Lexotanil®

Bromazepam

Anxiolytic

COMPOSITION

Active ingredient: bromazepam.

Excipients:

1.5 mg tablets:	tableting excipients
3 mg tablets:	tableting excipients
6 mg tablets:	colour: E132, tableting excipients

GALENICAL FORM AND AMOUNT OF ACTIVE INGREDIENT PER UNIT

1.5 mg tablets	white scored tablet, 1.5 mg bromazepam
3 mg tablets	light-red scored tablet, 3 mg bromazepam
6 mg tablets	green scored tablet, 6 mg bromazepam

INDICATIONS AND POTENTIAL USES

Emotional disorders: Anxiety and tension states, as adjuvant therapy for anxiety in depression, nervous tension, restlessness, and anxiety- and tension-related insomnia.

Functional or psychosomatic impairments of various organs caused or exacerbated by anxiety and tension, possibly as an adjuvant to treatment of underlying disease of the

- cardiovascular and respiratory systems (e.g. pseudoangina, precordial anxiety, tachycardia, hypertension of emotional origin, dyspnea, hyperventilation);
- gastrointestinal tract (e.g. adjuvant treatment of irritable bowel syndrome, ulcerative colitis, epigastric pain, spasm, abdominal distension, diarrhea);
- urogenital system (e.g. irritable bladder, urinary frequency, adjuvant treatment of dysmenorrhea);
- other psychosomatic disorders (e.g. adjuvant treatment of psychogenic headache, psychogenic dermatoses).

Lexotanil is also suitable for treatment of anxiety and tension states due to chronic organic disease and as an adjuvant to psychotherapy in psychoneuroses.

DOSAGE AND ADMINISTRATION

Standard dosage

Average dose for outpatient treatment: 1.5 – 3 mg up to three times daily.

In severe cases, especially for inpatients: 6 – 12 mg two to three times daily.

The doses indicated represent general guidelines and must be individually tailored in each case. Treatment of outpatients should begin with low doses, which should be gradually titrated to the optimum level. The duration of treatment should be as short as possible. The patient's condition should be reassessed at regular intervals and the need for continuation of treatment determined, especially when the patient's symptoms have resolved. As a general rule, the total duration of treatment should not exceed 8 – 12 weeks, including a tapering-off period. In certain cases, treatment may need to be continued beyond the maximum recommended duration, but only after careful reassessment of the patient's condition and the indication.

Special dosage instructions

As with other benzodiazepines, Lexotanil should only be given to children and adolescents after careful consideration of the relative risks and benefits. If treatment with Lexotanil is considered by a doctor to be indicated, the dose should be adjusted to the child's lower body weight.

Lower doses are also required in elderly patients and in patients with hepatic and/or renal impairment, on account of the differences in response and in the pharmacokinetics.

Duration of treatment

At the outset it may be useful to inform the patient that the duration of treatment will be for a limited time only and that the dose will be gradually reduced at the end of the treatment period. It is important for the patient to be aware that rebound effects and withdrawal symptoms may occur when treatment is discontinued.

Withdrawal symptoms may also occur when switching from one benzodiazepine to another drug in the same class with a substantially shorter elimination half-life.

CONTRAINDICATIONS

Lexotanil must not be used in patients with hypersensitivity to benzodiazepines, severe respiratory insufficiency, sleep apnea syndrome, myasthenia gravis or severe hepatic impairment (benzodiazepines are not indicated in severe hepatic impairment as they may exacerbate hepatic encephalopathy).

Patients known or suspected to be dependent on CNS depressants, including alcohol, must not take benzodiazepines.

Lexotanil must not be used by patients in whom abuse of alcohol, medicinal products, or illegal drugs has previously been diagnosed.

Hypersensitivity to the active ingredient or to any of the excipients listed under *Composition*.

WARNINGS AND PRECAUTIONS

Caution should be exercised in patients with chronic respiratory insufficiency, in view of the risk of respiratory depression.

Benzodiazepines are not suitable for the primary treatment of a psychotic disorder.

Benzodiazepines should not be used alone to treat depression or anxiety states associated with depression.

At the start of treatment patients should be closely monitored with the aim of keeping the dose and/or frequency of use as low as possible and avoiding the risk of overdose of the product due to accumulation.

Amnesia

Benzodiazepines can cause anterograde amnesia. This means that things may happen (usually a few hours) after taking the medication that the patient cannot later remember. This risk increases with the dose.

Dependence

The use of benzodiazepines may cause physical and psychological dependence. This risk is increased with prolonged use, at high dosages and in predisposed patients in whom abuse of alcohol, medicinal products, or illegal drugs has previously been diagnosed. Withdrawal symptoms occur mainly after abrupt discontinuation and in milder cases are limited to tremor, restlessness, sleep disturbances, anxiety, headache and impaired concentration. However, other symptoms may also occur, such as sweating, muscle and abdominal cramps, sensory disturbances and, in rare cases, delirium and seizures.

Depending on the duration of action of the substance, the onset of withdrawal symptoms can vary from a few hours to a week or more after discontinuation of treatment.

To keep the risk of dependence to a minimum, benzodiazepines should be prescribed only after careful assessment of the indication and should be used for the shortest possible period (e.g. as a hypnotic they should not generally be used for longer than 4 weeks). The need for continued treatment must be reviewed periodically. Longer-term treatment is only indicated in certain patients (e.g. for panic attacks), the benefits being less clear in relation to the risks.

To prevent withdrawal symptoms, tapering off is recommended as the standard method of discontinuation, i.e. the dose should be gradually reduced. Should withdrawal symptoms occur, the patient will require close medical supervision and support.

General precautions

Concomitant use of alcohol/CNS depressants

The concomitant use of Lexotanil with alcohol and/or CNS depressants should be avoided. Such concomitant use can potentially intensify the clinical action of Lexotanil, possibly with heavy sedation and clinically relevant respiratory and/or cardiovascular depression (see *Interactions*).

Lexotanil must not be used by patients in whom abuse of alcohol, medicinal products, or illegal drugs has previously been diagnosed.

Tolerance

Repeated use of Lexotanil for long periods can lead to a reduction in the response to the action of benzodiazepines.

Lexotanil tablets contain lactose. Patients with rare hereditary galactose intolerance, lactase deficiency, or glucose-galactose malabsorption should not take Lexotanil tablets.

INTERACTIONS

Pharmacodynamic interactions (DDI)

Increased sedation and heightened respiratory and hemodynamic effects are possible if Lexotanil is used in combination with CNS depressants, including alcohol.

Alcohol should be avoided by patients taking Lexotanil (see also *General precautions*).

Advice on other CNS depressants, including alcohol, is also given under *Overdosage*.

In the case of narcotic analgesics intensification of euphoria can occur, which can lead to increased psychological dependence.

In patients receiving muscle relaxants, the increased risk of muscular weakness should be borne in mind.

There is an increased risk of respiratory depression.

Pharmacokinetic interactions (DDI)

There is a possibility that drugs (e.g. antimycotics such as ketoconazole, itroconazole) that inhibit certain hepatic enzymes (particularly cytochrome P_{450}) may influence the activity of benzodiazepines metabolised by these enzymes.

The effects of Lexotanil may be transiently potentiated by cisapride as a result of an increased rate of absorption.

The elimination half-life of bromazepam is increased by the concomitant administration of therapeutic doses of cimetidine.

PREGNANGY AND LACTATION

Pregnancy

Lexotanil should not be used during pregnancy unless it is clearly necessary and there is no safer alternative available.

If the drug is prescribed to a woman of child-bearing age, she should be advised to tell her doctor if she plans to become or suspects that she is pregnant, so that treatment may be discontinued.

The safety of bromazepam in pregnant women has not been established. There is no evidence from spontaneously reported adverse drug reactions that the incidence is any higher than would be expected in a similar, untreated group of patients. Several studies have reported an increased risk of congenital malformations when tranquillisers

(diazepam, meprobamate or chlordiazepoxide) are taken during the first trimester of pregnancy.

In humans, the risk of malformation associated with the use of therapeutic doses of benzodiazepines in early pregnancy appears to be low, although some epidemiological studies have pointed to an increased risk of cleft palate. There are case reports of malformations and mental retardation in children exposed prenatally after overdose and intoxication.

Use of bromazepam during the last trimester of pregnancy or during labour is allowed only if the clinical indication has been rigorously established, as the pharmacological action of the product means that effects on the neonate such as hypothermia, hypotonia and moderate respiratory depression can be expected.

Moreover, infants born to mothers who took benzodiazepines regularly during the later stages of pregnancy may have developed physical dependence and may therefore be at risk of developing withdrawal symptoms in the postnatal period.

Lactation

As benzodiazepines pass into breast milk, Lexotanil should not be taken by nursing mothers or else breastfeeding should be discontinued.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As a consequence of the action and possible side effects of the drug, the ability to drive, operate machinery or undertake any other hazardous activities may be impaired. Patients should therefore abstain from such activities entirely or at the very least for the first few days of treatment. The decision in each individual case must be made by the doctor in charge of the patient's treatment on the basis of individual reaction and the administered dose. The patient must also be warned to abstain from alcohol while on the drug, as this combination can potentiate the undesirable effects of both substances.

UNDESIRABLE EFFECTS

Post-marketing experience

During treatment with bromazepam, the following adverse effects can be expected to occur with the greatest frequency: sedation, dizziness, drowsiness, hypotension, poor concentration and slow reactions. There have been frequent reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Psychiatric disturbances

Numbed emotions, reduced alertness, confusion. These effects occur primarily at the start of treatment and generally disappear with continued use.

Pre-existing depression may be unmasked during treatment with benzodiazepines.

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, fits of rage, nightmares, hallucinations, psychosis, inappropriate behaviour and other adverse behavioural effects are known to occur in patients treated with benzodiazepines or benzodiazepine-like substances (see *Warnings and precautions*). Such reactions are more likely in children and the elderly than in other groups. If they do occur, use of the drug should be discontinued.

Nervous system

Common:

Fatigue, drowsiness, headache, poor concentration, dizziness, slow reactions.

Rare:

Ataxia, anterograde amnesia.

These effects occur primarily at the start of treatment and generally disappear with continued use.

Anterograde amnesia may occur at therapeutic doses, with the risk increasing at higher doses. This means that things may happen (usually a few hours) after taking the medication that the patient cannot later remember.

Eyes

Double vision

This effect occurs primarily at the start of treatment and generally disappears with continued use.

Ear and inner ear

Common:

Dizziness

This effect occurs primarily at the start of treatment and generally disappears with continued use.

Heart

Hypotension. Heart failure, including cardiac arrest.

Respiratory organs

Respiratory depression.

Gastrointestinal disturbances

Uncommon:

Gastrointestinal disturbances

Rare:

Nausea, dry mouth, increased appetite.

Skin

Uncommon:

Dermatological reactions

Musculoskeletal system

Rare:

Muscle weakness

Reproductive system and breast

Uncommon:

Decreased libido

Dependence

Long-term use (even at therapeutic doses) can lead to physical dependence: withdrawal symptoms or rebound effects may occur when the drug is discontinued (see *Warnings and precautions*). Psychological dependence is likewise possible. There have been reports of benzodiazepine abuse.

OVERDOSAGE

Symptoms

Overdosage with benzodiazepines commonly leads to stupor, ataxia, dysarthria, and nystagmus.

Although overdosage with Lexotanil is rarely life-threatening when the product has been taken on its own, it can lead to areflexia, apnea, hypotension, cardiorespiratory depression, and coma. If coma develops, it generally lasts only a few hours, but can sometimes be protracted and cyclic, particularly in the elderly. Respiratory depression caused by benzodiazepines is more severe in patients with respiratory illnesses.

Benzodiazepines potentiate the effects of other CNS depressants, including alcohol.

Treatment

Monitor the patient's vital functions and instigate whatever supportive measures are indicated by his/her clinical state. Patients may, in particular, require symptomatic treatment of cardiorespiratory or CNS effects.

Further absorption should be prevented by appropriate means, e.g. by treatment with activated charcoal within 1–2 h. In drowsy patients, airway protection is essential if activated charcoal is administered. If more than one substance has been ingested, gastric lavage may be considered, but is not a routine countermeasure.

In patients with serious CNS depression, administration of the benzodiazepine antagonist flumazenil (Anexate®) should be considered. This product must, however, be administered under close supervision and, because it only has a short half-life (about one hour), patients administered flumazenil must be kept under supervision once its effects have worn off. Flumazenil must be used with extreme caution after ingestion of substances that lower the seizure threshold (e.g. tricyclic antidepressants). For further

information on the correct use of flumazenil (Anexate®), refer to the prescribing information for the product.

PROPERTIES/EFFECTS

ATC code: ***N05BA08.***

Mechanism of action/pharmacodynamics

Benzodiazepines bind to specific benzodiazepine receptors that form part of the gamma-aminobutyric acid type A (GABAA) receptor complex. By opening chloride ion channels in the cell membrane, they potentiate the action of GABA, the most important inhibitory neurotransmitter in the central nervous system.

At low doses, Lexotanil relieves anxiety, tension and nervousness. At high doses, it has sedative and muscle relaxant effects.

Clinical efficacy

Clinical efficacy has been demonstrated in various clinical studies.

PHARMACOKINETICS

Absorption

After oral administration of bromazepam, peak plasma concentrations are reached within 2 h. The absolute bioavailability of the tablets (relative to the i.v. solution) is 60%.

Distribution

The mean plasma protein binding of bromazepam is 70%. The mean volume of distribution (V_D) is approximately 50 L.

Metabolism

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

Elimination

Bromazepam has an elimination half-life of about 20 h. On average, only 2.3% of the dose is excreted unchanged in the urine. The two principal metabolites, 3-hydroxybromazepam and 2-(2-amino-5-bromo-3-hydroxybenzoyl)-pyridine, are eliminated via the urine (recoveries of 27% and 40% respectively).

As a consequence of rapid glucuronidation, 3-hydroxybromazepam does not occur in clinically relevant concentrations. The benzoylpyridine metabolite is inactive.

The total plasma clearance is on average approximately 40 ml/min.

Pharmacokinetics in special populations

The half-life may be longer in the elderly (see *Special dosage instructions*).

For further information see *Special dosage instructions*.

PRECLINICAL DATA

Carcinogenicity
Carcinogenicity studies in rats have not brought to light evidence of any carcinogenic potential for bromazepam.

Mutagenicity
In-vitro and in-vivo tests have not brought to light evidence of any mutagenic potential for bromazepam.

Impairment of fertility
Daily oral administration of bromazepam in rats had no effect on the animals' fertility and general reproductive ability.

Teratogenicity
An increase in fetal mortality and in the number of stillbirths and a reduction in the survival rate of the offspring was observed after administration of bromazepam to pregnant rats. In embryotoxicity/teratogenicity studies, no teratogenic effects were observed at dosages of up to 125 mg/kg/day.

After oral doses of up to 50 mg/kg/day in pregnant rabbits, reduced maternal weight gain, lower fetal weight, and increased occurrence of fetal reabsorption were observed.

Chronic toxicity
In long-term toxicology studies, no deviations from normal values were observed other than an increase in liver weight. Histopathological investigation revealed centrolobular hepatocellular hypertrophy, which was attributed to enzyme induction due to bromazepam. After administration of high doses, the following side effects have been observed: mild to moderate sedation, ataxia, individual cases of seizures of short duration, occasional serum alkaline phosphatase elevations, and borderline SGPT (ALT) elevation.

SPECIAL REMARKS

Shelf life
The product may only be used up to the date shown on the pack next to 'EXP'.

Special instructions for storage
Do not store above 30°C. Keep out of reach of children.

PACKS

1.5 mg tablets (scored; white)	30, 100
3 mg tablets (scored; light red)	30, 100
6 mg tablets (scored; green)	30, 100

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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