IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0405/023/002
Case No: 2061617

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

Generics (UK) Limited

12 Station Close, **Potters Bar**, **Hertfordshire EN6 1TL**, **United Kingdom**

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

Trilam 250 microgram 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 **28/06/2009**.

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

Trilam 250 microgram Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 microgram Triazolam.
Excipients: Contains lactose 83.38mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Flat, bevelled edge, light blue rectangular shaped tablet marked ‘‘TR Breakline 250’’ on one side and ‘‘G’’ on the reverse face.
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

Insomnia

Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

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.

Dose:

The recommended dose for adults is 125 micrograms - 250 micrograms.

The recommended dose for the elderly and for patients with impaired liver and/or renal function is 125 micrograms.

The product should be taken just before going to bed.

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded because of the increased risk of unacceptable CNS adverse effects.

4.3 Contraindications

Triazolam is contra-indicated in patients with myasthenia gravis, hypersensitivity to benzodiazepines, severe respiratory insufficiency, sleep apnoea syndrome or severe hepatic insufficiency and in children.

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 be 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, 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.

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 group

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.
Triazolam should be used with great caution in patients with major psychiatric disorders.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose 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.

Pharmacokinetic interactions may occur when triazolam is administered with drugs that interfere with its metabolism. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P4503A4) may increase the concentration of triazolam and enhance its activity. Data from clinical studies with triazolam, in vitro studies with triazolam and clinical studies with drugs metabolised similarly to triazolam provide evidence for varying degrees of interaction with triazolam and a number of drugs:

- Itraconazole and ketoconazole
- H2-blockers, such as cimetidine
- Macrolide antibiotics, such as azithromycin, clarithromycin, erythromycin, roxithromycin and
- Trolandomycin
- Isoniazid
- Calcium channel blockers, such as diltiazem and verapamil
- HIV protease inhibitors, such as ritonavir
- Modafinil

A study investigating the effect of modafinil on triazolam concluded that drug-drug interactions are likely to occur with compounds that undergo extensive gastrointestinal cytochrome P3A4/5-mediated first pass metabolism.

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 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 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 increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour. (see Warnings and precautions).

Data from several sources suggest that anterograde amnesia may be observed with this product at a higher rate than with other hypnotics. However, conclusive evidence based on comparative studies is lacking.

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 may be quite severe with this product.

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). Psychological dependence may occur. Abuse of benzodiazepines has been reported in polydrug abusers.

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 medical 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

ATC code: N05CD05

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

5.2 Pharmacokinetic properties

In adults with a single dose of 250 micrograms, a Cmax of 2.02 ± 0.15 mg/ml is reached at a Tmax of 0.96 ± 0.1 hr. The elimination half life is 1.5-5.5 hours. In the elderly Cmax is increased with approximately 50%. Tmax and t½ are unchanged. In healthy volunteers, the distribution volume was about 0.67 1/kg (range 0.57-0.86 1/kg after a dose of 125 micrograms - 1mg).

Triazolam is bound to plasma proteins, the free fraction ranging from 9.9-25.7%. The fraction is unchanged in the elderly.

Triazolam is metabolised via cytochrome P450. There is one active metabolite α-hydroxy-benzodiazepine which has a t½ of 3.9 hours.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber which are additional to those already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize Starch
Microcrystalline Cellulose
Povidone K30
Silica, colloidal anhydrous
Sodium laurilsulfate
Sodium Starch Glycolate Type A
Magnesium Stearate
Indigo carmine (E132)

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

PP securitainers in pack sizes of 30, 100, 250, 500 and 1000 tablets.
Green uPVC/A1 foil blister strips in pack sizes of 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics (UK) Limited
12 Station Close
Potters Bar
Hertfordshire
EN6 1TL
England

8 MARKETING AUTHORISATION NUMBER

PA 405/23/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 June 1989

Date of last renewal: 28 June 2009

10 DATE OF REVISION OF THE TEXT

May 2010