Lexotan®

Bromazepam

Roche

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Anxiolytic
ATC code: N05BA08

1.2 Type of Dosage Form

Tablets

1.3 Route of Administration

Oral

1.4 Qualitative and Quantitative Composition

Active ingredient: bromazepam.
Tablets 1.5 mg, 3 mg and 6 mg.
Excipients: Lexotan tablets contain lactose. For warning related to lactose, see 2.4.1 General (Warnings and Precautions).

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Anxiety, tension and other somatic or psychiatric complaints associated with the anxiety syndrome.
Adjunctive use for treatment of anxiety or excitation associated with psychological disorders, such as mood disorders or schizophrenia.
Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

2.2 Dosage and Administration

Standard dosage
Average dosing for outpatient therapy: 1.5–3 mg up to three times daily.
Severe cases, especially in hospital: 6–12 mg two or three times daily.
These amounts are general recommendations, and dosage should be individually determined. Treatment of outpatients should begin with low doses, gradually increasing to the optimum level. The duration of treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free. The overall treatment generally should not be more than 8–12 weeks, including a tapering off process. 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 with special expertise.

2.2.1 Special Dosage Instructions

Lexotan is usually not indicated in children, but if the physician feels Lexotan treatment is appropriate, then the dose should be adjusted to their low body-weight (about 0.1–0.3 mg/kg body-weight).
Elderly patients (see 3.2.5 Pharmacokinetics in special populations) and those with impaired hepatic function require lower doses because of individual variations in sensitivity and pharmacokinetics.

2.3 Contraindications

Lexotan must not be administered to patients with known hypersensitivity to benzodiazepines, severe respiratory insufficiency, severe hepatic insufficiency (benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may cause encephalopathy) or sleep apnea syndrome.

2.4 Warnings and Precautions

2.4.1 General

Amnesia
Benzodiazepines may induce anterograde amnesia. Anterograde amnesia may occur using higher therapeutic dosages (documented at 6 mg), the risk increasing at higher dosages.

Duration of treatment
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. It is important that the patient should be aware of the possibility of rebound phenomena that may occur while the drug is being discontinued (see 2.4.2 Drug Abuse and Dependence).

General precautions
The patient should be checked regularly at the start of treatment in order to minimize the dosage and/or the frequency of administration and to prevent overdose due to accumulation.
When benzodiazepines are used, withdrawal symptoms may develop when changing to a benzodiazepine with a considerably shorter elimination half-life (see 2.4.2 Drug Abuse and Dependence).
Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).
Benzodiazepines are not recommended for the primary treatment of psychotic illness.
Patients with known or presumed dependence on alcohol, medicines or drugs should not take benzodiazepines, except in rare situations under medical supervision (see 2.4.2 Drug Abuse and Dependence).

Specific patient groups
In patients with myasthenia gravis who are prescribed Lexotan, care should be taken on account of pre-existing muscle weakness. Particular care is required in patients with chronic respiratory insufficiency due to the risk of respiratory depression.
If containing lactose, patients with rare hereditary problems of galactose intolerance (the Lapp lactase deficiency or glucose-galactose malabsorption) should not take this medicine.

2.4.2 Drug Abuse and Dependence

Dependence
The use of benzodiazepines and benzodiazepine-like agents may lead to the development of physical and psychological dependence upon these products (see 2.6 Undesirable effects). The risk of dependence increases with dose and duration of treatment; it is also greater in predisposed patients with a history of alcohol or drug abuse.

Withdrawal
Once physical dependence has developed, 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: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures (see 2.6 Undesirable effects).
Rebound anxiety, a transient syndrome whereby the symptoms that led to treatment with Lexotan 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 and rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually.

2.4.3 Ability to Drive and Use Machines

Sedation, amnesia and impaired muscular function may adversely affect the ability to drive or to use machinery. This effect is increased if the patient has taken alcohol.

2.4.4 Interactions with other Medicinal Products and other Forms of Interaction

As with all psychoactive substances, the effect of Lexotan may be intensified by alcohol. Concomitant intake with alcohol should be avoided.
If Lexotan is combined with other centrally active drugs, its central-sedative effect may be enhanced. These drugs may include antidepressants, hypnotics, narcotic analgesics, antipsychotics, anxiolytics/sedatives, antiepileptic drugs, sedative antihistamines and anesthetics.
In the case of narcotic analgesics enhancement of euphoria may also occur, leading to an increase in psychological dependence.
There is a possibility that compounds, which inhibit certain hepatic enzymes, may influence the activity of those benzodiazepines that are metabolized by these enzymes. Co-administration of cimetidine may prolong the elimination half-life of Bromazepam.

2.5 Use in Special Populations

2.5.1 Pregnancy

The safety of bromazepam for use in human pregnancy has not been established. A review of spontaneously reported adverse drug events shows no greater incidence than would be anticipated from a similar untreated population. An increased risk of congenital malformations associated with the use of minor tranquilizers (diazepam, meprobamate and chlordiazepoxide) during the first trimester of pregnancy has been suggested in several studies. Bromazepam should be avoided during pregnancy unless there is no safer alternative.
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.
Administration of bromazepam during the last three months of pregnancy or during labor is allowed only in the event of a strict medical indication as, due to the pharmacological action of the product, effects on the neonate can be expected, such as hypothermia, hypotonia and moderate respiratory depression.
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.

2.5.2 Labor and Delivery

See 2.5.1 Pregnancy.

2.5.3 Nursing Mothers

As benzodiazepines pass into breast milk, nursing mothers should not take Lexotan.

2.5.4 Pediatric Use

See 2.2.1 Special Dosage Instructions.

2.5.5 Geriatric Use

See also 2.2.1 Special Dosage Instructions, 2.6 Undesirable Effects and 3.2.5 Pharmacokinetics in Special Populations.

2.5.6 Hepatic Impairment

See 2.2.1 Special Dosage Instructions.

2.6 Undesirable Effects

2.6.1 Post Marketing

Lexotan is well tolerated in therapeutic doses. The following undesirable effects may occur: fatigue, drowsiness, muscle weakness, numbed emotions, reduced alertness, confusion, headache, dizziness, ataxia, or double vision. These phenomena occur predominantly at the start of therapy and usually disappear with prolonged administration. Gastrointestinal disturbances, changes in libido and skin reactions have been reported occasionally.
Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnesiac effects may be associated with inappropriate behavior. Pre-existing depression may be unmasked during benzodiazepine use.

Paradoxical reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behavior and other adverse behavioral effects are known to occur when using benzodiazepines or benzodiazepine-like agents (see 2.4.2 Drug Abuse and Dependence). Should this occur, the use of the drug should be discontinued. They are more likely to occur in children and elderly patients than in other patients.
Chronic use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of therapy may result in withdrawal or rebound phenomena (see 2.4.1 General (Warnings and Precautions) and 2.4.2 Drug Abuse and Dependence). Psychological dependence may occur. Abuse of benzodiazepines has been reported**.**
An increased risk for falls and fractures has been recorded in elderly benzodiazepine users.

2.7 Overdose

Symptoms
Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Coma, hypotension and respiratory depression occasionally occur but are seldom serious if these drugs are taken alone. Coma, if it occurs, usually lasts only a few hours but it may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.
Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.

Management
Consider activated charcoal in adults or children who have taken an overdose of benzodiazepines within 1–2 hours. Airway protection is imperative in drowsy patients (e.g. use of a nasogastric tube could be considered). Induction of vomiting is not generally recommended. If the overdose is known to be small, observation of the patient and monitoring of their vital signs only may be appropriate. Gastric lavage is not recommended as a routine measure but may be considered in the presence of mixed ingestion. Patients who are asymptomatic at four hours are unlikely to develop symptoms. Institute supportive measures as indicated by the patient's clinical state.
If CNS depression is severe consider the use of flumazenil (Anexate®), a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is contraindicated in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil (Anexate®), for further information on the correct use of this drug.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

In low dosage, Lexotan selectively reduces tension and anxiety. In high dosage, sedative and muscle-relaxant properties appear.

3.2 Pharmacokinetic Properties

3.2.1 Absorption

Peak plasma concentrations are reached within 2 hours of oral administration of bromazepam. The absolute (versus i.v. solution) and relative (versus oral solution) bioavailability of the tablet is 60% and 100%, respectively.

3.2.2 Distribution

On average, 70% of bromazepam is bound to plasma proteins. The volume of distribution is 50 liters.

3.2.3 Metabolism

Bromazepam is metabolized in the liver. Quantitatively, two metabolites predominate: 3-hydroxy-bromazepam and 2-(2-amino-5-bromo-3-hydroxybenzoyl) pyridine.

3.2.4 Elimination

The urinary recovery of intact bromazepam and the glucuronide conjugates of 3-hydroxy-bromazepam and 2-(-2-amino-5-bromo-3-hydroxybenzoyl) pyridine is 2%, 27% and 40% of the administered dose.
Bromazepam has an elimination half-life of about 20 hours. The clearance is 40 ml/min.

3.2.5 Pharmacokinetics in Special Populations

Elderly
The elimination half-life may be prolonged in elderly patients (see 2.2.1 Special dosage instructions).

3.3 Preclinical safety

3.3.1 Carcinogenicity

Carcinogenicity studies conducted in rats did not reveal any evidence of a carcinogenic potential for bromazepam.

3.3.2 Mutagenicity

Bromazepam was not genotoxic in *in-vitro* and *in-vivo* tests.

3.3.3 Impairment of Fertility

Daily oral administration of bromazepam did not have any affect on the fertility and general reproductive performance of rats.

3.3.4 Teratogenicity

Increases in fetal mortality, an increase in the stillbirth rate and a reduction in pup survival have been observed when bromazepam was given to pregnant rats. In studies on embryotoxicity/teratogenicity no teratogenic effect was detected up to a dosage of 125 mg/kg/day.
Following per os administration with doses of up to 50 mg/kg/day to pregnant rabbits a reduction in maternal weight gain, a reduction in fetal weight and an increase in the incidence of resorptions have been observed.

3.3.5 Other

Chronic toxicity
No deviations from normal were observed in long-term toxicology studies except for an increase in liver weight. Histopathological examination revealed centrolobular hepatocellular hypertrophy which was considered to be indicative of enzyme induction by bromazepam. Adverse effects observed after high doses were slight to moderate sedation, ataxia, isolated brief convulsive seizures, occasional elevation in serum alkaline phosphatase and a borderline increase in SGPT (ALT).

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

This medicine should not be used after the expiry date (EXP) shown on the pack.

4.2 Packs

Tablets (scored) 1.5 mg	30, 100, 1000
Tablets (scored) 3 mg	30, 100, 1000
Tablets (scored) 6 mg	30, 100, 1000

Medicine: keep out of reach of children

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