IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA0465/182/001
Case No: 2054664

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

PCO Manufacturing Limited

Unit 10, Ashbourne Business Park, **Rath**, **Ashbourne**, **Co. Meath**, **Ireland**

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

Xanax 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 **20/10/2008** until **07/09/2011**.

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

Xanax 250 microgram Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 micrograms alprazolam.
Excipients: Lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Product imported from Greece:
White, oval, biconvex tablets scored on one side and marked 'Upjohn 29' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Anxiety

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

4.2 Posology and method of administration

Anxiety

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

It is usual to commence with a dose of 500 micrograms to 1 mg daily in divided doses, with increments (no greater than 1 mg every 3-4 days), to the level of optimal control usually 3 to 4 mg daily.
In the elderly or debilitated patient a regimen of 250 micrograms twice daily should be used initially with gradual increments if required and tolerance is assured.

Treatment should be started with the lower recommended dose. The maximum dose should not be exceeded.

Initial doses may be given at bedtime to minimise daytime lethargy. If side effects occur with the starting dose, the dose should be lowered.
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.

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, depersonalisation, 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) but should not exceed eight to twelve weeks 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 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 long 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 patient). Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse. Due to the myorelaxant effect, there is a risk of falls and consequently of hip fractures in elderly patients.

Excipients
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) may enhance the activity of benzodiazepines that are metabolised. 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 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 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 gastrointestinal disturbances, changes in libido, hyperprolactin-aemia or skin reactions have been reported occasionally.

Amnesia
Anterograde amnesia may occur using therapeutic dosages, the risk 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 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). 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 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

Alprazolam, like other benzodiazepines, has a high affinity for the benzodiazepine binding site in the brain. It facilitates the inhibitory neurotransmitter action of gamma-aminobutyric acid which mediates both pre- and post-synaptic inhibition in the central nervous system (CNS).

5.2 Pharmacokinetic properties

Following oral administration, peak plasma concentrations are reached in about 1.7 hours. After a single oral dose of 500 micrograms, the average maximal concentration was 7.1 nanograms/ml. There is a linear relationship between the dose and plasma concentration. At least 80% of the oral dose is absorbed. About 70% of the absorbed dose is bound to plasma proteins. Alprazolam is extensively metabolised in the liver, primarily to hydroxylated metabolites, but about 20% of the dose is excreted as unchanged alprazolam. Elimination occurs mostly via the kidneys; 80% of the dose is excreted into the urine and only 7% into the faeces. The mean elimination half-life is 10-12 hours.

5.3 Preclinical safety data

None given.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Colloidal anhydrous silica
Maize starch
Magnesium stearate
Docusate sodium with sodium benzoate (E211)

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25^{o} C.
Store in the original package.

6.5 Nature and contents of container

PVC/aluminium foil blister strips of 10 tablets, packed 3 strips to a box.

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 Parallel Product Authorisation Holder

PCO Manufacturing Ltd.
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 Parallel Product Authorisation Number

PPA 465/182/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 8th September 2006

10 DATE OF REVISION OF THE TEXT

October 2008