Leaflet 1,5 mg **Lexotan MY**
DRAFT (DATE) 05.02.2025 [12:58 uhr] (1)
COLOURS Pantone Black linework
DIMENSIONS 140 x 780 mm
MATERIAL NUMBER 90002931/11
FONT SIZE 9 pt
PRODUCT CODE AESICA 4024388
LAETUS CODE 12/524 4619

PACK INSERT FOR MALAYSIA

Lexotan®

Bromazepam

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
The tablets are of a slightly yellowish colour.
Excipients: Lexotan tablets contain lactose. For warning related to lactose, see section 2.4.1 General (Warnings and Precautions).

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Emotional disturbances. Acute tension and anxiety states. Difficulties in interpersonal contact. Agitation, insomnia. Anxious, agitated depressive reactions.
Functional disturbances in the vascular and respiratory systems (pseudoangina pectoris, precordial anxiety, tachycardia, emotiogenic hypertension, dyspnea, hyperventilation); in the gastrointestinal system (irritable bowel syndrome, epigastric pain, spasm, bloating diarrhea, etc); in the genitourinary system (frequency, irritable bladder; dysmenorrhea).
Psychosomatic disorders. Psychogenic headache. Psychogenic dermatosis. Asthma. Gastric and duodenal ulcer, ulcerative colitis.
Emotional reactions to chronic organic disease.
Adjuvant to psychotherapy in psychoneurosis.

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.

Duration of treatment
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.
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.

2.2.1 Special Dosage Instructions

Pediatric use
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).

Geriatric use
Elderly patients (see section 2.5 Use in Special Populations and 3.2.5 Pharmacokinetics in Special Populations) require lower doses because of potentially increased sensitivity and changed pharmacokinetics.

Hepatic impairment
Patients with severe hepatic impairment should not be treated with Lexotan tablets (see section 2.3 Contraindications). In patients with mild or moderate hepatic impairment, the lowest dose possible should be given.

2.3 Contraindications

Lexotan is contraindicated in patients with:

- known hypersensitivity to benzodiazepines or any of the excipients
- severe respiratory insufficiency
- severe hepatic impairment as benzodiazepines may precipitate hepatic encephalopathy
- 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 section 2.4.2 Drug Abuse and Dependence).

General precautions
Concomitant use of alcohol / CNS depressants
The concomitant use of Lexotan with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of Lexotan possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression, that could result in coma or death (see section 2.7 Overdose and 2.8 Interactions with other Medicinal Products and other Forms of Interaction).

Medical history of alcohol or drug abuse
Lexotan should be used with extreme caution in patients with a medical history of alcohol or drug abuse (see section 2.4.2 Drug Abuse and Dependence).

Tolerance
Some loss of response to the effects of Lexotan may develop after repeated use for a prolonged time.
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.

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 the excipients include lactose (see section 1.4 Qualitative and Quantitative Composition), patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling) which can occur as early as the first time the product is taken.
Complex sleep-related behaviours which may induce sleep driving, making phone calls, preparing and eating food (while asleep).

Hepatic impairment
Benzodiazepines may have a contributory role in precipitating episodes of hepatic encephalopathy in patients with severe hepatic impairment (see section 2.3 Contraindications). Special caution should be exercised when administering Lexotan to patients with mild to moderate hepatic impairment.

Psychiatric and 'paradoxical' reactions
Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, anxiety, delusion, anger, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, the use of the drug should be discontinued. They are more likely to occur in children and in the elderly.

Risks from concomitant use with opioids
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Lexotan with opioids. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.
If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.
Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Lexotan is used with opioids.
Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined.
Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of opioids (see section 2.8 Interactions with other Medicinal Products and other Forms of Interaction).

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 section 2.6 Undesirable Effects). The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol or drug abuse. Therefore, Lexotan should be used with extreme caution in patients with a history of alcohol and drug abuse. Abuse has been reported more commonly in poly-drug abusers.

Withdrawal
Once physical dependence has developed, termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, diarrhea, 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 convulsions (see section 2.6 Undesirable Effects).
When benzodiazepines are used, withdrawal symptoms may develop when switching to a benzodiazepine with a considerably shorter elimination half-life.

Rebound anxiety
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 (see section 2.8 Interactions with other Medicinal Products and other Forms of Interaction).

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 section 2.5.1 Pregnancy.

2.5.3 Lactation

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

2.5.4 Pediatric Use

See section 2.2.1 Special Dosage Instructions.

2.5.5 Geriatric Use

See also section 2.2.1 Special Dosage Instructions, 2.6 Undesirable Effects and 3.2.5 Pharmacokinetics in Special Populations.
The pharmacological effects of benzodiazepines appear to be greater in elderly patients than in younger patients, even at similar plasma benzodiazepine concentrations, possibly because of age-related changes in drug-receptor interactions, post-receptor mechanisms and organ function. A reduction in dose for patients above 50 years is recommended.

2.5.6 Hepatic Impairment

See section 2.2.1 Special Dosage Instructions, 2.3 Contraindications and 2.4.1 General (Warnings and Precautions).

2.6 Undesirable Effects

2.6.1 Post Marketing

Description of selected adverse drug reactions from post marketing experience
Lexotan is well tolerated in therapeutic doses. The following undesirable effects may occur:
Psychiatric Disorders: Confusional state, disorientation, emotional and mood disturbance. These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration. Change in libido have been reported occasionally.
Depression: Pre-existing depression may be unmasked during benzodiazepine use.
Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, anger, nightmares, hallucinations, psychoses, inappropriate behaviour, nervousness, anxiety, abnormal dreams, hyperactivity and other adverse behavioural effects are known to occur. They are more likely to occur in children and elderly patients than in other patients.
Dependence: Chronic use (even at therapeutic doses) may lead to the development of physical and psychological drug dependence; discontinuation of therapy may result in withdrawal or rebound phenomena (see section 2.4.1 General (Warnings and Precautions) and 2.4.2 Drug Abuse and Dependence).
Abuse of benzodiazepines is more common in poly-drug abusers.
Nervous System Disorder: Drowsiness, headache, dizziness, decreased alertness, ataxia. These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration.
Anterograde amnesia may occur at therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.
Eye Disorders: Diplopia, this phenomenon occurs predominantly at the start of therapy and usually disappears with repeated administration.
Gastrointestinal Disorders: Gastrointestinal disorders have been reported occasionally.
Skin and Subcutaneous Tissue Disorders: Skin reactions have been reported occasionally.
Musculoskeletal and Connective Tissue Disorders: Muscle weakness, this phenomenon occurs predominantly at the start of therapy and usually disappears with repeated administration.
General Disorders and Administration Site Conditions: Fatigue, this phenomenon occurs predominantly at the start of therapy and usually disappears with repeated administration.
Injury, Poisoning and Procedural Complications: There have been reports of falls and fractures in benzodiazepine users.

The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Leaflet 1,5 mg **Lexotan MY**
DRAFT (DATE) 05.02.2025 [12:58 uhr] (1)
COLOURS Pantone Black linework
DIMENSIONS 140 x 780 mm
MATERIAL NUMBER 90002931/11
FONT SIZE 9 pt
PRODUCT CODE AESICA 4024388
LAETUS CODE 12/524 4619

Respiratory Disorders: Respiratory depression.
Cardiac Disorders: Cardiac failure including cardiac arrest.

2.7 Overdose

Symptoms
Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of Lexotan is seldom life-threatening if the drug is take alone, but may lead to areflexia, apnea, hypotension, cardiorespiratory depression and coma. 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.

Treatment
Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.
Further absorption should be prevented using an appropriate method e.g. treatment within 1-2 hours with activated charcoal. If activated charcoal is used airway protection is imperative for drowsy patients. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.
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 to be used with extreme caution 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.

2.8 Interactions with Other Medicinal Products and Other Forms of Interaction

Pharmacokinetic Drug-drug Interaction (DDI)
There is a possibility that compounds, which inhibit key oxidative hepatic enzymes, may enhance the activity of benzodiazepines. Co-administration of cimetidine, a multi-CYP inhibitor, and possibly propanolol - may prolong the elimination half-life of bromazepam through a substantially reduced clearance (with cimetidine: reduction by 50%). Combined administration with fluvoxamine, an inhibitor of CYP1A2, results in significantly increased bromazepam exposure (AUC, 2.4-fold) and elimination half-life (1.9-fold).
Bromazepam did not affect antipyrine metabolism, which is a surrogate marker for CYP1A2, CYP2B6, CYP2C, CYP3A activity. Furthermore, bromazepam did not induce major CYP450 isozymes in-vitro at the level of mRNA; also it did not activate nuclear hormone receptors. Therefore, bromazepam is unlikely to cause pharmacokinetic drug-drug interactions based on CYP450 induction.

Pharmacodynamic Drug-Drug Interaction (DDI)
Enhanced side effects such as sedation and cardiorespiratory depression may also occur when bromazepam is co-administered with any centrally acting depressants including alcohol. Alcohol should be avoided in patients receiving bromazepam (see section 2.4.1 General (Warnings and Precautions)). See section 2.7 Overdose for warning of other central nervous system depressants, including alcohol.
In the case of narcotic analgesics enhancement of euphoria may also occur, leading to an increase in drug dependence.

Opioids
Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.
The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see section 2.4 Warnings and Precautions). Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

The central actions of benzodiazepines are mediated through an enhancement of the GABAergic neurotransmission at inhibitory synapses. In the presence of benzodiazepines, the affinity of the GABA receptor for the neurotransmitter is enhanced through positive allosteric modulation resulting in an increased action of released GABA on the postsynaptic transmembrane chloride ion flux.
At low dosage, Lexotan selectively reduces tension and anxiety. At high dosage, sedative and muscle-relaxant properties appear.

3.2 Pharmacokinetic Properties

3.2.1 Absorption

Bromazepam is absorbed quickly and reaches peak plasma concentrations within 2 hours after oral administration. The absolute bioavailability of bromazepam from the tablet is 60%.
Food may decrease the bioavailability of bromazepam, however, the clinical relevance of this has not been established. During multiple dosing of bromazepam the extent of absorption remains constant; predictable steady-state concentrations are observed and confirm linear kinetics for the drug. Steady-state plasma concentrations are reached in around 5-9 days. Following multiple oral doses of 3 mg given three times daily, the average maximum concentration of bromazepam at steady-state was 120 ng/mL which is 3- to 4- fold higher than that observed after a single 3 mg dose.

3.2.2 Distribution

After absorption, bromazepam is rapidly distributed in the body. On average, 70% of bromazepam is bound by hydrophobic interaction to plasma proteins; binding partners are albumin and α1-acid glycoprotein. The volume of distribution is around 50 liters.

3.2.3 Metabolism

Bromazepam is extensively metabolized in the liver. No metabolites with a half-life longer than that of the parent drug are formed. Quantitatively, two metabolites dominate, 3-hydroxy-bromazepam (less active than bromazepam) and 2-(2-amino-5-bromo-3-hydroxybenzoyl) pyridine (inactive).
Bromazepam is metabolized, at least in part, through cytochrome P450 (CYP450). However, the specific CYP isozymes involved have not been identified. Nevertheless, the observations that a strong CYP3A4 inhibitor (itraconazole) and a moderate CYP2C9 inhibitor (fluconazole) had no effect on the pharmacokinetics of bromazepam suggest that these isozymes are not involved to a major extent. The pronounced interaction with fluvoxamine (see section 2.8 Interactions with other Medicinal Products and other Forms of Interaction – Pharmacokinetic Drug-drug Interaction) points to involvement of CYP1A2.

3.2.4 Elimination

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

3.2.5 Pharmacokinetics in Special Populations

Geriatric population
Elderly patients may have significantly higher peak concentrations, a smaller volume of distribution, increased serum free fraction, lower clearance and hence also a prolonged elimination half-life. This indicates that steady-state concentrations of bromazepam at any given dosing rate will be on average nearly twice as high in an elderly subject as compared to a younger individual. (see section 2.2.1 Special Dosage Instructions).

Renal impairment
No formal pharmacokinetic study has been conducted and no population PK data was collected in patients with renal impairment.

Hepatic impairment
No formal pharmacokinetic study has been conducted and no population PK data was collected in patients with hepatic impairment.

3.3 Nonclinical safety

3.3.1 Carcinogenicity

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

3.3.2 Genotoxicity

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 effect on the fertility and general reproductive performance of rats.

3.3.4 Reproductive Toxicity

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 oral 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.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

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

4.2 Special Instructions for Use, Handling and Disposal

The release of pharmaceutical in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

4.3 Packs

Tablets (scored) 1.5 mg 100

Medicine: keep out of reach of children

MYLexotan1118CDS8.0

Revision Date: August 2024

Made for CHEPLAPHARM Arzneimittel GmbH, Greifswald, Germany,
By Aesica Pharmaceuticals GmbH, Zwickau, Germany