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

Prior to starting treatment with Zopiclone, a discussion should be held with patients to put in place a strategy for ending treatment with Zopiclone in order to minimise the risk of dependence, addiction and drug withdrawal syndrome (see section 4.4).

Treatment should be given for the shortest possible duration.

Posology

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:
Accumulation of zopiclone or its metabolites has not been seen during treatment of insomnia in patients with renal insufficiency. However, it is recommended that patients with reduced renal function should start treatment with3.75 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.

As with all hypnotics, long term use of zopiclone is not recommended.

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.

Treatment should be as short as possible and should not exceed four weeks including any tapering off. Extension beyond the maximum treatment period should not take place without re-evaluation of the patient's status, since the risk of abuse and dependence increases with the duration of treatment (see section 4.4).

The product should be taken just before retiring for the night.

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

4.3. Contraindications

Zopiclone is contra-indicated in the following cases:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Myasthenia gravis
- Respiratory failure
- Severe sleep apnoea syndrome
- Children and adolescents under 18 years of age

- Severe hepatic insufficiency
- Who have previously experienced complex sleep behaviours after taking Zopiclone

As with all hypnotics zopiclone should not be used in children.

4.4. Special warnings and precautions for use

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

Specific patient groups

Use in hepatic insufficiency: A reduced dosage is recommended, (see section 4.2 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 section 4.2 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)

Drug withdrawal syndrome
Prior to starting treatment with zopiclone, a discussion should be held with patients to explain the risk of dependence, addiction, and drug withdrawal syndrome. A withdrawal strategy for ending treatment with zopiclone should also be put in place with the patient before starting treatment (there may be exceptions to this in specific clinical situations such as symptom management in end of life palliative care).
Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take in excess of weeks or months. Patients should be informed of this when the medication is first prescribed.
The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve

before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person's preferences, changes to their circumstances and the response to dose reductions.
Suggest a slow stepwise rate of reduction proportionate to the existing dose, so that decrements become smaller as the dose is lowered, unless clinical risk is such that rapid withdrawal is needed.
If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level.
If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

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 off the dose before discontinuation. (See also section 4.8.)

Suicidal ideation/suicide attempt/suicide depression
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 be addressed before symptomatic treatment to avoid under treating potentially serious effects of depression.

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 symptoms or rebound symptoms may be increased after prolonged treatment, or abrupt discontinuation of therapy, it is, therefore, recommended to reduce the dosage gradually and to advice the patient accordingly.

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 the tapering off process (see section 4.8).

Drug dependence, tolerance and potential for abuse

Drug addiction comprises behavioural, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use and possible tolerance or physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.

For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of drug misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced. Patients may also supplement their treatment with additional medications to achieve the same effect. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for treatment with zopiclone should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.

Some loss of efficacy to the hypnotic effect of benzodiazepines and benzodiazepine-like substances may develop after repeated use for a few weeks.

However, with zopiclone, there is an absence of any marked tolerance has occurred during a treatment period of up to 4 weeks.

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 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, 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 with opioids
Concomitant use of opioids with benzodiazepines or other sedative-hypnotic drugs, including zopiclone, and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe zopiclone concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation (see section 4.5).

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
Complex sleep behaviour, including sleepwalking and other associated behaviours such as “sleep driving”, preparing and eating food, making phone calls having sex, with amnesia for the event, have been reported in patients who had taken zopiclone and were not fully awake. These events may occur following the first or any subsequent use of zopiclone. Discontinue treatment immediately if a patient experiences a complex sleep behaviour, due to the risk to the patient and others (see section 4.3). 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.

Important information regarding the ingredients in this medicine

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

Sodium: Zopiclone tablet contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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

Association not recommended:
The sedative effect of zopiclone may be enhanced when used in combination with alcohol, concomitant use is therefore not recommended. In particular, this could affect the ability to drive or operate machines.

Associations to be taken into 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.

Since zopiclone is metabolised by the cytochrome P450 (CYP)3A4 isoenzyme (see section 5.2 Pharmacokinetic Properties), plasma levels of zopiclone may be increased when co-administered with CYP3A4 inhibitors, such as erythromycin, clarithromycin, azole antimycotics such as ketoconazole, itraconazole and ritonavir. 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 phenobarbital, phenytoin, carbamazepine, rifampicin and St John's wort 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 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 CYP 3A4. As a consequence, the hypnotic effect of zopiclone may be enhanced.

Opioids:
The concomitant use of benzodiazepines and other sedative-hypnotic drugs, including zopiclone, and opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see section 4.4)

4.6. Fertility, pregnancy and lactation

Pregnancy
The use of zopiclone is not recommended during pregnancy.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Zopiclone crosses the placenta.

A large amount of data on pregnant women (more than 1000 pregnancy outcomes) collected from cohort studies has not demonstrated evidence of the occurrence of malformations following exposure to benzodiazepines or benzodiazepine-like substances during the first trimester of pregnancy. However, certain case-control studies, reported an increased incidence of cleft lip and palate associated with use of benzodiazepines during pregnancy.

Cases of reduced fetal movement and fetal heart rate variability have been described after administration of benzodiazepines or benzodiazepine-like substances during the second and/or third trimester of pregnancy.

Administration of benzodiazepines or benzodiazepine-like substances, including zopiclone, during the late phase of pregnancy or during labour have been associated with effects on the neonate, such as hypothermia, hypotonia, feeding difficulties ('floppy infant syndrome'), and respiratory depression, due to the pharmacological action of the product. Cases of severe neonatal respiratory depression have been reported.

Moreover, infants born to mothers who took sedative/hypnotics agents chronically during the latter stages of pregnancy may have developed physical dependence and may be at risk of developing withdrawal symptoms in the postnatal period. Appropriate monitoring of the newborn in the postnatal period is recommended.

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

Breastfeeding
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 complex sleep behaviours including somnambulism, Drug 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

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 website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google play or Apple App Store.

4.9. Overdose

Fatal dose not known.

Symptoms
Overdose 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.

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: hypnotic-sedative, Benzodiazepine related drugs
ATC code: N05C F01

Mechanism of action

Zopiclone is a hypnotic agent, and a member of the cyclopyrrolones group of compounds. 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, anxiolytic, anticonvulsant and muscle relaxant actions. These are related to its high affinity and specific agonistic effect at central receptors belonging to the 'GABA' macromolecular receptor complex modulating the opening of chloride ion channels. However, it has been shown that 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 absorbed rapidly. Peak concentrations are reached within 1.5 - 2 hours and they are approximately 30ng/ml and 60ng/ml after administration of 3.75mg and 7.5mg respectively. Absorption is not modified by gender, food or repetition of doses.

Distribution
Zopiclone 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 and 15 mg, 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 extensively metabolised in humans to two major metabolites, N-oxide zopiclone (pharmacologically active in animals) and the 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 of the compound 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 8.4 ml/min) compared with the plasma clearance (232 ml/min) indicated that zopiclone clearanceis mainly metabolic. Zopiclone is eliminated in 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 its metabolites have been detected 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. 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

Bristol Laboratories Ltd.
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8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0122

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