IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1327/006/001
Case No: 2062149

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

Orion Corporation

Orionintie 1, **FIN-02200 Espoo**, **Finland**

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

Tenox 10mg 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 **15/04/2009**.

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

Tenox 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg of temazepam.

Excipients: contains 72.3mg lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
A white to pale yellow round, flat scored, bevelled edge, uncoated tablet with 7mm diameter.
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As a hypnotic for the short-term management of insomnia only when it is severe, disabling or subjecting the individual to extreme distress.

For premedication prior to minor surgery or other related procedures.

4.2 Posology and method of administration

Oral.

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. The tapering-off process should be tailored to the individual. 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 on retiring or up to 30 minutes before going to bed.

Insomnia
Adults: 10 - 20mg. In exceptional circumstances the dose may be increased to 30 - 40mg.

Elderly: 10mg. In exceptional circumstances the dose may be increased to 20mg.

Premedication
The usual dose is 20 - 40mg, 30 to 60 minutes before procedure.

Children: Not recommended for use in children.

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded. Patients with impaired liver function should have a reduced dose.

4.3 Contraindications

Myasthenia gravis, hypersensitivity to temazepam, benzodiazepines, or to any of the excipients, severe respiratory insufficiency, sleep apnoea syndrome, severe hepatic insufficiency.

4.4 Special warnings and precautions for use

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at high dosages. The condition occurs most often several hours after ingesting the product, therefore patients should ensure that they will be able to have an uninterrupted sleep of 7 - 8 hours. Amnesic effects may be associated with inappropriate behaviour. Pre-existing depression may be unmasked during benzodiazepine use.

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur with using Benzodiazepines. These reactions are more likely to occur in children and the elderly. Should this occur, use of the product should be discontinued.

Use (even at therapeutic doses) may lead to the development of physical dependence: Discontinuation of the therapy may result in withdrawal or rebound phenomena. Psychic dependence may occur. Abuse has been reported in polydrug abusers.

Some loss of efficacy to the hypnotic effects of short-acting benzodiazepines may develop after repeated use for a few weeks.

Use of benzodiazepines may lead to the development of physical and psychic dependence upon use of 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: derealisation; depersonalisation; hyperacusis; numbness and tingling of the extremities; hypersensitivity to light, noise and physical contact; hallucinations; or epileptic seizures.

A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine 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.

The duration of treatment should be as short as possible (see Posology) depending on the indication, but should not exceed 4 weeks including the tapering off process. Extension beyond this period should not take place without re-evaluation 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 with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

For the elderly: see dose recommendation. A lower dose is also recommended for patients with chronic respiratory

insufficiency due to the risk of respiratory depression. Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as it may precipitate encephalopathy. Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

Due to the myorelaxant effect the risk of falls and consequently of hip fractures in elderly patients is increased.

Benzodiazepines should also be used with extreme caution in patients with a history of alcohol or drug abuse.

Sedation, amnesia, impaired concentration and impaired muscular function may adversely effect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medication.

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, antiepileptic 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.

Concomitant use of disulfiram may slow down the elimination of temazepam.

Concomitant use of oral contraceptive steroids may enhance the elimination of temazepam and slightly decrease the drug effects.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines and benzodiazepine - like agents.

4.6 Pregnancy and lactation

Insufficient data are available on temazepam to assess its safety during pregnancy and lactation. 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 pregnant or suspects that she is pregnant.

If, for compelling medical reasons, temazepam is administered during the late phase of pregnancy, or during labour, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected due to the pharmacological action of the product.

Moreover, infants born to mothers who took benzodiazepines chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period. Temazepam may pass into breast milk, consequently its use during breast feeding is not recommended.

4.7 Effects on ability to drive and use machines

Not recommended: The temazepam is sedating especially with concomitant use of alcohol. This affects the ability to drive or use machines.

Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive our use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased. Patients affected by drowsiness while taking benzodiazepines should not drive or operate machinery. Drowsiness is most likely to occur after initiation of the use of benzodiazepines and gradually subsides. The driving skills are usually not affected

in the morning after taking 20mg dose of temazepam in the preceding evening.

4.8 Undesirable effects

Psychiatric disorders
Numbed emotions, (this phenomenon occurs predominantly at the start of therapy and usually disappears with repeated administration).
Anterograde amnesia may occur using therapeutic dosages, the risk increasing at high dosages. Amnesic effects may be associated with inappropriate behaviour. (See Section 4.4).
Changes in libido have been reported occasionally.
Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur with using Benzodiazepines. These reactions are more likely to occur in children and the elderly. Should this occur, use of the product should be discontinued. (See Section 4.4).

Nervous system disorders
Drowsiness during the day, reduced alertness, impaired concentration, fatigue, headache, dizziness, ataxia, and restless sleep. These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration.

Eye disorders
Double vision, (this phenomenon occurs predominantly at the start of therapy and usually disappears with repeated administration).

Gastrointestinal disorders
Dryness of the mouth or gastro-intestinal disturbances have been reported occasionally
Skin and subcutaneous tissue disorders
Skin reactions have been reported occasionally

Musculoskeletal, connective tissue and bone disorders
Muscle weakness (this phenomenon occurs predominantly at the start of therapy and usually disappears with repeated administration). Due to the myorelaxant effect the risk of falls and consequently of hip fractures in elderly patients is increased.

Withdrawal reactions:
Withdrawal of treatment may be accompanied by mood changes, anxiety, sleep disturbances or restlessness. The risk of withdrawal / rebound phenomena is greater after abrupt discontinuation of treatment. It is recommended that the dosage is decreased gradually.

The use of benzodiazepines may lead to the development of physical and psychic dependence. Once physical dependence has occurred, abrupt termination of treatment will be accompanied by withdrawal symptoms. These include headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases symptoms may include derealisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. (See Section 4.4)

4.9 Overdose

As with other benzodiazepines, 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 may have been taken. Following overdose with oral benzodiazepines, 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. The value of dialysis has not been determined for temazepam.

3-OH benzodiazepines are, as a rule, not dialysable and their metabolites (glucuronides) only dialysable with difficulty. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Overdosage of benzodiazepines 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 D07

Temazepam is a benzodiazepine: it has anxiolytic, sedative and hypnotic characteristics as well as possible muscle relaxant and anticonvulsant characteristics.

5.2 Pharmacokinetic properties

Absorption: Pharmacokinetic studies have shown that temazepam is well absorbed (90 - 100% and the first pass effect is slight [about 5%]). The time to reach peak plasma levels is usually about 50 minutes when given orally. Maximum plasma levels observed after doses of 20mg are 660 - 1100 ng /mg.

With multiple dosing steady state is obtained by the third day and there is little or no accumulation of parent drug or metabolites.

Distribution: The volume of distribution is 1.3 to 1.5 l / kg body weight, for the unbound fraction 43-68 l/kg. Approximately 96% of unchanged drug is bound to plasma proteins.

Metabolism: Temazepam is metabolised principally in the liver where most of the unchanged drug is directly conjugated to the glucuronide and excreted in the urine. Less than 5% of the drug is demethylated to oxazepam and eliminated as the glucuronide. The glucuronides of temazepam have no demonstrable CNS activity.

Elimination: Temazepam is rapidly eliminated, most studies showing an elimination half life in the range of 7 - 11 hours (mean 8 hours). Following a single dose, 80% of the dose appears in the urine, mostly as the conjugates and 12% of the dose appears in the faeces. Less than 2% of the dose is excreted unchanged in the urine.

Elimination in reduced renal function: In established renal insufficiency the metabolic clearance of temazepam as well as the plasma level of the non-protein bound temazepam remain within the normal range. The elimination half life for temazepam glucuronide is however increased by which this inactive metabolite accumulates. As stated under “Overdose” it is unlikely that temazepam may be significantly removed by dialysis.

5.3 Preclinical safety data

The acute LD_{50} dose for temazepam in mice has been determined as 85 mg/kg after intraperitoneal administration and 2600 mg/kg after oral administration. Repeated dose toxicity studies lasting up to six months did not reveal specific organ toxicity in mice, rats or dogs. A slight increase in the incidence of liver adenomas was found in female mice given 160 mg/kg temazepam in the diet for 18 months. Temazepam did not produce DNA strand breaks in the rat livers. No animal data is available on teratogenic effects of temazepam.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Maize Starch
Gelatin
Talc
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package and keep the container tightly closed.

6.5 Nature and contents of container

10, 30 and 100 tablets are presented in an amber glass bottle.

The amber glass bottle is composed of soda lime silica glass and is fitted with an aluminium pilfer-proof screw cap.

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

Orion Corporation
Orionintie 1
FIN-02200 Espoo
Finland

8 MARKETING AUTHORISATION NUMBER

PA 1327/6/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 September 1995

Date of last renewal: 27 April 2008

10 DATE OF REVISION OF THE TEXT

April 2009