Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lexotan 1.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1.5 mg bromazepam.

Excipient(s) with known effect: Also contains 96.1 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Off white to slightly yellow, cylindrical, biplane tablets scored on one side and marked 1.5 on the reverse.
The tablets can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Anxiety
Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Anxiety
Treatment should be as short as possible. The overall duration of treatment generally should not be more than 8 – 12 weeks, including a tapering off process.

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 patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free.

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.

Posology

Adults
The lowest dose which can control symptoms should be used.

The optimum dosage and frequency of administration of Lexotan should be based on the individual patient, the severity of symptoms and previous psychotropic drug history.

The usual dosage in general practice is from 3 mg to 18 mg daily in divided doses.

In exceptional circumstances, in hospitalised patients, up to the maximum daily dosage of 60 mg in divided doses, may be given.

A reduction in dose for elderly patients is recommended. Treatment should always be tapered off gradually. Patients who have taken benzodiazepines for a prolonged time may require a longer period during which doses are reduced. Specialist help may be appropriate.

Elderly and/or debilitated patients
Elderly patients require lower doses because of individual variations in sensitivity and pharmacokinetics; doses should not exceed half those normally recommended (see section 5.2).

Patients with hepatic impairment
Patients with severe hepatic impairment should not be treated with Lexotan tablets (see section 4.3 Contra-indications).
Patients with mild or moderate impaired hepatic and/or renal function require the lowest dose possible because of individual variations in sensitivity and pharmacokinetics.
With the elderly and patients with impaired renal and/or hepatic function, it is advisable to review treatment regularly and to discontinue use as soon as possible.

Children
Lexotan should not be used in children less than 12 years of age. The safety and efficacy of Lexotan in children less than 12 years has not been established. Currently available data are described in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made.

4.3 Contraindications

Bromazepam is contraindicated in patients with:

- known hypersensitivity to benzodiazepines or to any of the excipients listed in section 6.1.
- severe respiratory insufficiency.
- severe hepatic impairment as benzodiazepines may precipitate hepatic encephalopathy.
- myasthenia gravis or sleep apnea syndrome.

4.4 Special warnings and precautions for use

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 several hours. Amnestic effects may be associated with inappropriate behaviour (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.

Duration of treatment
The duration of treatment should be as short as possible (see section 4.2 Posology) and should not exceed eight to twelve weeks, including a tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.

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.

Concomitant use of alcohol / CNS depressants:
The concomitant use of bromazepam with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of bromazepam possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression, that could result in coma or death (see section 4.5 and section 4.9).

The patient should be checked regularly at the start of treatment in order to minimise the dosage and/or the frequency of administration and to prevent overdose due to accumulation.

Tolerance
Some loss of efficacy to the effects of benzodiazepines may develop after repeated use for a few weeks.

Specific patient groups
Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum.

Elderly should be given a reduced dose (see section 4.2 Posology).

In patients with myasthenia gravis who are prescribed Lexotan, care should be taken on account of pre-existing muscle weakness.

A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients). Therefore, bromazepam 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.

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse (see section 4.5).

Hepatic impairment
Benzodiazepines may have a contributory role in precipitating episodes of hepatic encephalopathy in patients with severe hepatic impairment (see section 4.3 Contra-indications). Special caution should be exercised when administering Lexotan to patients with mild to moderate hepatic impairment.

Dependence
Use of benzodiazepines may lead to the development of physical and psychological 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. Therefore, bromazepam should be used with extreme caution in patients with a history of alcohol or drug abuse. Abuse has been reported more commonly in poly-drug abusers.

When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, diarrhoea, 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 convulsions (see section 4.8 Undesirable effects).

Rebound anxiety
Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine 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/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsoption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic Interaction
Benzodiazepines may produce enhanced side effects such as sedation and cardio-respiratory depression when co-administered with alcohol or other CNS depressants. Concomitant intake with alcohol is not recommended.

Bromazepam should be used with caution when combined with other CNS depressants. Enhancement of the central depressive effect may occur in case of concomitant use with antipsychotics (neuroleptics), anxiolytics/sedatives, some antidepressant agents, opioids, anticonvulsants, sedative H1-antihistamines.

Special care should be made with drugs depressing respiratory function such as opioids (analgesics, antitussives, substitutive treatments), notably in elderly people.

Warning for overdose of other central nervous system depressants, including alcohol (see section 4.9).

Pharmacokinetic Interaction
Pharmacokinetic interactions can occur when bromazepam is administered along with drugs that inhibit the hepatic enzyme CYP3A4 by increasing the plasma levels of bromazepam. To a lesser degree this also applies to benzodiazepines that are metabolized only by conjugation.

The co-administration of bromazepam with strong CYP3A4 inhibitors (for example azole antifungals, protease inhibitors or some macrolides) should be made with caution and a substantial dose reduction considered. In the case of narcotic analgesics enhancement of euphoria may also occur, leading to an increase in drug dependence.
Co-administration of cimetidine, a known inhibitor of many isozymes of the cytochrome P450 enzyme system (specifically CYP3A3/4, CYP2C9, CYP1A2, CYP2C18, CYP2D6) may prolong the elimination half-life of bromazepam through a substantially reduced clearance of approximately 50%.

Co-administration of propranolol prolongs the elimination half-life of bromazepam by approximately 20% and results in a non-significant increase in bromazepam clearance.

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 and 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.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
Although no specific clinical data are available for bromazepam, a large amount of data based on cohort studies indicate that first trimester exposure to benzodiazepine is not associated with an increase in the risk of major malformation. However, some early case-control epidemiological studies have found an increased risk of oral clefts. The data indicated that the risk of having an infant with an oral cleft after maternal benzodiazepine exposure is less than 2/1000 compared with an expected rate for such defects of approximately 1/1000 in the general population.

Benzodiazepine treatment at high dose, during the second and/or the third trimester of pregnancy, has revealed a decrease of foetal active movements and a variability of foetal cardiac rhythm.

When treatment has to be administered for medical reasons during the last part of pregnancy, even at low doses, floppy infant syndrome such as axial hypotonia, sucking troubles leading to a poor weight gain may be observed. These signs are reversible but they may last from 1 up to 3 weeks, according to the half-life of the product. At high doses, respiratory depression or apnea and hypothermia in newborns may appear. Moreover, neonatal withdrawal symptoms with hyperexitability, agitation and tremor may be observed a few days after birth, even if no floppy infant syndrome is observed.

Taking into account these data, the use of bromazepam during pregnancy may be considered, if therapeutic indications and posology are strictly respected.

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 bromazepam treatment is necessary during the last part of pregnancy, high doses should be avoided and withdrawal symptoms and/or floppy infant syndrome should be monitored in newborns.

Animal studies with benzodiazepines have shown minor effects on the foetus while a few studies have reported a late behavioral disturbance in offspring exposed *in utero*.

Lactation
Since bromazepam is transferred to breast milk, breast feeding is not recommended during treatment.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see also section 4.5*)*. This effect is increased if the patient has taken alcohol.

4.8 Undesirable effects

Lexotan is well tolerated in therapeutic doses.

The following undesirable effects have been reported during treatment with bromazepam with the following frequencies:
Very common: ≥1/10;
Common ≥1/100 to <1/10;
Uncommon ≥1/1,000 to <1/100
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

MedDRA System Organ Class	Undesirable effects
Immune System Disorders	
frequency not known	Hypersensitivity**, anaphylactic shock, angioedema
Psychiatric Disorders	
frequency not known	Confusional state*, disorientation, emotional and mood disturbances*, changes in libido, drug dependence**, drug abuse**, withdrawal syndrome** Depression Paradoxical reactions such as restlessness**, agitation**, irritability**, aggressiveness**, delusion**, anger, nightmares**, hallucinations**, psychoses**, inappropriate behaviour**, nervousness, anxiety, abnormal dreams, hyperactivity Anterograde amnesia**, memory impairment
Nervous System Disorders	
frequency not known	Somnolence*, headache*, dizziness*, decreased alertness*, ataxia*
Eye Disorders	
frequency not known	Diplopia*
Cardiac Disorders	
frequency not known	Cardiac failure including cardiac arrest
Respiratory, Thoracic and Mediastinal Disorders	
frequency not known	Respiratory depression
Gastrointestinal Disorders	
frequency not known	Nausea*, vomiting*, constipation
Skin and Subcutaneous Tissue Disorders	
frequency not known	Rash, pruritus, urticaria
Musculoskeletal and Connective Tissue Disorders	
frequency not known	Muscle weakness*
Renal and Urinary disorders	

frequency not known	Urinary retention
General Disorders and Administration Site Conditions	
frequency not known	Fatigue*
Injury, Poisoning and Procedural Complications	
frequency not known	Falls, fractures***

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

** see 4.4 Warnings and Precautions

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2. Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms
Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of bromazepam is seldom life-threatening if the drug is taken alone, but may lead to slurred speech areflexia, apnea, hypotension, cardiorespiratory depression and coma. Coma, if it occurs, usually lasts 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytic, ATC code: N05BA08.

Bromazepam is a pyridylbenzodiazepine compound with anxiolytic properties.

5.2 Pharmacokinetic properties

Absorption
Bromazepam is rapidly absorbed from the gastro-intestinal tract and reaches peak plasma concentrations within 2 hours of 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.

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 a1-acid glycoprotein. The volume of distribution is around 50 liters.

Biotransformation
Bromazepam is extensively metabolised 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). Metabolites of Lexotan do not contribute significantly to the effects of the drug.

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 4.5 Interaction with other medicinal products and other forms of interaction) points to co-involvement of CYP1A2.

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.

Pharmacokinetics in special populations

Elderly population
Older people may have significantly higher peak concentrations, a smaller volume 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 4.2 ''Posology and method of administration'').

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 elderly patients is recommended.

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.

5.3 Preclinical safety data

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

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

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose monohydrate
Magnesium stearate
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVDC blister packs: 5 years
HDPE bottles: 5 years
PVC blister packs: 5 years
PVC/PVDC/aluminium blister packs: 5 years

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

PVDC blister packs of 4, 10, 20, 60 or 100 tablets.
HDPE bottles of 100 tablets.
PVC blister packs of 30 tablets.
PVC/PVDC/aluminium blister packs of 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Cheplapharm Arzneimittel GmbH
Ziegelhof 24
17489
Greifswald
Germany

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 October 1980

Date of last renewal: 31 October 2010

10 DATE OF REVISION OF THE TEXT

July 2025