

European PSUR Work Sharing Project

CORE SAFETY PROFILE

Lendormin, 0.25mg, tablets Brotizolam

4.2 Posology and method of administration

Unless otherwise prescribed by the physician, the following dosages are recommended:

Adults:	0.25 mg
Elderly:	0.125 mg - 0.25 mg

Lendormin should be taken with a little liquid just before going to bed. Alternatively, the tablet may be allowed to dissolve under the tongue.

Lendormin should be taken on an empty stomach. Patients must allow a 6 - 7 hour's period after taking Lendormin to rest/sleep.

Treatment should be started with the lowest recommended dose. The maximum dose of 0.25 mg should not be exceeded because of the increased risk of unacceptable CNS-adverse effects. In patients with impaired liver function the dose should be reduced. In cases of impaired renal function, the data available show that a dose adaptation is not necessary.

Treatment should be as short as possible. The duration of treatment varies from a few days to a maximum of two weeks. The tapering-off-process should be tailored to the individual.

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

Lendormin is contraindicated in patients with myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome and in patients with severe hepatic insufficiency (see section 4.4).

Lendormin is contraindicated in patients with a known hypersensitivity to the active ingredient brotizolam, any of the excipients or to other benzodiazepines.

The available dosage forms are only suitable for adults and no investigations have been performed in children. Therefore, **Lendormin** should not be given to children and adolescents up to the age of 18.

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 over a few weeks.

Dependence

Physical and psychic dependence may develop. 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 withdrawal symptoms may vary in degree of severity ranging from slight disturbances, e.g. headaches or muscle pain, to severe psychiatric symptoms such as extreme anxiety and tension, restlessness, confusion or irritability. In severe cases the following symptoms may occur: derealization, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise or physical contact, hallucinations or epileptic seizures.

One of the first symptoms of the development of dependence is the occurrence of rebound phenomena, whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form after withdrawal of the drug. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

Since the risk of withdrawal/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be gradually decreased.

Duration of treatment

The duration of treatment should be as short as possible (see Posology), but should not exceed 2 weeks. The tapering off process should be tailored to the individual.

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.

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 sufficient uninterrupted sleep, generally of 7-8 hours (see also section 4.8).

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.

Specific patient groups

For the elderly and patients with impaired liver function, a reduction in dosage should be taken under consideration. The same precaution applies for patients with chronic respiratory insufficiency with hypercapnia due to the risk of respiratory depression, especially at night.

Brotizolam alone is not recommended for the treatment of psychotic illness. It should not be used alone to treat depression or anxiety associated with depression, as suicidal behaviour may be precipitated in such patients.

Brotizolam should not be used in patients with a history of alcohol or drug abuse.

Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy (see section 4.3).

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

When Brotizolam is prescribed with other CNS depressants, potentiation of central nervous effects may occur. Such potential interactions must be considered with a variety of agents including anti-psychotics (neuroleptics), hypnotics, anxiolytics, sedatives, antidepressants, narcotic analgesics, antiepileptics, anaesthetics and sedative antihistamines.

In the case of narcotic analgesics, potentiation of euphoria may enhance psychic dependence.

In vitro interaction investigations suggest a relevant contribution of CYP 3A4 in the hepatic metabolism of brotizolam. The potential for pharmacokinetic drug-drug interactions and resulting alterations of brotizolam activity should therefore be taken into account, if brotizolam is administered together with substrates for CYP 3A4 or even inhibitors of CYP 3A4 (e.g. ketoconazole).

Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

4.6 Pregnancy and Lactation

Insufficient data are available on brotizolam to assess its safety during pregnancy and lactation. Consequently, the use of brotizolam is not recommended during 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, although not recommended, brotizolam has been administered during the late phase of pregnancy, or during labour, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression (Floppy Infant Syndrome), 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 for developing withdrawal symptoms in the postnatal period.

Since benzodiazepines are found in the breast milk, brotizolam is not recommended for use in breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or to use machines. Concurrent use of alcohol and/or CNS-depressant drugs will potentiate this impairment. If sleep is of insufficient duration, the likelihood of impaired alertness is increased.

4.8 Undesirable effects

For determination of the frequencies of side effects pooled data from studies, in which altogether 2,603 adult healthy volunteer and patients have been treated with brotizolam over 1 day to 26 weeks, have been brought up. The following listed frequencies refer to 1,259 healthy volunteers and patients, receiving brotizolam in the recommended dose of 0.25 mg.

Frequency according MedDRA-convention

Very common ($\geq 1/10$)

Common ($\geq 1/100, < 1/10$)

Uncommon ($\geq 1/1,000, < 1/100$)

Rare ($\geq 1/10,000, < 1/1,000$)

Very rare ($< 1/10,000$),

Not known (cannot be estimated from the available data)

Psychiatric disorders

Uncommon: Aggravation of the pre-existing depression (see paragraph "Depression"), intense nightmares

Rare: numbed emotion, restlessness, agitation, irritability, changed libido, confusion

Nervous system disorders

Common: drowsiness during the day, headache

Uncommon: dizziness

Rare: reduced alertness, ataxia, anterograde amnesia (see paragraph "Amnesia")

Eye disorders

Rare: visual disorders (double vision)

Gastrointestinal disorders

Common: gastrointestinal disturbance

Hepatobiliary disorders

Rare: Hepatic dysfunction including alteration of liver function parameters, jaundice

Skin and subcutaneous tissue disorders

Rare: skin reactions

Musculoskeletal and connective tissue disorders

Rare: muscle-weakness

General disorders and administration site conditions

Rare: fatigue, paradoxical reactions (particularly in elderly patients), symptoms of withdrawal or rebound-effects (see section 4.4)

Drowsiness during the day, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or double vision. *

Intense nightmares, restlessness, agitation and irritability. **

*These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration.

** In occurrence of these adverse reactions Lendormin should be discontinued.

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 section 4.4). Psychic dependence may occur. Abuse of benzodiazepines has been reported.

Amnesia

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour (see section 4.4).

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.

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 an 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, active charcoal should be given to reduce absorption. Special attention should be given to the 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 severe cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

Flumazenil may be used as an antidote. Flumazenil product information should be consulted prior to use.