Core Safety Profile

Active substance: Triazolam
Pharmaceutical form(s)/strength: 0,25 mg tablet
P-RMS: FI/H/PSUR/0016/002
Date of FAR: 16.01.2014
4.3. Contraindications

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

The co-administration of triazolam with ketoconazole, itraconazole, nefazodone, and efavirenz is contraindicated.

4.4. Special warnings and precautions for use

Caution must be used in treating patients with mild to moderate hepatic insufficiency. In patients with compromised respiratory function, respiratory depression and apnea have been reported infrequently.

Benzodiazepines produce an additive effect when co-administered with alcohol or other CNS depressants. Concomitant intake with alcohol is not recommended. Triazolam should be used with caution when combined with CNS depressants (see Section 4.5. Interaction with other medicinal products and other forms of interaction).

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

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.

Withdrawal symptoms: Once 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: Rebound insomnia is a transient syndrome wherein the indication for treatment (insomnia) that led to treatment with a benzodiazepine recurs, with greater severity than at baseline, 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.

Although benzodiazepines are not depressogenic, they may be associated with mental depression, which may or may not be associated with ideas of suicide or actual suicide attempts. This occurs in a rare and unpredictable fashion. Therefore, triazolam 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.

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.

In elderly and/or debilitated patients, it is recommended that treatment with triazolam be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. In other adults the recommended dose is 0.25 mg (See Section 4.2 Posology and method of administration).

Triazolam is not recommended for use in children and adolescents below the age of 18 years due to insufficient data on safety and efficacy.

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.

Complex sleep behavior-related events such as “sleep driving” (i.e. driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported in patients who are not fully awake after taking a sedative-hypnotic, including triazolam. These and other complex sleep behavior-related events may occur with sedative-hypnotics, including triazolam, alone at therapeutic doses. The use of alcohol and other CNS depressants with sedative-hypnotics appears to increase the risk of such behaviors, as does the use of sedative-hypnotics at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community,
discontinuation of sedative-hypnotics should be strongly considered for patients who report such events (see Section 4.8 Undesirable effects).

Severe anaphylactic and anaphylactoid reactions, including rare fatal cases of anaphylaxis, have been reported in patients receiving triazolam. Cases of angioedema involving the tongue, glottis, or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including triazolam (see Section 4.8 Undesirable effects).

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

Pharmacokinetic interactions can occur when triazolam is administered along 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 metabolized similarly to triazolam provide evidence for varying degrees of interaction and possible interaction with triazolam for a number of drugs. Based on the degree of interaction and the type of data available, the following recommendations are made:

- The co-administration of triazolam with ketoconazole, itraconazole, and nefazodone is contraindicated.
- The co-administration of triazolam with other azole-type antifungals is not recommended.
- Caution and consideration of dose reduction is recommended when triazolam is coadministered with cimetidine or macrolide antibiotics such as erythromycin, clarithromycin, and troleandomycin.
- Caution is recommended when triazolam is co-administered with isoniazid, fluvoxamine, sertraline, paroxetine, diltiazem, and verapamil.
- Oral contraceptives and imatinib may lead to enhanced clinical effects of triazolam due to the inhibition of the CYP3A4 isoenzyme. Caution is therefore recommended in case of concomitant use with triazolam.
- Rifampicin and carbamazepin cause CYP3A4 induction. Therefore, the effect of triazolam may be diminished significantly during therapy with rifampicin or carbamazepin. Patients should be switched to alternative hypnotics, which are mainly eliminated as glucuronides.
- Interactions involving HIV protease inhibitors (e.g. ritonavir) and triazolam are complex and time dependent. Low doses of ritonavir resulted in a large impairment of triazolam clearance, prolonged its elimination half-life and enhanced clinical effects. However, upon extended exposure to ritonavir, CYP3A induction offset this inhibition. This interaction will require a dose-reduction or discontinuation of triazolam.
- Efavirenz inhibits the oxidative metabolism of triazolam and may cause life-threatening effects, such as prolonged sedation ad respiratory depression. As a precaution, concomitant treatment is therefore contraindicated.
• Aprepitant: enhancement of the clinical effects may occur in cases of concomitant use with triazolam due to the inhibition of the enzyme CYP3A4. This interaction may require a dose-reduction of triazolam.

• Benzodiazepines produce an additive effect when co-administered with alcohol or other CNS depressants. Concomitant intake with alcohol is not recommended. Triazolam should be used with caution when combined 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 products, anaesthetics and sedative antihistamines. In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychic dependence. (see Section 4.4 Special warnings and precautions for use).

• Increased bioavailability of triazolam has been shown when taken concomitantly with grapefruit juice.

4.6. Pregnancy and lactation

The data concerning teratogenicity and effects on postnatal development and behavior following benzodiazepine treatment are inconsistent. There is evidence from some early studies with other members of the benzodiazepine class that in utero exposure may be associated with malformations. Later studies with the benzodiazepine class of drugs have provided no clear evidence of any type of defect. Infants exposed to benzodiazepines during late third trimester of pregnancy or during labor have been reported to exhibit either the floppy infant syndrome or neonatal withdrawal symptoms. If triazolam is used during pregnancy, or of the patient becomes pregnant while taking triazolam, the patient should be apprised of the potential hazard to the fetus. Triazolam should not be used by nursing mothers.

4.7. Effects on ability to drive and use machines

Triazolam can have a major influence on the ability to drive and operate machines. Patients should be advised not to drive or operate machinery during treatment until it has been established that they are not affected by daytime drowsiness or dizziness. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see also Section 4.4 Special warnings and precautions for use).
4.8. Undesirable effects

*Table 1: Adverse Reactions*

Frequency of adverse reactions observed from placebo-controlled clinical trials and post-marketing experience frequency ‘Not known.

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<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1000 to &lt;1/100)</th>
<th>Rare (≥1/10000 to &lt;1/1000)</th>
<th>Very rare (&lt;1/10000)</th>
<th>Not Known</th>
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<tr>
<td><strong>Immune system disorders</strong></td>
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<td></td>
<td>Anaphylactic shock, Anaphylactoid reaction, Angioedema, Allergic oedema, Hypersensitivity, (see Section 4.4 Special warnings and precautions for use)</td>
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<td><strong>Psychiatric Disorders</strong></td>
<td>Confusional state, Insomnia*</td>
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<td></td>
<td>Aggression, Hallucination, Somnambulism, Anterograde amnesia, Restlessness, Agitation, Irritability, Delusion, Rages, Nightmares, Psychoses, Inappropriate behaviour (see Section 4.4 Special warnings and precautions for use)</td>
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<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Somnolence, Dizziness, Ataxia, Headache</td>
<td>Memory impairment</td>
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<td>Syncope, Sedation, Depressed level of consciousness, Speech disorder, Disturbance in attention, Dysgeusia</td>
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### Very Common
($\geq 1/10$)
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<th>Common</th>
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### Eye Disorders

- Visual impairment

### Respiratory, thoracic and mediastinal disorders

- In patients with compromised respiratory function: Respiratory depression

### Skin and subcutaneous tissue disorders

- Rash

### Musculoskeletal and connective tissue disorders

- Myasthenia

### Reproductive system and breast disorders

- Change in libido

### Injury, poisoning and procedural complications

- Fall

* these adverse reactions also occurred in post-marketing experience

### 4.9. Overdose

Symptoms of overdose with triazolam are extensions of its pharmacological action and include drowsiness, slurred speech, motor in coordination, coma, and respiratory depression. Serious sequelae are rare unless other drugs and/or ethanol are concomitantly ingested. Treatment of overdosage is primarily supportive of respiratory and cardiovascular function. The value of dialysis has not been determined. Flumazenil may be used as an adjunct to the management of respiratory and cardiovascular function associated with overdose.