IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PPA1328/043/001
Case No: 2082023

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

B & S Healthcare

Unit 4, Bradfield Road, **Ruislip**, **Middlesex**, **HA4 0NU**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Zimovane 7.5mg Film-coated Tablets

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **26/07/2010** until **26/11/2011**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zimovane 7.5mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 7.5 mg zopiclone.
Excipients: Lactose, Wheat starch.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Product imported from the UK:
White, elliptical, film-coated tablets with a score line on one side and plain on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Short term treatment of insomnia, 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

Adults: The recommended dose is one Zimovane tablet (7.5mg zopiclone) 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 impaired renal function should start treatment with 3.75mg.

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.

Route of administration

Oral. Each tablet should be swallowed whole without sucking, chewing or breaking.

4.3 Contraindications

Zimovane is contraindicated in patients with myasthenia gravis, respiratory failure, severe sleep apnoea syndrome, severe hepatic insufficiency and those people with a hypersensitivity to zopiclone. As with all hypnotics Zimovane should not be used in children.

4.4 Special warnings and precautions for use

'Patients withrare hereditary problems of galactose intolerance, the lapp lactase definciency or glucose-galactose malabsorbtion should not take this medicine'.

Use in hepatic insufficiency: A reduced dosage is recommended, see Posology.
Use in renal insufficiency: A reduced dosage is recommended, see Posology.
Risk of dependence: Clinical experience to date with Zimovane suggests that the risk of dependence is minimal when the duration of treatment is limited to not more than 4 weeks.
Use of benzodiazepines and benzodiazepine-like agents (even at therapeutic doses) may lead to the development of physical and psychological dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol and 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 has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (see warnings and precautions). 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.
Withdrawal: The termination of treatment with Zimovane 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: Zopiclone does not constitute a treatment for depression. 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 effect of benzodiazepines and benzodiazepine-like agents may develop after repeated use for a few weeks. However, with Zimovane there is an absence of any marked tolerance during treatment periods of up to 4 weeks.
Rebound insomnia is 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, decreasing the dosage in a stepwise fashion may be helpful.
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 also section 4.8 Undesirable Effects).
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, 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.
Driving: 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.

4.5 Interaction with other medicinal products and other forms of interaction

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 patient's ability to drive or use machines.

In combination with CNS depressants an enhancement of the central depressive effect may occur.

The therapeutic benefit of co-adminstration with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines should therefore be carefully weighed. Concomitant use of benzodiazepines or benzodiazepine-like agents with narcotic analgesics may enhance their euphoric effect and could lead 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.

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. 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-adminstered with CYP3A4 inhibitors such as erythromycin, clarithromycin, ketoconazole, itraconazole and ritonavir. A dose reduction for zopiclone may be required when it is co-adminstered with CYP3A4 inhibitors.
Conversely, plasma levels of zopiclone may be decreased when co-administered with CYP3A4 inducers such as rifampicin, carbamazepine, phenobarbital, phenytoin and St. John's wort. A dose increase for zopiclone may be required when it is co-adminstered with CYP3A4 inducers.

4.6 Pregnancy and lactation

Use during pregnancy: Experience of use of zopiclone during pregnancy in humans is limited although there have been no adverse findings in animals. Use in pregnancy is therefore not recommended. 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 used 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, hypnotic 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.
Use during lactation: Zopiclone is excreted in breast milk and use in nursing mothers must be avoided.

4.7 Effects on ability to drive and use machines

Although residual effects are rare and generally of minor significance, patients should be advised not to drive or operate machinery the day after treatment until it is established that their performance is unimpaired. The risk is increased by concomitant intake of alcohol (see section 4.4 Special Warnings and Precautions for Use).

4.8 Undesirable effects

A mild bitter or metallic after-taste is the most frequently reported adverse effect. Less commonly, mild gastrointestinal disturbances, including nausea and vomiting, dizziness, headache, drowsiness and dry mouth have occurred. Psychological and behavioural disturbances, such as irritability, aggressiveness, confusion, depressed mood, anterograde amnesia, hallucinations and nightmares have been reported. Rarely these reactions may be severe and may be more likely to occur in the elderly. Rarely allergic and allied manifestations such as urticaria or rashes have been observed and, more rarely, light headedness and incoordination. Angiodema and/or anaphylactic reactions have been reported very rarely.
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, anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, hallucinations, panic attacks, muscle aches/cramps, gastrointestinal disturbances and irritability. In very rare cases, seizures may occur. Mild to moderate increases in serum transaminases and/or alkaline phosphatase have been reported very rarely.

4.9 Overdose

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 serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression and coma. Other risk factors, such as combining zopiclone with other CNS depressants (including alcohol), the presence of concomitant illness and the debilitated state of the patient, may contribute to the severity of the symptoms and very rarely can result in fatal outcome.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Zopiclone is an hypnotic agent, and a member of the cyclopyrrolone 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. Its pharmacological properties include hypnotic, sedative, anxiolytic, anticonvulsant and muscle-relaxant actions. These are related to its high affinity and specific agonist action at central receptors belonging to the 'GABA' macromolecular receptor complex modulating the opening of the chloride ion channel. 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 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
Calcium hydrogen phosphate
Wheat starch
Sodium starch glycolate
Magnesium stearate
Hypromellose
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container

Zimovane are provided in clear PVC/aluminium foil blisters containing 28 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1328/43/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 27th November 2006

10 DATE OF REVISION OF THE TEXT

February 2007