IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0408/006/001
Case No: 2030492

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

Ranbaxy Ireland Limited

Spafield, Cork Road, **Cashel**, **Co. Tipperary**, **Ireland**

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

Rimapam Diazepam Tablets BP 2mg

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 **18/12/2006**.

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

Rimapam Diazepam Tablets BP 2mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2mg diazepan.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Round, white, flat, bevel-edged tablets embossed 'RIMA' on one face and 'D/2' on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Standard dosage
For optimal effect, the dosage should be carefully individualized. Treatment should begin at the lowest effective dose appropriate to the particular condition.

1. Anxiety.
2. Insomnia.
   Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.
3. In the control of muscle spasm including that associated with tetanus.
   In the management of epilepsy.
4. As pre-operative medication in minor surgery.

4.2 Posology and method of administration

1. Anxiety:

Treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free. The overall duration of treatment generally should not be more than 8-12 weeks, including a tapering off process.

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 with special expertise.

2. Insomnia

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 process 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.

Duration of treatment.

The duration of treatment should be as short as possible (see Posology) depending on the indication, but should not exceed 4 weeks for insomnia and 8 to 12 weeks in case of anxiety, including tapering off process. Extension beyond these periods 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 dosage interval, especially when the dosage is high. When benzodiazepines with a large duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Adults:
Mild anxiety states: 2mg three times daily.
Moderate to severe states: 10 to 30mg daily in divided doses.
Insomnia: 5 to 15mg before retiring.
Muscle spasm: 2 to 15mg daily in divided doses.
Premedication: The usual dose is 5mg the night before, 5mg upon awakening in the morning and 5mg two hours prior to the dental appointment.

Elderly:
Doses should not normally exceed half those normally recommended for adults.

Children:
Muscle spasm: As for adults.
Premedication: Dosing schedule as for adults but using a 2mg dose.

Infants and neonates:
Not recommended.

Special groups:
Debilitated patients: Doses should not exceed half those normally recommended for adults.

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded. The patient should be checked regularly at the start of the treatment in order to decrease if necessary, the dose or frequency of administration to prevent overdose due to accumulation.

4.3 Contraindications

Myasthenia gravis.
Hypersensitivity to benzodiazepines.
Severe respiratory insufficiency.
Sleep apnoea syndrome.
Severe hepatic insufficiency.
Phobic or obsessional states.
Chronic psychoses.

4.4 Special warnings and precautions for use

Tolerance:
Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Dependence:
Use of benzodiazepines 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 and anxiety:
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.

Duration of treatment:
The duration of treatment should be as short as possible (see Posology) depending on the indication, but should not exceed 4 weeks for insomnia and 8 to 12 weeks in case of anxiety, including tapering off process. Extension beyond these periods 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. When benzodiazepines with a large duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Amnesia:
Benzodiazepines 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 Undesirable Effects).

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. Should this occur, use of the drug should be discontinued. They are more likely to occur in children and the elderly.

Specific patient groups:
Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum. Elderly should be given a reduced dose (see Posology). 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 they may precipitate encephalopathy.

Benzodiazepines are not recommended for the primary treatment of psychotic illness. Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).
Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

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

Due to myorelaxant effect there is a risk of falls and consequently of hip fracture in elderly patients.

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 effects may occur in cases of concomitant use with anti-psychotics (neuroleptics), hypnotics, anxiolytics/sedatives, anti-depressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative anti-histamines.

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) may enhance the activity of benzodiazepines. To a lesser degree this also applies to benzodiazepines that are metabolised only by conjugation.

4.6 Pregnancy and lactation

Animal studies with benzodiazepines have shown minor effects on the foetus while a few studies have reported late behavioural disturbances in offspring exposed in utero. If the product is prescribed to a woman of child-bearing 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.

If, for compelling medical reasons, the product 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 compound. 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 for developing withdrawal symptoms in the post-natal period.

Since benzodiazepines are found in the breast milk, benzodiazepines should not be given 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).

4.8 Undesirable effects

Drowsiness (when the product is used as a hypnotic it should be stated explicitly: drowsiness during the day), numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or double vision. These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration.

Other side effects like gastro-intestinal disturbances, changes in libido or skin reactions have been reported occasionally.

Amnesia:
Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (See Warnings and Precautions).

Depression:
Pre-existing depression may be unmasked during benzodiazepine 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 benzodiazepine or benzodiazepine-like agents. They are more likely to occur in children and the elderly.

Dependence:
Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see Warnings and Precautions). Psychic dependence may occur. Abuse of benzodiazepines has been reported.

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 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 the respiratory and cardiovascular functions in intensive care.

Overdose 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

A benzodiazepine with anxiolytic, sedative, muscle relaxant and anti-convulsant properties.

5.2 Pharmacokinetic properties

Diazepam is readily absorbed from the gastro-intestinal tract, peak plasma concentrations occurring within about 30 to 90 minutes of oral administration; the rate of absorption is age-related and tends to be delayed in the elderly. Diazepam has a biphasic half-life with an initial rapid distribution phase followed by a prolonged terminal elimination phase of 1 or 2 days; its action is further prolonged by the even longer half-life of 2 to 5 days of its principal active metabolite, desmethyldiazepam (Nordazepam), the relative proportion of which increases in the body on long-term administration. Diazepam is very extensively bound to plasma proteins.

5.3 Preclinical safety data

There are no pre-clinical 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 Monoydrate
Maize starch

Magnesium stearate (E572)
Sodium starch glycollate (Type A)

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

White polypropylene containers with tamper evident polypropylene closures.

Pack sizes: 500 and 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

Ranbaxy Ireland Limited
Spafield
Cork Road
Cashel
Co. Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 408/6/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th July 1986
Date of last renewal: 15th July 2006

10 DATE OF REVISION OF THE TEXT

December 2006