IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0408/002/001
Case No: 2050207

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

Rima 10 Chlordiazepoxide 10 Milligram Capsules Hard

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 **24/04/2008**.

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

Rima 10 Chlordiazepoxide Capsules BP 10 mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 10mg chlordiazepoxide hydrochloride.

Also contains 170mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, hard

Capsules with black cap and green body, containing a white powder and printed "RIMA 10".

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1 Anxiety.
2 In the control of muscle spasm.
3 In the management of alcohol withdrawal.

4.2 Posology and method of administration

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.

Adults:
Anxiety states including muscle spasm:

The usual total daily dosage is up to 30mg in divided doses. In severe cases this may be increased to a total daily dosage of 40-100mg in divided doses.

Management of symptoms of alcohol withdrawal:

The usual dosage is 25-100mg repeated in 2-4 hours if necessary.

In the elderly or debilitated:

The usual daily dosage should not exceed half those normally recommended.

4.3 Contraindications

Myasthenia gravis
Hypersensitivity to benzodiazepines
Severe respiratory insufficiency
Sleep apnoea syndrome
Severe hepatic insufficiency

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 treatment 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 8-12 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.

When benzodiazepines with a long duration of action (such as Chlordiazepoxide) 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 the patients should ensure that they will be able to have an uninterrupted sleep of 7 of 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 galactose intolerance, the Lapp lactase deficiency or glucose malabsorption should not take this medicine.

Due to the myorelaxant effect there is a risk of falls and consequently of hip fractures 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 with 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 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) 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

Benzodiazepines should only be used during pregnancy or lactation if considered essential by the physician. Animal studies with benzodiazepines have shown minor effects on the foetus while a few studies have reported late behavioural disturbance in offspring exposed in utero.

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. 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 take 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 postnatal 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 insufficient 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 gastrointestinal disturbances, changes in libido or skin reactions have been reported occasionally.

Amnesia:

Anterograde amnesia may occur using therapeutic dosages, the risk of increasing at higher dosages. Amnesic 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 benzodiazepines or benzodiazepine like agents. They may be quite severe with this product. They are more likely to occur in children and the elderly.

Dependence:

Use (event 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 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 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 and muscle relaxant properties.

5.2 Pharmacokinetic properties

A benzodiazepine tranquillizer well absorbed, metabolised via demethylation in liver to active metabolites and excreted in urine with a T½ of 6-30 hours. Pharmacologically active metabolites include desmethyl chlordiazepoxide demoxepen, desmethyl diazepam and oxazepam with a t½ of 50-120 hours. Elimination is via the kidney.

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 Monohydrate
Starch Maize
Magnesium Stearate

Capsule Shell Body
Quinoline Yellow (E104)
Titanium Dioxide (E171)
Patent Blue V (E131)
Gelatin

Capsule Shell Cap
Black Iron Oxide (E172)
Titanium Dioxide (E171)
Gelatin

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Keep in the original container.

6.5 Nature and contents of container

White polypropylene containers with tamper evident closures, containing 1,000, 500 or 100 capsules.
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 Ltd.
Spafield, Cork Road
Cashel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 408/2/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th December 1986
Date of last renewal: 17th December 2006

10 DATE OF REVISION OF THE TEXT

February 2007