code: N05C F01.

Zopiclone is a hypnotic agent belonging to the cyclopyrrolone class of psychotherapeutic agents. Although structurally unrelated to the benzodiazepines, zopiclone binds with high affinity and specificity to the $GABA_A$-benzodiazepine chloride channel macromolecular receptor complex. Zopiclone binds to a site different to the benzodiazepines and induces different conformational changes to the receptor complex thus modifying the activity of the chloride ion channel.

Pharmacological properties are: anxiolysis, sedation, hypnosis, anticonvulsion and muscle relaxation.

5.2 Pharmacokinetic properties

Absorption
Zopiclone is swiftly absorbed. Maximum plasma concentrations are achieved after 1½ - 2 hours and are approximately 30 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 or repetition of doses.

Distribution
Zopiclone is swiftly distributed from the vascular compartment. The plasma protein binding is at least 45% and is not saturable.

The decrease in plasma level does not depend on the dose between 3.75 and 15 mg.

The elimination half-life is approximately 5 hours at the recommended doses.

No accumulation occurs after repeated administration and individual differences appear slight.

Less than 1.0% of the dose ingested by the mother is eliminated in breast milk.

Biotransformation
The most important metabolites are the N-oxide derivative (pharmacologically active in animals) and the N-desmethyl metabolite (pharmacologically inactive in animals). Their apparent half-life times are approximately 4.5 hours and 7.4 hours respectively. No significant accumulation of the compound as seen following repeat dosing. (15 mg) for 14 days. In animals, no enzyme induction has been observed even at high doses.

Elimination
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%).

Special patient groups:
In various trials with elderly patients, no accumulation of zopiclone was observed in the plasma after repeated doses, in spite of a slight reduction in the hepatic function and extension of the eliminated half-life to approximately 7 hours.

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

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

5.3 Preclinical safety data

Hepatotoxic effects were observed in repeat dose toxicity studies conducted in rats and dogs. In dogs, anaemia was observed in some studies.

Zopiclone is not mutagenic in either in-vitro or in vivo tests.

Increased incidence of mammary carcinomas in female rats at high multiples of the maximum plasma concentration from therapeutic doses in humans has been attributed to increased 17-beta-estradiol serum levels. Increased incidence of thyroid tumours in rats has been associated with increased TSH serum levels. In humans zopiclone has no effects on thyroid hormones.

Fertility was impaired in two rat studies.

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

Lactose
Calcium hydrogen phosphate
Maize starch
Povidone
Magnesium Stearate
Hypromellose
Titanium dioxide (E171)
Macrogol 400

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

Cartons containing PVC/PVdC/Aluminium blister strips of 5 or 7 tablets, available in packs of 5, 7, 10, 14, 20, 21, 28, 30, 56, 60, 84, 90 and 100 tablets.

Also available in bulk packs of 100 and 500 tablets in a polypropylene container.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Viatris Limited
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Mulhuddart
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8 MARKETING AUTHORISATION NUMBER

PA23266/009/001

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