IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0840/001/001
Case No: 2068712

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

Synthon B.V.

Microweg 22, **6545 CM Nijmegen**, **Netherlands**

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

Zorclone 3.75 mg Film-Coated Tablets.

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 **08/09/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zorclone 3.75 mg Film-Coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Zopiclone 3.75 mg.

Excipients: also includes Lactose Monohydrate 30.8mg per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Orange, round, biconvex, film-coated tablets debossed with “ZOC 3.75” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Short-term treatment of insomnia

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

4.2 Posology and method of administration

Treatment should be as short as possible. Generally the duration of treatment varies from a few days to two weeks with a maximum, including tapering off of four weeks. In certain cases extension beyond the maximum treatment period may be necessary; if so it should not take place without re-evaluation of the patient's status.
The product should be taken just before retiring for the night.

Dose

Adults
The recommended dose for adults is 7.5 mg. This dose should not be exceeded.

Elderly
A lower dose of 3.75 mg 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 3.75 mg zopiclone is recommended.

Patients with renal insufficiency
Although in case of renal insufficiency no accumulation of zopiclone or of its metabolites has been detected, it is recommended that patients with impaired renal function should start treatment with 3.75 mg.

Patients with chronic respiratory insufficiency
Treatment should be initiated on a dose of 3.75 mg.

Peadiatric patients
Zorclone® is contraindicated in children aged less than 18 years (see Section 4.3)

4.3 Contraindications

Myasthenia gravis
Hypersensitivity to zopiclone or any of the excipients of Zorclone™ tablets
Severe respiratory insufficiency
Sleep apnoea syndrome
Severe hepatic insufficiency.
Use in children aged less than 18 years

4.4 Special warnings and precautions for use

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 there is an absence of any marked tolerance for treatment periods of up to 4 weeks.

Dependence

Use of benzodiazepines and benzodiazepine - like agents may lead to the development of physical and psychic 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 or drug abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound insomnia
A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine and benzodiazepine - like agents recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Duration of treatment

The duration of treatment should be as short as possible (see section 4.2) depending on the indication, but should not exceed 4 weeks for insomnia including tapering off process.

Extension beyond these periods should not take place without reevaluation of the situation.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased.

Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising

anxiety over such symptoms should they occur while the medicinal product is being discontinued.

There are indications that, in the case of benzodiazepines and benzodiazepine - like agents with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

Amnesia

Benzodiazepines and benzodiazepine - like agents may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see also Section 4.8).

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 and benzodiazepine - like agents (see also Section 4.8). Should this occur, use of the drug should be discontinued.

These reactions are more likely to occur in the elderly.

Specific patient groups

Elderly should be given a reduced dose (see section 4.2). A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression. Benzodiazepines and benzodiazepine - like agents are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.

Benzodiazepines and benzodiazepine - like agents are not recommended for the primary treatment of psychotic illness. Benzodiazepines and benzodiazepine - like agents should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

Benzodiazepines and benzodiazepine - like agents should be used with extreme caution in patients with a history of alcohol or drug abuse.

Due to the myorelaxant effects there is a risk of falls and consequently of hip fractures in the elderly.

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 Concomitant intake with alcohol

The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

Take into account Combination with CNS depressants

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines.

In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychic dependence.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) such as erythromycin, clarithromycin, ketoconazole, itraconazole and ritonavir may enhance the activity of benzodiazepines and benzodiazepine - like agents. A dose reduction for zopiclone may be required when it is co-adminstered with CYP3A4

inhibitors.

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

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

4.6 Pregnancy and lactation

Insufficient data are available on Zopiclone to assess its safety during pregnancy and lactation, therefore its use is not recommended.

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

Administration of the medicinal product during the last three months of pregnancy or during labour is only allowed on strict medical indication as, due to the pharmacological action of the product, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected.

Moreover 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 for developing withdrawal symptoms in the postnatal period.

Since benzodiazepine and benzodiazepine - like agents are found in the breast milk, zopiclone should not be administered to breast-feeding mothers.

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. If sufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see also Interactions).
Patients should be advised not to drive or operate machinery until it is established that their performance is not impaired.

4.8 Undesirable effects

Bitter taste is the most common side-effect observed with zopiclone.

Undesirable effects reported are listed according to the following frequency: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1000 to ≤ 1/100); rare (≥ 1/10,000 to ≤ 1/1000); very rare (≤ 1/10,000), not known (cannot be estimated from the available data).

Immune system disorders

Rare:	Allergic reactions, including skin reactions such as rash and pruritus.
Very rare:	Anaphylactic reactions and angioedema

Psychiatric disorders

Rare:	Numbed emotions*, confusion*, depression, restlessness, agitation, irritability,aggression, delusions, rages, nightmares, hallucinations, psychoses, inappropriate behaviour, other behavioural disturbances
Very rare:	Change in libido
Unknown:	Dependence

Nervous system disorders
Common: Drowsiness*, reduced alertness*, headache*, dizziness
Rare: Anterograde amnesia, ataxia*

Eye disorders
Rare: Double vision*

Gastrointestinal disorders
Very common: Bitter after taste.
Common: Gastro-intestinal disturbances.

Skin and subcutaneous tissue disorders
Unknown: Skin reactions

Musculoskeletal and connective tissue disorders
Rare: Muscle weakness*.

General disorders and administration site conditions
Uncommon: Fatigue.

Injury and poisoning
Unknown: Fall (see also section 4.4)

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

*These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration.

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

Depression
Pre-existing depression may be unmasked during benzodiazepines and benzodiazepine-like agents use.

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 and benzodiazepine-like agents. They may be quite severe with this product but long experience is still lacking. They are more likely to occur in the elderly.

Dependence
Use (even at therapeutic doses) may lead to the development of physical dependence. Psychic dependence may occur. Abuse of benzodiazepines and benzodiazepine-like agents has been reported. Discontinuation of the therapy may result in withdrawal or rebound phenomena. Withdrawal syndrome has been reported upon discontinuation of zopiclone (see section 4.4). Withdrawal symptoms vary and may include rebound insomnia, anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, hallucinations, and irritability. In very rare cases seizures may occur.

4.9 Overdose

As with other benzodiazepines and benzodiazepine - like agents, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol).
In the management of overdose with any medicinal product, it should be borne in mind that multiple agents have been taken.

Following overdose with any medicinal product, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Overdose of benzodiazepines and benzodiazepine - like agents is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma.

In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.
Flumazenil may be useful as an antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-code: N05C F01
Zopiclone is a benzodiazepine - like hypnotic agent, a member of the cyclopyrrolone group of compounds. Its pharmacological properties are: anxiolytic, sedative, hypnotic, anticonvulsant, and muscle-relaxant.

These effects are related to a specific agonist action at central receptors belonging to the "GABA-omega (BZ1 + BZ2) macromolecular receptor" complex modulating the opening of the chloride ion channel.

5.2 Pharmacokinetic properties

Absorption

Zopiclone is absorbed rapidly. Peak concentrations are reached within 1h30 to 2h and they are approximately 30, 60 and 115 ng/ml after administration of 3.75 mg and 15 mg respectively. Absorption is not modified by sex, time of intake 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 a very little risk of drug interactions due to protein binding.
Plasma level decrease: between 3.75 and 15mg, the decrease in plasma level does not depend on the dose. The elimination half life is approximately 5 h.
After repeated administration, there is no accumulation and inter individual variations appeared to be very low.

During lactation, the kinetic profiles of zopiclone in breast milk and in plasma are similar. The estimated percentage of the dose ingested by a nursing child would not exceed 0.2% of the dose administered to the mother over 24 h.

Metabolism

Among the metabolites, the main ones are the N-oxide derivative (pharmacologically active in animals) and the N-Desmethyl metabolite (pharmacologically inactive in animals).

Their apparent half-lives evaluated from the urinary data are approximately 4h.30 and 1h30 respectively, in accord with the fact that they do not significantly accumulate 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/mn) compared with the plasma clearance (232

ml/mn) 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-demethyl derivatives) and in the faeces (Approximately 16%).

Physio-pathological variations

In elderly patients, notwithstanding a slight decrease in hepatic metabolism and a lengthening of elimination half-life to approximately 7 hours, various studies have failed to show plasma accumulation of zopiclone or of its metabolites has been detected after prolonged administration. Zopiclone crosses the dialysing membrane.

In patients with liver cirrhosis, 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

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 failed to show mutagenicity produced by zopiclone.
Increased incidence of mammary carcinomas in female rats at high multiple of the maximum plasma concentrations from therapeutic doses in human has been attributed to increased 17-beta-estradiol serum levels.
Increased incidence in thyroid tumours in rats were associated with increased TSH 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 change in ejaculate volume, sperm concentration, sperm motility as well as morphology.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
Calcium hydrogen phosphate dihydrate
Maize starch
Croscarmellose sodium
Magnesium stearate

Film coat:
Titanium dioxide (E171)
Hypromellose (E464)
Iron oxide yellow (E172)
Iron oxide red (E172)

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

Lithographed carton boxes containing 1, 3 or 6 PVC/PVDC/A1 blister strips of 10 tablets, and lithographed carton boxes containing 1, 2 or 4 PVC/PVDC/A1 blister strips of 14 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

Synthon BV
Microweg 22
6545 CM Nijmegen
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 840/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th June 1999
Date of last renewal: 15th April 2008

10 DATE OF REVISION OF THE TEXT

March 2009