IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0593/018/001
Case No: 2043112

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

Stada Arzneimittel AG

Stadastrasse 2-18, **D-61118 Bad Vilbel**, **Germany**

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

Zopicalm Tablets 7.5 mg

The particulars of which are set out in Part I and Part II of 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 **13/02/2008** until **21/09/2008**.

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

Zopicalm Tablets 7.5 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 7.5 mg zopiclone.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets.

White, round biconvex film-coated tablets. The film-coated tablets are embossed with “ZOC 7,5” on one side and scored on both sides. The film-coated tablets are breakable.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Short-term treatment of insomnia.

Benzodiazepines and benzodiazepine-like substances are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Treatment with Zopiclone should be for as short a period as possible.

The period of treatment should generally vary between a few days to 2 weeks, with a maximum of 4 weeks including the tapering off phase. In certain cases it may be necessary to prolong treatment beyond the maximum period. If this is the case, however, it should only take place after re-evaluation of the patient’s condition.

The recommended dose for adults is 7.5 mg (one tablet). This dose should not be exceeded.

The product should be taken immediately before going to bed.

In the elderly, patients with hepatic insufficiency or chronic respiratory insufficiency, treatment should be started at a dosage of 3.75 mg, i.e. a half tablet.

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.

The tablets can be broken as follows:
- lay the tablet on a desk
- take the left and right thumb or forefinger and press on both sides of the scoring line.

4.3 Contraindications

Zopiclone is contra-indicated in the following cases:
- Hypersensitivity to the active or to any of the excipients
- Myasthenia gravis
- Severe respiratory insufficiency
- Sleep apnoea syndrome
- Patients under the age of 18
- Severe hepatic insufficiency

4.4 Special warnings and precautions for use

Dependence
The use of benzodiazepines and benzodiazepine-like substances can lead to physical and psychological dependence on these agents. The risk of dependence increases the higher the dose and the longer the period of treatment; the risk of dependence is also greater in patient with a history of alcohol or drug abuse or those who have marked personality disorders. If physical dependence occurs, sudden discontinuation of the treatment will be accompanied by withdrawal symptoms. 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.
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. 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 abrupt interruption of the treatment it is advisable to reduce the dosage gradually.

Period of treatment
The period of treatment should be as short as possible (see Posology and method of administration) 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.

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.

Anterograde amnesia
Benzodiazepines and benzodiazepine-like substances may cause anterograde amnesia, in particular a few hours after taking the product. In order to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see section 4.8 Undesirable effects).

Psychiatric and "paradoxical" reactions
It is known that reactions such as restlessness, agitation, irritability, aggression, delusions, outbursts of rage, nightmares, hallucination, 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. The risk of these reactions is greater in children and the elderly.

Specific patient groups
For the elderly: see Posology and method of administration. A lower dose is advised for patients with chronic

respiratory insufficiency due to the risk of respiratory depression. 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.

Benzodiazepines and benzodiazepine-like substances are not recommended as the primary treatment of psychoses. Benzodiazepines and benzodiazepine-like substances should not be used as the sole treatment of depression or anxiety linked with depression (suicide may be triggered in such patients). Benzodiazepines and benzodiazepine-like substances should be administered with extreme caution to patients with a previous history of alcohol or drug abuse.

Before starting treatment with zopiclone any underlying cause of insomnia should be addressed carefully.

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

Not recommended:
Simultaneous ingestion with alcohol is not recommended because the sedative effect of zopiclone may be intensified. This may affect the ability to drive or operate machines.

Take account of:
Combination with other central depressive agents, such as antipsychotic agents (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressants, narcotic analgesics, anti-epileptics, anaesthetics and sedative antihistamines may increase the suppressive effect of zopiclone on the central nervous system and should therefore be carefully weighed. In the case of narcotic analgesics potentiation of euphoria may also occur, which can lead to increased psychological dependence.
Combination of zopiclone with muscle relaxants may increase the muscle relaxing effect.

Since zopiclone is metabolised by CYP3A4, 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 macrolide antibiotics, azole antimycotics and HIV protease inhibitors, as well as grape fruit juice. Dose reduction should be considered if zopiclone is co-administered with CYP3A4 inhibitors. 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.

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 CYP3A4. As a consequence, the hypnotic effect of zopiclone may be enhanced.

4.6 Pregnancy and lactation

The safety of use in pregnant women and during lactation has not been established. To date zopiclone has not produced injurious effects in animal studies except at very high maternally toxic doses. Zopiclone is excreted in breast milk.
If zopiclone is prescribed during the last three months of pregnancy or during labour, effects on the neonate, such as hypothermia, hypotonia and respiratory depression may be expected due to the pharmacological properties of the product. Because of the development of physical dependence, withdrawal symptoms may occur in neonates of mothers who have used zopiclone for long periods during the last months of pregnancy.
Although the concentration of zopiclone in breast milk is very low, zopiclone should not be prescribed to women during the lactation period.
If zopiclone is prescribed to women of child-bearing age, they should be advised that if they are planning to become pregnant or think they may be pregnant, they should contact their doctor about discontinuing the treatment.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscular function may reduce the capability to drive or operate machines. The risk is increased with concomitant alcohol intake. The risk is even higher when sleep duration is insufficient. Patients should be warned not to drive or operate machines until treatment has finished or it has been established that performance is unimpaired. Due to residual effects this warning should also be considered the morning after administration of zopiclone.

4.8 Undesirable effects

The following side effects have been observed in patients treated with zopiclone:

Psychiatric disorders
Dulling of sensitivity, confusion, change in libido, depression, restlessness, agitation, irritability, aggression, delusions, outbursts of rage, nightmares, hallucinations, psychoses, behavioural disturbances, dependence.
See also below under “Depression”, “Psychiatric and paradoxical reactions” and “Dependence”.

Nervous system disorders
Amnesia, sleepiness during the following day, reduced alertness, headache, dizziness, ataxia (occurs chiefly at the beginning of treatment and generally disappears after repeated administration).
See also below under “Amnesia”.

Eye disorders
Double vision (occurs chiefly at the beginning of treatment and generally disappears after repeated administration).

Gastrointestinal disorders
Gastro-intestinal problems (including nausea and vomiting). Bitter taste or metallic after taste.

Skin and subcutaneous tissue disorders
Skin reactions (including urticaria).

Musculoskeletal and connective tissue disorders
Muscle weakness.

General disorders and administration site conditions
Tiredness.

Amnesia
Anterograde amnesia may occur on therapeutic doses, and the risk is increased the higher the dose. Amnesia may be accompanied by unsuitable behaviour (see Special warnings and special precautions for use).

Depression
Pre-existent depression may become manifest during the use of benzodiazepines and benzodiazepine-like substances.

Psychiatric and paradoxical reactions
Reactions such as restlessness, agitation, irritability, aggression, delusions, outbursts of rage, nightmares, hallucinations, psychoses, unsuitable behavior and other behavioral disturbances may occur during the use of benzodiazepines and benzodiazepine-like substances. In some cases they may become quite severe with this agent. The risk of these reactions is greater in children and the elderly.

Dependence
Use may lead to physical dependence even at therapeutic dosages: discontinuation of the treatment may lead to withdrawal or rebound phenomena (see Special warning and special precautions for use). Psychological dependence may also occur. Misuse has been reported.

4.9 Overdose

In the few cases where overdosage with zopiclone has been reported, these reports were not accompanied by life-threatening effects unless the agent was ingested in combination with other medicaments which have a suppressive effect on the central nervous system, including alcohol. The most important phenomena are dizziness, lethargy and ataxia.

Overdose of benzodiazepines or benzodiazepines-like agents is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma.
Treatment should be aimed at supporting vital functions and is chiefly symptomatic (e.g. induce vomiting, monitor the heart function and respiration).
Haemodialysis is not useful because of the high distribution volume of zopiclone. Flumazenil may be beneficial as an antidote.

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. The pharmacological properties are: 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. These effects are similar to those of benzodiazepines.

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.

Metabolism
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 is seen following repeat dosing, (15mg) for 14 days.

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 by approximately 40%. For this reason the dosage should be adjusted for these patients.

5.3 Preclinical safety data

Hepatotoxic effects were elicited in repeated dose toxicity studies conducted in rats and dogs. In dogs, anaemia was evident in some studies.
Both in vitro and in vivo studies failed to show mutagenicity produced by zopiclone.
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 in thyroid tumours in rats were associated with increased TSH serum levels. In humans zopiclone has no effects on thyroid hormones.
Fertility was impaired in two rat studies, whereas zopiclone had no adverse effects on fertility in rabbits. 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 as well as morphology.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Calcium hydrogen phosphate dihydrate
Maize starch
Sodium carmellose
Magnesium stearate
Titanium dioxide (E171)
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/PVDC/Al blister

Packs containing 5, 10, 14, 20, 28, 30, 50, 56, 60, 90, 100, 150, 200, 250, 300, 400, 500 or 1000 tablets.

Not all pack sizes may be marketed.

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 MARKETING AUTHORISATION HOLDER

Stada Arzneimittel AG
Stadastrasse 2-18
D-61118 Bad Vilbel
Germany

8 MARKETING AUTHORISATION NUMBER

PA 593/18/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st October 1999
Date of last renewal: 22nd September 2003

10 DATE OF REVISION OF THE TEXT

June 2007