Core Safety Profile

Active substance: Alprazolam
Pharmaceutical form(s)/strength: Tablet uncoated, sugar coated, film coated, 0.25mg
Tablet uncoated, 0.4 mg
Tablet uncoated, sugar coated, film coated, prolonged release, modified release, 0.5mg
Tablet uncoated, 0.8mg
Tablet uncoated, sugar coated, prolonged release, modified release, 1mg
Tablet uncoated, modified release, prolonged release, 2mg
Tablet uncoated, 2.5mg
Tablet modified release, prolonged release, 3mg
Tablet uncoated, 5mg
Solution, 0.75mg/ml

P-RMS: FR/H/PSUR/0036/001
Date of FAR: 09.11.2011
4.3. Contraindications

Alprazolam is contraindicated in patients with a known hypersensitivity to benzodiazepines, alprazolam or to any component of the product’s formulation. Benzodiazepines are also contraindicated in patients with myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome, severe hepatic insufficiency.

4.4. Special warnings and precautions for use

Specific patient groups
Safety and efficacy of alprazolam have not been established in children and adolescents below the age of 18 years; therefore use of alprazolam is not recommended.

Caution is recommended when treating patients with impaired renal function or mild to moderate hepatic insufficiency

It is recommended that the general principle of using the lowest effective dose be followed in elderly and/or debilitated patients to preclude the development of ataxia or oversedation.

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse (see section 4.5 Interaction with other medicinal products and other forms of interactions).

In patients presenting with major depression or anxiety associated with depression, benzodiazepines and benzodiazepine-like agents should not be used alone to treat depression as they may precipitate or increase the risk of suicide. Therefore, alprazolam should be used with caution and the prescription size should be limited in patients with signs and symptoms of a depressive disorder or suicidal tendencies.

Additional information when panic disorder is an approved indication

Panic disorder have been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients. Therefore, the same precaution must be exercised when using the higher doses of /…/ in treating patients with panic disorders as is exercised with the use of any psychotropic drug in treating depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

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. Pharmacodependency may occur at therapeutic doses and/or in patients with no individualised risk factor. There is an increased risk of pharmacodependency with the combined use of several benzodiazepines regardless of the anxiolytic or hypnotic indication. Cases of abuse have also been reported
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, 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 the treatment should be as short as possible (see Posology) depending on the indication, but should not 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 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 minimizing anxiety over such symptoms should they occur while the medicinal product is being discontinued. There are indications that, in the case of benzodiazepines with short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

When benzodiazepines with long duration of action are being used it is important to warn against changing in benzodiazepine with short duration of action, as withdrawal symptoms may develop.

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 medicinal product should be discontinued. They are more likely to occur in children and the elderly.

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.

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

Alprazolam drops
This medicinal product contains ethanol (alcohol).
4.5. Interaction with other medicinal products and other forms of interaction

Benzodiazepines produce an additive effect when co-administered with alcohol or other CNS depressants.

Concomitant intake with alcohol is not recommended.
Special care should be made with drugs depressing respiratory function such as opioids (analgesics, antitussives, substitutive treatments), notably in the elderly people.

Alprazolam should be used with caution when combined with other CNS depressants. Enhancement of the central depressive effect may occur in case of concomitant use with antipsychotics (neuroleptics), anxiolytics/sedatives, some antidepressant agents, opioids, anticonvulsants, sedative H1-antihistamines.

Pharmacokinetic interactions can occur when alprazolam is administered along with drugs that inhibit the hepatic enzyme CYP3A4) by increasing the plasma levels of alprazolam.

The co-administration of alprazolam with strong CYP3A4 inhibitors like azole antifungals (ketoconazole, itraconazole, posaconazole, voriconazole), protease inhibitors or some macrolides (erythromycin, clarithromycin, telithromycin) should be made with caution and a substantial dose reduction considered.

4.6. Pregnancy and lactation

Pregnancy:
A large amount of data based on cohort studies indicate that first trimester exposure to benzodiazepine is not associated with an increase in the risk of major malformation. However, some early case-control epidemiological studies have found an increased risk of oral clefts. The data indicated that the risk of having an infant with an oral cleft after maternal benzodiazepine exposure is less than 2/1000 compared with an expected rate for such defects of approximately 1/1000 in the general population.

Benzodiazepine treatment at high dose, during the second and/or the third trimester of pregnancy, has revealed a decrease of foetal active movements and a variability of foetal cardiac rhythm.

When treatment has to be administered for medical reasons during the last part of pregnancy, even at low doses, floppy infant syndrome such as axial hypotonia, sucking troubles leading to a poor weight gain may be observed. These signs are reversible but they may last from 1 up to 3 weeks, according to the half life of the product. At high doses, respiratory depression or apnea and hypothermia in newborn may appear. Moreover, neonatal withdrawal symptoms with hyperexcitability, agitation and tremor may be observed a few days after birth, even if no floppy infant syndrome is observed. The apparition of withdrawal symptoms after birth depends on the half life of the substance.

Taking into account these data, the use of alprazolam during pregnancy may be considered, if therapeutic indications and posology are strictly respected.

If alprazolam treatment is necessary during last part of pregnancy, high doses should be avoided and withdrawal symptoms and/or floppy infant syndrome should be monitored in newborn.
Breastfeeding:
Alprazolam is excreted in breast milk at low level. However, alprazolam is not recommended during breast feeding.

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 Interaction with other medicinal products and other forms of interactions).

4.8. Undesirable effects

The following undesirable effects have been observed and reported during treatment with alprazolam with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Frequency</th>
<th>Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine disorders</td>
<td>Uncommon</td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Common</td>
<td>Blurred vision</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Constipation, Nausea</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Vomiting</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Asthenia, Irritability</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Peripheral oedema</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Uncommon</td>
<td>Abnormal liver function, Jaundice</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Investigations</td>
<td>Uncommon</td>
<td>Change in weight, Increased intraocular pressure</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Confusion, Depression</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Hallucinations, Rage, Aggressive behavior, Hostile behavior, Anxiety, Agitation, Changes in libido, Insomnia, Thinking abnormal, Nervousness; Stimulation</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Decreased appetite</td>
</tr>
<tr>
<td>MedDRA System Organ Class</td>
<td>Frequency</td>
<td>Undesirable Effects</td>
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<tr>
<td>---------------------------</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Uncommon</td>
<td>Musculoskeletal weakness</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>Sedation, Drowsiness</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Ataxia, Coordination disorders, Memory impairment, Slurred speech, Concentration difficulties, Dizziness, Headache, Lightheadedness</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Amnesia, Dystonia, Tremor</td>
</tr>
<tr>
<td></td>
<td>Not Known</td>
<td>Autonomic manifestations</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Uncommon</td>
<td>Sexual dysfunction, Menstrual irregularities;</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Uncommon</td>
<td>Incontinence, Urinary retention</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon</td>
<td>Dermatitis</td>
</tr>
</tbody>
</table>

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

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 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.