Core Safety Profile

Active substance: Clotiazepam
Pharmaceutical form(s)/strength: Tablets 5 mg and 10 mg
P-RMS: BE/H/PSUR/0002/002
Date of FAR: 16.06.2011
4.3 Contraindications

<Product name> is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients, to thieno or benzodiazepines
- Myasthenia gravis
- Severe chronic respiratory insufficiency
- Acute narrow angle glaucoma
- Obstructive sleep apnoea syndrome
- Severe hepatic impairment
- Children under 6 years of age

4.4 Special Warnings and Precautions for Use

Tolerance:
A decrease in the hypnotic effect of benzodiazepines may occur following repeated use of the medicinal product for a few weeks.

Dependence:
The use of thieno- or benzodiazepines may induce physical and psychic dependence. The risk increases with dose and duration of treatment; it is greater in patients who have a history of alcohol or drug abuse.

Once physical dependence has appeared, abrupt discontinuation of treatment may cause withdrawal symptoms such as headaches, muscle pain, extreme anxiety, tension, agitation, confusion and irritability. In severe cases, the following symptoms may appear: derealisation, depersonalisation, hyperacusia, numbness and tingling in the extremities, hypersensitivity to light, to noise and to physical contact, hallucinations and epileptic seizures.

Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that originally led to treatment with clotiazepam recur in an enhanced form, may occur on discontinuing treatment. This may be accompanied by other reactions such as mood swings, anxiety or sleep disorders and agitation. Since the risk of withdrawal syndrome or rebound effect is greater when treatment is discontinued abruptly, it is recommended to stop the treatment gradually.

Duration of treatment:
The period of treatment should be as short as possible (see section 4.2 "Posology and method of administration") depending on the indication. It should not exceed 4 weeks in insomnia patients and 8 to 12 weeks in anxiety patients, including the period of dose reduction. Treatment should not be prolonged unless the patient’s status has been re-assessed.

When starting treatment, the patient should be informed that the duration of treatment will be limited and it should be explained to him or her exactly how the dose will be reduced gradually. Moreover it is important that the patient is aware of the possibility of a rebound effect so that he or she is less worried by these symptoms should they occur while discontinuing treatment.

Amnesia:
Benzodiazepines may induce anterograde amnesia, which occurs most often several hours after ingesting the product. To reduce this risk, patients should ensure that they have an uninterrupted sleep of 7-8 hours (see also section 4.8 "Undesirable effects").
Psychiatric and paradoxical reactions:
Reactions such as impatience, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behavior and other undesirable behavioral effects are known to occur when benzodiazepines are used. Should these occur, use of the product must be discontinued. These effects are more likely to occur in children and elderly patients.

When treatment with the maximum recommended dosages fails or ceases to produce the expected beneficial effects, further increase in the dosage is not recommended at risk of increasing the undesirable effects and the risk of dependence.

Treatment must be initiated with caution in epileptic patients.

Use in elderly patients/patients with organic brain disorders/ respiratory insufficiency:
A reduced dose should be administered to elderly patients (see section 4.2 "Posology and method of administration"). A reduced dose is also recommended in patients with organic brain disorders, chronic respiratory insufficiency (because of the risk of respiratory depression) or of a very advanced age.

Use in renal impairment:
An appropriate dosage regimen is recommended in patients with serious renal disorders. In renal impairment it is necessary to reduce the dose of clotiazepam.

Use in hepatic impairment:
Benzodiazepines are not indicated in severe hepatic impairment, because they may trigger encephalopathy. In mild to moderate hepatic impairment, it is necessary to reduce the dose of clotiazepam. If hepatic function disorders occur, appropriate therapeutic measures, such as discontinuing administration, must be taken.

Use in heart insufficiency:
An appropriate dosage regimen is recommended in patients with heart disorders.

Use in children:
Benzodiazepines can only be administered to children after a very careful assessment of whether such treatment is necessary. The period of treatment should be as short as possible. Use of benzodiazepines in children under the age of 6 is reserved for specific, rare indications, following the decision and under monitoring of a specialist (neuropaediatrician, psychiatrist). Children are more sensitive to the effects of benzodiazepines on the CNS. The incomplete development of metabolic pathways may impede the formation of inactive metabolites or render metabolism incomplete.

Benzodiazepines are not recommended in the primary treatment of psychotic disorders.

Benzodiazepines cannot be used alone to treat depression or anxiety associated with depression (they may promote suicide in these patients).

Benzodiazepines must be used with extreme caution in patients with a history of alcohol or drug abuse.

Lactose:
This medicinal product must not be used in patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.
4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Effects of other medicinal products on <product name>.

Specific studies:
Concomitant intake of alcohol and clotiazepam is not recommended: use of the product with alcohol may potentiate the sedative effect which may in turn affect the ability to drive vehicles and use machines.

Caution is also recommended when administering clotiazepam with CNS depressors: central nervous system depressant effects may occur with concomitant use of antipsychotics (neuroleptics), hypnotics, anxiolytics, sedatives, antidepressants, narcotic analgesics, antiepileptics, anaesthetics, and sedative antihistamines.

Narcotic analgesics may also potentiate euphoria, which leads to increased psychic dependence.

Compounds which inhibit certain hepatic enzymes (in particular cytochrome P450) may potentiate the activity of benzodiazepines. This also applies to a lesser extent to benzodiazepines which are metabolised only by conjugation.

Metabolic clearance of clotiazepam is not significantly influenced by the concomitant administration of oral contraceptives, cimetidine or isoniazide.

Theophylline is a benzodiazepine antagonist.

4.6 Fertility, Pregnancy and Lactation

Pregnancy
An increased risk of congenital deformities has been reported in numerous studies when administering treatment with products in the same therapeutic group during the first trimester of pregnancy. Since the use of this type of product is not generally urgent, the use of <product name> during the first trimester of pregnancy is to be avoided. After that period, it should be used with caution, and only if a net therapeutic benefit can be expected.

When clotiazepam is prescribed to a woman of child-bearing potential, she must be warned to contact her doctor if she wishes to become pregnant or if she suspects that she is pregnant, so that the doctor can decide whether to interrupt the treatment.

If, for medical reasons, high doses of clotiazepam are administered at the end of pregnancy or during labour, effects such as hypothermia, hypotonia and a mild respiratory distress syndrome may appear in the newborn infant because of the pharmacological action of the active substance.

Moreover, children whose mothers have taken benzodiazepines repeatedly at the end of pregnancy may have developed physical dependence and can present withdrawal symptoms in the postpartum period.

Lactation
Since benzodiazepines are found in the maternal milk, their administration to breastfeeding mothers is not recommended.
4.7 Effects on Ability to Drive and Use Machines

Sedation, amnesia, impaired concentration and altered muscle function may adversely influence the ability to drive vehicles and use machines. If insufficient sleep duration occurs, the risk of impaired alertness is increased (see also section 4.5 "Interaction with other medicinal products and other forms of interaction").

4.8 Undesirable Effects

The undesirable effects of benzodiazepines result directly from their pharmacological properties: their frequency increases with age and depends on both dose and duration of treatment.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>leucopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>very rare anaphylactic reactions</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headaches(^1), drowsiness(^1), confusion(^1), lethargy(^1), ataxia, &quot;hang-over&quot; effect (drowsiness on waking up) when taken late in the evening, confusion in the elderly, memory disorders, personality disorders and paranoiac symptoms</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>diplopia and visual disorders</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Dizziness(^1), hypotension, syncope</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>respiratory depression in patients with chronic respiratory insufficiency</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Xerostomia(^1), nausea, vomiting, increase in appetite</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>alterations of hepatic function particularly with icterus and raised transaminase levels (see section 4.4)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>allergic cutaneous reactions, erythema, urticaria</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>decrease in muscle tone(^1)</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>sexual disorders, menstruation and ovulation disorders, gynaecomastia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>emotional numbness(^1), fatigue(^1)</td>
</tr>
</tbody>
</table>

\(^1\) These effects are more prevalent at the start of treatment

Amnesia:
Therapeutic doses of benzodiazepines may induce anterograde amnesia; the risk increases with the dose and the amnesia generally appears a few hours after administration. Its effects may be accompanied by inappropriate behavior (see section 4.4 "Special warnings and precautions for use").

Depression:
Pre-existing depression may sometimes be revealed.
Psychiatric and paradoxical reactions:
Reactions such as impatience, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behavior and other undesirable behavioral effects are known to occur when using benzodiazepines or benzodiazepine-like agents. These reactions may be very severe with this product. They are more likely to occur in children and elderly patients.

Dependence:
The use of tranquillizers even when administered at therapeutic doses may lead to physical dependence: discontinuation of treatment may induce withdrawal symptoms or a rebound effect (see section 4.4 “Special warnings and precautions for use”). Psychic dependence may occur. Abuse of benzodiazepines has been reported.

Sedation may sometimes occur in an individual and unpredictable manner. This effect, however, is uncommon, and is mostly transient. If necessary, decreasing the dose should be considered.

4.9 Overdose
In humans experience with clotiazepam overdose is limited.

Symptoms:
In less severe cases: look of stupor, confusion, lethargy.
In more severe cases: ataxia, hypotonia, hypotension, respiratory distress, rarely coma and very rarely death.

Treatment:
Treatment is symptomatic and inducing vomiting within the hour (if the patient is conscious) or performing evacuation by gastric lavage with the airway protected (if the patient is unconscious) and/or administration of activated charcoal (in order to reduce absorption if gastric lavage produces no results) are recommended.

Antidote:
Flumazenil is indicated in cases of serious intoxication with coma and/or respiratory insufficiency. The recommended initial IV dose is 0.3 mg. If the degree of consciousness required is not achieved within 60 seconds, further injections can be given until the patient regains consciousness or until a total maximum dose of 2 mg is achieved. Concomitant intake of tricyclics or other medicinal products that may cause convulsions, as well as ECG abnormalities (such as an increased QRS or QT interval) are major contraindications to using flumazenil.

Intoxication combined with ingestion of alcohol or other medicinal products, or in the case of underlying pathology, requires immediate hospitalisation since this may be a life-threatening situation. Respiratory and cardiovascular functions should then to be monitored in an intensive care unit.