SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zopiclone 3.75mg Film-coated Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 3.75 mg zopiclone
Excipient: Each film-coated tablet contains 15.91 mg lactose.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-Coated Tablets (Tablets)

Blue coloured, round, biconvex film coated tablets plain on both sides.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Short-term treatment of insomnia in adults, including difficulties in falling asleep, nocturnal awakening and early awakening, transient, situational or chronic insomnia, and insomnia secondary to psychiatric disturbances, in situations where the insomnia is debilitating or is causing severe distress for the patient. Long term continuous use is not recommended. A course of treatment should employ the lowest effective dose.

4.2. Posology and method of administration

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

Adults: The recommended dose for adults is 7.5 mg (two tablets of 3.75 mg or one tablet of 7.5 mg) by the oral route shortly before retiring.

Elderly: A lower dose of 3.75mg 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 3.75mg zopiclone nightly is recommended. The standard dose of 7.5mg zopiclone may be used with caution in some cases, depending on effectiveness and acceptability.

Renal insufficiency:

Although no accumulation of zopiclone or its metabolites have been found in patients with renal insufficiency, it is advisable to begin treatment of patients with reduced renal function at 3.75 mg.

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 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.

Treatment duration
Transient insomnia 2 - 5 days. Short term insomnia 2 - 3 weeks. A single course of treatment should not continue for longer than 4 weeks including any tapering off. . Extension beyond the maximum treatment period should not take place without re-evaluation of the patient's status.
The product should be taken just before retiring for the night.

Route of administration
For oral use. Each tablet should be swallowed without sucking, chewing or breaking

4.3. Contraindications

Zopiclone is contra-indicated in the following cases:
- Hypersensitivity to Zopiclone or to any of the excipients
- Myasthenia gravis
- Respiratory failure
- Severe sleep apnoea syndrome
- Children and adolescents under 18 years of age
- Severe hepatic insufficiency

4.4. Special warnings and precautions for use

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 contraindications)

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 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)

Risk of dependence: Clinical experience to date with Zopiclone suggests that the risk of dependence is minimal when the duration of treatment is limited to not more than 4 weeks.

The use of benzodiazepines and benzodiazepine-like substances (even at therapeutic doses) can lead to the development of physical and psychological dependence or abuse upoon these products. The risk of dependence or abuse increases the higher the dose and the longer the period of treatment; the risk of dependence or abuse is also greater in patient with a history of alcohol or other pshychotropics or drug abuse or those who have marked personality disorders. The decision to use a hypnotic in such patients should be taken only with this clearly in mind. If physical dependence occurs, sudden discontinuation of the treatment will be accompanied by withdrawal symptoms (see warnings and precautions). These may be expressed as 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 or 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 duration of treatment is limited to 4 weeks. Patients may benefit from tapering of the dose before discontinuation. (See also section 4.8. Undesirable Effects).

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 insomnia should be addressed carefully before symptomatic treatment to avoid under treating potentially serious effects of depression.

Rebound insomnia
After discontinuation of treatment with a benzodiazepine or a benzodiazepine-like substance, a temporary syndrome may occur in which the symptoms which led to the treatment with the benzodiazepine or a benzodiazepine-like substance return in a more severe form after discontinuation of therapy. This syndrome may be accompanied by other reactions, including mood changes, anxiety and restlessness. Since the risk of withdrawal symptoms or rebound symptoms is greater after prolonged treatment, or abrupt interruption of the treatment it is advisable to reduce the dosage 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. The period of treatment should be as short as possible but not longer than 4 weeks including the tapering off process (see section 4.8).

Tolerance
The hypnotic effect of short-acting benzodiazepines and benzodiazepine-like substances may diminish after repeated use for a few weeks. For zopiclone however, no pronounced tolerance has occurred during a treatment period of up to 4 weeks.

Amnesia
Amnesia is rare. Benzodiazepines and benzodiazepine-like substances may cause anterograde amnesia, especially when sleep is interrupted or when retiring to bed is delayed after taking the tablet. In order to reduce the risk patients should ensure that they take the tablet when certain of retiring for the night and will be able to have a full night's sleep (an 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, includingimpaired driving ability, is increased if: zopiclone is taken within 12 hours of performing activities that require mentalalertness, a dose higher than the recommended dose is taken, or zopiclone is co-administered with other CNSdepressants, alcohol or with other drugs that increase the blood levels of zopiclone (see section 4.5). Patients should becautioned 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.

Other Psychiatric and paradoxical reactions
Other psychiatric and paradoxical reactions have been reported (see section 4.8 Undesirable effects), like restlessness, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, inappropriate behaviour and other adverse behavioural effects are known to occur when using sedative/hypnotic agents like zopiclone. Should this occur, use of zopiclone 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).

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

4.5. Interaction with other medicinal products and other forms of interaction

Association not recommended:
Concomitant use with alcohol is not recommended because the sedative effect of zopiclone may be intensified when used in combination with alcohol. In particular, this may affect the ability to drive or operate machines.

Associations to be taken in to account:
In combination with CNS depressants an enhancement of the central depressive effect may occur. The therapeutic benefit of co-administration with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines should therefore be carefully weighed. In the case of narcotic analgesics, enhancement of 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.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines and benzodiazepine-like agents. Since zopiclone is metabolised by P450 (CYP)3A4 isoenzyme (see section 5.2 Pharmacokinetic Properties), the plasma levels of zopiclone and thus the effect of zopiclone may be increased when used in combination with drugs which inhibit CYP3A4, such as such as erythromycin, clarithromycin, azole antimycotics such as ketoconazole, itraconazole and ritonavir. Dose reduction should be considered if zopiclone is co-administered with CYP3A4 inhibitors.

Co-administration with Drugs which induce CYP3A4, like phenobarbital, phenytoin, carbamazepine, rifampicin and products containing St John's wort, may reduce zopiclone plasma levels and thus the effect of zopiclone. A dose increase for zopiclone may be required when it is co-administered with CYP3A4 inducers.

The effect of erythromycin on the pharmacokinetics of zopiclone has been studies 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 CYP 3A4. As a consequence, the hypnotic effect of zopiclone may be enhanced.

4.6. Fertility, pregnancy and lactation

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

Pregnancy
Experience of use of zopiclone during pregnancy in humans is limited although there have been no adverse findings in animals. Zopiclone should not be used during pregnancy. 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.

Moreover, if zopiclone is prescribed during the last three months of pregnancy or during labour, due to the pharmacological action of the product, effects on the neonate, such as hypothermia, hypotonia and respiratory depression can be expected

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 of developing withdrawal symptoms in the postnatal period.

Lactation
Zopiclone is excreted in breast milk, although the concentration of zopiclone in the breast milk is low, use in nursing mothers must be avoided.

4.7. Effects on ability to drive and use machines

Because of its pharmacological properties and its effect on central nervous system, Zopiclone may adversely affect the ability to drive or to use machines. 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.

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.

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).

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)

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

Respiratory, thoracic and mediastinal disorders

Rare: dyspnoea (see section 4.4)

Not known: respiratory depression (see section 4.4)

Eye disorders

Not known:	diplopia

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)

Withdrawal syndrome has been reported upon discontinuation of zopiclone. (See section 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9. Overdose

Fatal dose not known.

Symptoms
In the cases of overdosage reported,tOverdose is usually manifested by varying degrees of central nervous system depression ranging 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. 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.
Management
Symptomatic and supportive treatment in adequate clinical environment is recommended, attention should be paid to respiratory and cardiovascular functions.

Consider activated charcoal if an adult has ingested more than 150 mg or a child more than 1.5 mg/kg within one 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. 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: hypnotic-sedative

ATC code N05C F01

Zopiclone is a benzodiazepine-like hypnotic agent which belongs to the group of cyclopyrrolones. It rapidly initiates and sustains sleep without reduction of total REM sleep and with preservation of slow wave sleep. Negligible residual effects are seen the following morning. The pharmacological properties are: hypnotic, sedation, anxiolysis, anticonvulsion, muscle relaxation. These effects are related to a specific agonistic effect on central receptors belonging to the $GABA_A$, macromolecular complex which regulates the opening of chloride channels. However, it has been shownthat zopiclone and other cyclopyrrolones act on a different site to those of benzodiazepines including different conformational changes in the receptor complex.

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. There is very little risk of drug interactions due to protein binding. The volume of distribution is 91.8 – 104.6 litres. 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.

Metabolism
The most important metabolites are the N-oxide derivative (pharmacologically active in animals) and the N-desmethyl metabolite (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-life times are approximately 4.5 hours and 1.5 hours respectively. No significant accumulation of the compound is seen following repeat dosing, (15mg) 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 renal function and extension of the elimination 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. For this reason the dosage should be adjusted for 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

Tablet Core
Lactose monohydrate
Calcium hydrogen phosphate dihydrate
Sodium Starch Glycolate (Type A)
Povidone K 30
Maize Starch
Colloidal Anhydrous Silica
Magnesium Stearate

Film-coating
Hypromellose
Titanium Dioxide E 171
Talc
Macrogol 6000
Indigo Carmine Al Lake E 132

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from light.

6.5. Nature and contents of container

PVC/PVDC/Al blister of 10 or 14 tablets.

Pack containing 10, 20 or 28 tablets
Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

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PL 17907/0122

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