Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alprox 0.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5 mg of Alprazolam.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White or almost white, flat, round scored tablets with a diameter of 7 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the short-term management of anxiety states.

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

4.2 Posology and method of administration

For oral administration only.

Anxiety

The duration of treatment should be as short as possible but not longer than 8-12 weeks, including tapering off process.

It is usual to commence with a dose of 500 micrograms (0.5 mg) to 1 mg daily in divided doses, with increments (of 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 (0.25 mg) twice daily should be used initially with gradual increments if required and tolerance is assured.

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.

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

4.3 Contraindications

Myasthenia gravis.

Hypersensitivity to benzodiazepines or to any of the excipients.
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 short-acting 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: derealisation; 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) depending on the indication, but should not exceed eight to twelve weeks in case of anxiety including 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.

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 product should be discontinued.
These reactions 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 should 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 it 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 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, 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.

Compounds which inhibit certain 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

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 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 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. Amnesic effects may b 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 (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy ma 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 oral benzodiazepines, vomiting should be induced (within one hour) if the patient is conscious gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying th 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

Pharmacodynamic group: Anxiolytics, Benzodiazepine derivatives.
ATC Code: NO5B A12.

Alprazolam, like other benzodiazepines, has a high affinity for the benzodiazepine binding site in the brain. It facilitates the inhibitory neurotransmitter action of gammaaminobutyric acid which mediates both pre- and postsynaptic 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 0.5 mg, the average maximal concentration was 7.1 ng/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

There is no preclinical data of relevance to the prescriber which is additional to that already included in other sections of the Summary of Product Characteristics.

Preclinical data reveals no special hazard for humans based on conventional studies of Safety Pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize Starch
Gelatin
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Amber glass bottles (Type III Ph. Eur.)
Pack sizes: 100 tablets.

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
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8 MARKETING AUTHORISATION NUMBER

PA 1327/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 January 1995

Date of last renewal: 03 January 2005

10 DATE OF REVISION OF THE TEXT

June 2006