AUSTRALIAN PRODUCT INFORMATION
Lexotan® (bromazepam)

1. NAME OF THE MEDICINE
Bromazepam

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Lexotan 3 mg tablets contain bromazepam 3 mg

Lexotan 6 mg tablets contain bromazepam 6 mg

Excipients with known effect: contains sugars as lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablets

Lexotan 3 mg tablets are pale red, slightly speckled, cylindrical, biplanar tablets marked with /3 on one side and a simple break mark on the other side.

Lexotan 6 mg tablets are greenish-grey to greyish-green, slightly speckled, cylindrical, biplanar tablets marked with /6 on one side and a simple break mark on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Symptomatic relief of tension, anxiety and agitation. Anxiety and tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

4.2 DOSE AND METHOD OF ADMINISTRATION
Dose

As the effect of food on bromazepam absorption is unknown, doses should preferably be given on an empty stomach.

The maximum recommended dose is 60 mg daily.

Average dose for ambulatory patients
3 mg two or three times daily. It is often an advantage to make the evening dose larger than other doses, or when the total dose is low (e.g. 3 or 6 mg), to give the total dose in the evening.

Severe hospitalised cases
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. When treatment is ceased withdrawal should be gradual. The duration of treatment should be as short as possible.

Patients 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 of bromazepam.

The patient should be reassessed regularly and the need for continued treatment should be evaluated. The overall treatment should not be more than 2 – 4 weeks, followed by a tapering off process of up to 6 – 8 weeks (see section 4.4 Special warnings and precautions for use).

Special Dosage Instructions

Paediatric use

Bromazepam is not recommended in children as there is insufficient evidence of safety and efficacy in this group.

Use in elderly

Elderly patients require lower doses (see section 4.4 Special warnings and precautions for use).

Use in hepatic impairment

Patients with severe hepatic impairment should not be treated with Lexotan tablets (see section 4.3 Contraindications). In patients with mild or moderate hepatic impairment, the lowest dose possible should be given.

4.3 CONTRAINDICATIONS

Lexotan is contraindicated in patients with:

- known hypersensivity to benzodiazepines or any of the excipients
- severe respiratory insufficiency, including chronic obstructive airways disease with incipient respiratory failure
- severe hepatic impairment as it may precipitate hepatic encephalopathy
- sleep apnoea syndrome
- myasthenia gravis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Medical History of Alcohol or Drug Abuse

Patients with known or presumed dependence on alcohol or drugs should not take benzodiazepines unless under medical supervision.

Concomitant use of Alcohol/CNS Depressants

Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and concomitant use of Lexotan and alcohol 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 sections 4.5 Interactions with other medicines and other forms of interaction and 4.9 Overdose).

Duration of Treatment

In general, benzodiazepines should be prescribed for short periods only (e.g. 2 – 4 weeks). Continuous long-term use of Lexotan is not recommended. There is evidence that tolerance develops to the sedative effects of benzodiazepines. After as little as one week of therapy, withdrawal symptoms can appear following the cessation of recommended doses (e.g. rebound insomnia following cessation of a hypnotic benzodiazepine).

Following the prolonged use of Lexotan at therapeutic doses, withdrawal from the medication should be gradual. An individualised withdrawal timetable needs to be planned for each patient in whom

dependence is known or suspected. Periods from four weeks to four months have been suggested. As with other benzodiazepines, when treatment is suddenly withdrawn, a temporary increase in sleep disturbance can occur after use of Lexotan (see information on Dependence below).

Hypotension
Although hypotension has occurred rarely, Lexotan should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac or cerebral complications. This is particularly important in elderly patients.

Amnesia
Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines. Anterograde amnesia may occur at therapeutic dosages with the risk increasing at higher dosages. Amnesiac effects may be associated with inappropriate behaviour.

Myasthenia Gravis
Lexotan could increase the muscle weakness in myasthenia gravis and should not be used in patients with this condition (see section 4.3 Contraindications).

Acute Narrow-angle Glaucoma
Caution should be used in the treatment of patients with acute narrow-angle glaucoma because of atropine-like side effects.

Impaired Renal/Liver Function and Blood Dyscrasias
Patients with impaired renal or hepatic function should use benzodiazepine medication with caution and dosage reduction may be advisable. In rare instances, some patients taking benzodiazepines have developed blood dyscrasias, and some have had elevation of liver enzymes. As with other benzodiazepines, periodic blood counts and liver function tests are recommended.

Depression, Psychosis and Schizophrenia
Lexotan is not recommended as primary therapy in patients with depression, anxiety and/or psychosis. In such conditions, psychiatric assessment and supervision are necessary if benzodiazepines are indicated. Benzodiazepines may increase depression in some patients and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Pre-existing depression may be unmasked during benzodiazepine use. Suicidal tendencies may be present or uncovered and protective measures may be required.

Psychiatric and 'paradoxical' Reactions
Paradoxical reactions such as restlessness, agitation, irritability, rages, hallucinations, aggressiveness, anxiety, delusion, anger, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, acute rage, stimulation or excitement are known to occur with benzodiazepines. Should these occur, the use of the drug should be discontinued. They are more likely to occur in children and in the elderly.

Impaired Respiratory Function
Lexotan should be used with extreme caution in patients with respiratory depression. In patients with chronic obstructive pulmonary disease, benzodiazepines can cause increased arterial carbon dioxide tension and decreased oxygen tension (see section 4.3 Contraindications).

Epilepsy
When Lexotan is administered to persons with convulsive disorders, an increase in the frequency and/or severity of grand mal seizures may occur, necessitating increased anticonvulsant medication. Abrupt withdrawal of benzodiazepines in persons with convulsive disorders may be associated with a temporary increase in the frequency and/or severity of seizures.

Hereditary Problems
As Lexotan contains lactose, patients with rare hereditary problems such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this drug.

Abuse
Caution must be exercised in administering Lexotan to individuals known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescription without adequate medical supervision.

Dependence
The use of benzodiazepines may lead to dependence, as defined by the presence of a withdrawal syndrome on discontinuation of the medicine. 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, Lexotan 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.

Tolerance, as defined by a need to increase the dose in order to achieve the same therapeutic effect, seldom occurs in patients receiving recommended doses under medical supervision. Tolerance to sedation may occur with benzodiazepines, especially in those with drug seeking behaviour.

Withdrawal
Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepines or changing to a benzodiazepine with a considerably shorter elimination half-life. These symptoms range from headaches, diarrhoea, muscle pain, insomnia, tension, restlessness, confusion, irritability, anxiety, dysphoria, palpitations, panic attacks, vertigo, myoclonus, akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (e.g. feeling of motion, metallic taste), hyperacusis, numbness and tingling of the extremities, convulsions, depersonalisation, derealisation, delusional beliefs, hyperreflexia and loss of short term memory, to a major syndrome which may include convulsions, tremor, abdominal and muscle cramps, confusional state, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating (see section 4.8.Undesirable Effects (Adverse Effects)). Such manifestations of withdrawal, especially the more serious ones, are more common in patients who have received excessive doses over a prolonged period. However, withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels. Accordingly, Lexotan should be terminated by tapering the dose to minimise occurrence of withdrawal symptoms. Patients should be advised to consult with their physician before either increasing the dose or abruptly discontinuing the medication.

Rebound phenomena have been described in the context of benzodiazepine use. Rebound insomnia and anxiety mean an increase in the severity of these symptoms beyond pre-treatment levels following cessation of benzodiazepines. Rebound phenomena in general possibly reflect re-emergence of pre-

existing symptoms combined with withdrawal symptoms. Some patients prescribed benzodiazepines with very short half-lives (in the order of 2 – 4 h) may experience relatively mild rebound symptoms in between their regular doses. Withdrawal/rebound symptoms may follow high doses for relatively short periods.

The risk of withdrawal and rebound phenomena is greater after abrupt discontinuation of treatment.

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

Use in the Elderly
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.

Elderly or debilitated patients may be particularly susceptible to the sedative effects of benzodiazepines and associated giddiness, ataxia and confusion, which may increase the risk of a fall.

In a trial of 32 subjects, elderly people (aged 61 to 80 years) had significantly higher mean peak serum bromazepam concentrations, smaller volume of distribution, lower oral clearance, and increased serum free fraction compared to young people (aged 21 to 29 years). This association was statistically significant even when corrected for body weight. The average reduction in clearance in elderly patients compared to young patients was nearly 50%.

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.

Paediatric use
Benzodiazepines may impair mental alertness in children. Bromazepam is not recommended for use in children due to insufficient evidence of safety and efficacy in this age group.

Effects on laboratory tests
No data available

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Pharmacokinetic Drug-Drug Interaction
Lexotan undergoes hepatic microsomal oxidation via the cytochrome P450 liver enzymes. Therefore, caution should be taken in patients taking medicines that inhibit the P450 liver enzymes (e.g. azole antifungals, macrolide antibiotics, HIV protease inhibitors, calcium channel blocking agents).

Lexotan undergoes oxidative metabolism and, consequently, may interact with disulfiram or cimetidine resulting in increased plasma levels of Lexotan. Patients should be observed closely for evidence of enhanced benzodiazepine response during concomitant treatment with either disulfiram or cimetidine; some patients may require a reduction in benzodiazepine dosage. Co-administration of cimetidine, a multi-CYP inhibitor, and possibly propranolol, may prolong the elimination half-life of bromazepam through a substantially reduced rate of clearance (with cimetidine the mean rate of clearance was reduced

by 50%). In a trial of 18 healthy subjects there was no evidence of a drug interaction between bromazepam and oral contraceptives. 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).

In a trial of six healthy volunteers, bromazepam did not affect antipyrine metabolism, which is a surrogate marker for CYP1A2, CYP2B6, CYP2C and CYP3A activity.

Pharmacodynamic Drug-Drug Interaction
The benzodiazepines, including Lexotan, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression e.g. barbiturates, alcohol, sedatives, antidepressants, hypnotics, anxiolytics, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines, narcotic analgesics and anaesthetics (see section 4.4 Special warnings and precautions for use). Alcohol should be avoided in patients receiving Lexotan.

In the case of narcotic analgesics enhancement of euphoria may also occur, leading to an increase in psychic drug dependence.

The anticholinergic effects of atropine and similar medicines, antihistamines and antidepressants may be potentiated.

Interactions have been reported between some benzodiazepines and anticonvulsants, with changes in the serum concentration of the benzodiazepine or anticonvulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anticonvulsants are prescribed together and that serum level monitoring of the anticonvulsant be performed more frequently.

Other Interactions
Minor EEG changes, usually low voltage fast activity, of no known clinical significance, has been reported with benzodiazepine administration.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility
No data available.

Use in pregnancy
Category C
Benzodiazepines cross the placenta and may cause hypotonia, reduced respiratory function and hypothermia in the newborn infant. Continuous treatment during pregnancy and administration of high doses in connection with delivery should be avoided. Withdrawal symptoms in newborn infants have been reported with this class of medicines.

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.

If Lexotan is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuing Lexotan if she intends to become, or suspects that she is pregnant.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
As with all patients taking CNS-depressant medications, patients receiving Lexotan should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from Lexotan therapy. Sedation, amnesia and impaired muscular function may adversely affect the ability to drive or operate machinery. This is increased if the patient has taken alcohol concomitantly with Lexotan (see section 4.5 Interactions with other medicines and other forms of interaction). Abilities may be impaired on the day following use.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)
Most adverse effects encountered with Lexotan have been referable to the central nervous system.

Adverse Events in Clinical Trials
In clinical trials, in which the mean daily dose of Lexotan was 24 mg, the following adverse events were reported in ≥ 1% of patients treated with Lexotan.

Adverse event (frequency)
drowsiness (32%)
ataxia (13%)
dizziness (7.6%)
behaviour disorders (4%)
minor elevations of bilirubin (3%)
minor elevations of AST (3%)
minor elevations of ALT (3%)
minor elevations of SAP (3%)
minor elevations of BUN (3%)
speech disorders (2%)
sleep disorders (1%)
confusion (1%)
headache (1%)
depression (1%)
nausea (1%)
vomiting (1%)
gastrointestinal disturbances (1%)

Post-Marketing Adverse Reactions
Psychiatric Disorders
Confusional state, disorientation, emotional and mood disturbances, changes in libido, nervousness and depression have been reported.

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, anger, nightmares, sleep disorders, hallucinations, psychosis, 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 4.4 Special warnings and precautions for use).

Abuse of benzodiazepines is more common in poly-drug users**.**

Nervous System Disorders
Drowsiness and ataxia become less common with repeated administration. Headache, dizziness, decreased alertness, seizures, tremor, speech disorders and incontinence have been reported.

Anterograde amnesia may occur at therapeutic dosages with the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour.

Eye Disorders
Diplopia and blurred vision have been reported.

Gastrointestinal Disorders
Gastrointestinal disorders, dry mouth, nausea and vomiting have been reported.

Metabolic and Nutritional Disorders
Anorexia has been reported.

Skin and Subcutaneous Tissue Disorders
Skin reactions including pruritis and rash have been reported.

Musculoskeletal and Connective Tissue Disorders
Muscle weakness and muscle spasm have been reported.

General Disorders and Administration Site Conditions
Fatigue.

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.

Respiratory Disorders
Respiratory depression has been reported.

Cardiac Disorders
Cardiac failure including cardiac arrest, hypotension, tachycardia and palpitations have been reported.

Investigations
Instances of decreased haemoglobin and increased white cell counts have been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Overdosage 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. Overdose of Lexotan is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnoea, ataxia, hypotonia, hypotension, cardio-respiratory depression and coma. Coma 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. When combined with other CNS depressants, the effects of overdosage are likely to be severe and may prove fatal.

Treatment

Treatment of overdose is symptomatic; institute supportive measures as indicated by the patient's clinical state. If the overdosage is known to be small, observation of the patient and monitoring of their vital signs only may be appropriate. In adults or children who have taken an overdose of benzodiazepines within 1 – 2 hours, consider activated charcoal with airway protection if indicated.

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 medicines 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 medicine.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: anxiolytic, ATC code: N05BA08.

Mechanism of Action

Bromazepam is a benzodiazepine with anxiolytic action.

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

Clinical trials

No data available

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Bromazepam, taken in the fasting state, is almost completely absorbed. Peak plasma levels of bromazepam are reached between 0.5 – 4 hours and may be maintained for up to 12 hours. The mean peak bromazepam level after a 12 mg oral dose is about 140 ng/mL. There is significant variation between subjects.

The absolute (versus IV solution) bioavailability of the tablet is 60%.

There is no information on the effect of food on absorption.

Distribution
On average, 70% of bromazepam is bound to plasma proteins, which is considerably less than for diazepam and is attributed to the increased polarity of the molecule due to the presence of the pyridyl radical. The volume of distribution is about 50 L.

Metabolism
Bromazepam undergoes extensive metabolism. The main metabolic pathway involves hydroxylation in position 3 with subsequent glucuronidation and cleavage of the heterocyclic ring with subsequent hydroxylation in the benzene ring and conjugation. Two metabolites predominate: 3-hydroxy-bromazepam and 2-(2-amino-5-bromo-3-hydroxybenzoyl) pyridine.

Excretion
Less than 2% of a dose is excreted unchanged. 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 17 h (range 11 – 22 h). The clearance is about 40 mL/min.

Pharmacokinetics in Special Populations
Elderly
The elimination half-life may be prolonged in elderly patients. The average reduction in clearance in elderly patients compared to young subjects is nearly 50%.

5.3 PRECLINICAL SAFETY DATA
Genotoxity

No data available.

Carcinogenicity
No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Microcrystalline cellulose
Lactose monohydrate
Magnesium stearate

Purified talc
Iron oxide red (3 mg tablet)
Indigo carmine aluminium lake (6 mg tablet)
Iron oxide yellow (6 mg tablet)

6.2 INCOMPATIBILITIES
Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE
In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

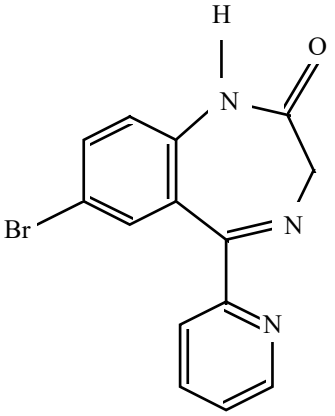
6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER
Lexotan 3 mg is available in PVC/Al or PVC/PE/PVDC/Al blister packs of 30 tablets.

Lexotan 6 mg is available in PVC/Al or PVC/PE/PVDC/Al blister packs of 30 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSIOCHEMICAL PROPERTIES
Chemical structure



CAS number: 1812-30-2

Bromazepam is a pale yellow, odourless, crystalline powder, with melting point 243 – 251°C. Its solubility is 0.1% in water at 25°C and 10% in dilute hydrochloric acid. Bromazepam differs from other benzodiazepines in the presence of bromine in position 7 and a pyridine ring in position 5, in place of a phenyl ring.

The chemical name for bromazepam is 7-bromo-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one. The molecular formula is $C_{14}H_{10}BrN_3O$ and molecular weight is 316.16.

7. MEDICINE SCHEDULE (POISONS STANDARD)
S 4 – Prescription only medicine

8. SPONSOR

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Chatswood, NSW 2067
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9. DATE OF FIRST APPROVAL

9 May 1995

10. DATE OF REVISION OF THE TEXT

24 October 2024

Summary table of changes

Section Changed	Summary of new information
8	Update sponsor address