1.3.1.1 PACKAGE INSERT

SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

LEXOTAN® 3 (Tablets)

LEXOTAN® 6 (Tablets)

COMPOSITION

LEXOTAN contains 3 mg or 6 mg bromazepam per tablet.

Excipients

LEXOTAN 3: Microcrystalline cellulose, lactose, iron oxide red (E172), magnesium stearate, talc.

LEXOTAN 6: Microcrystalline cellulose, lactose, indigotine aluminium lake (E132), iron oxide yellow (E172), magnesium stearate, talc.

LEXOTAN tablets contains lactose; see WARNINGS AND SPECIAL PRECAUTIONS

PHARMACOLOGICAL CLASSIFICATION

A 2.6 Tranquilisers

PHARMACOLOGICAL ACTION

Pharmacodynamics

Bromazepam is a benzodiazepine derivative with anxiolytic, sedative, muscle-relaxant and anticonvulsant properties. In low doses it diminishes anxiety and tension. In higher dosages the sedative and muscle-relaxant properties appear.

Bromazepam has, at therapeutic doses, primarily a selective inhibitory action on the limbic system. The cortical centres respond only to relatively high doses. The muscle-relaxing effect is produced by the inhibition of spinal reflexes as well as by influencing central substrates related to the limbic, thalamic and hypothalamic systems.

Pharmacokinetics

Absorption: Peak plasma concentrations are reached within 2 hours of oral administration of bromazepam. The absolute bioavailability of the unchanged substance is 60 % to 70 %.

Distribution: On average, 70 % of bromazepam is bound to plasma proteins. The apparent volume of distribution is 50 litres.

Metabolism and elimination: Bromazepam is metabolized in the liver. Two active metabolites predominate: 3-hydroxy-bromazepam and 2-(2-amino-5-bromo-3-hydroxybenzoyl) pyridine. The urinary recovery of intact bromazepam and the glucuronide conjugates of 3-hydroxy-bromazepam and 2-(-2-amino-5-bromo-3-hydroxybenzoyl) pyridine is 2 %, 27 % and 40 % of the administered dose.

Bromazepam has an elimination half-life of about 20 hours. The clearance is 40 mℓ/min.

Pharmacokinetics in special populations

Elderly: The elimination half-life is prolonged to 30 – 35 hours in elderly patients. See DOSAGE AND DIRECTIONS FOR USE.

INDICATIONS

LEXOTAN is indicated for the short term (2 - 4 weeks) symptomatic treatment of anxiety that is severe, disabling and subjecting the individual to extreme distress, occurring alone or in association with insomnia, or short term psychosomatic, general medical illness or psychotic disorders.

Treatment should be as short as possible. The patient should be assessed regularly and the need for continued treatment should be re-evaluated especially when the patient is symptom-free.

CONTRAINDICATIONS

- Myasthenia gravis.
- Pregnancy and lactation.
- Hypersensitivity to bromazepam, any other ingredient of LEXOTAN, or other benzodiazepines.
- Respiratory insufficiency, respiratory depression.

Initial: _____

- Severe hepatic insufficiency (LEXOTAN is not indicated for the treatment of patients with severe hepatic insufficiency as it may cause encephalopathy).
- Psychotic patients and in those suffering from mental depression or suicidal tendencies, unless there is a marked component of anxiety in their illness.
- Sleep apnoea syndrome.
- **Safety and efficacy of LEXOTAN has not been established in children**. Paradoxical reactions such as excitement and irritability may occur in children. Smaller children are more prone to these reactions.
- Phobic or obsessional states.

WARNINGS AND SPECIAL PRECAUTIONS

LEXOTAN should not be used alone to treat depression or anxiety associated with depression, suicide may be precipitated in such patients.

LEXOTAN is not recommended for the primary treatment of psychotic illness.

Amnesia

It should be borne in mind that LEXOTAN may induce anterograde amnesia. Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour. The condition usually occurs several hours after taking the product and therefore, to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 7 to 8 hours. In cases of loss or bereavement, psychological adjustment may be inhibited by LEXOTAN.

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 medicine is being discontinued. See WARNINGS AND SPECIAL PRECAUTIONS - Medicine Abuse and Dependence.

Initial: _____

General

When LEXOTAN is used, withdrawal symptoms may develop when changing to a benzodiazepine with a considerably shorter elimination half-life, see WARNINGS AND SPECIAL PRECAUTIONS - Medicine Abuse and Dependence.

Treatment should be kept to a minimum and given close medical supervision. Little is known regarding the efficacy or safety of benzodiazepines such as LEXOTAN in long term use.

Patients with known or presumed dependence on alcohol, medicines or drugs should not take benzodiazepines such as LEXOTAN, except in rare situations under medical supervision. See WARNINGS AND SPECIAL PRECAUTIONS - Medicine Abuse and Dependence.

Specific patient groups

Particular care is required in patients with chronic respiratory insufficiency, due to the risk of respiratory depression. In patients with respiratory insufficiency the dose should be decreased.

Particular caution should be exercised with the elderly and debilitated who are at particular risk of over sedation, respiratory depression and ataxia. (The initial oral dosage should be reduced in these patients). See DOSAGE AND DIRECTIONS FOR USE.

Patients with rare hereditary problems of galactose intolerance (the Lapp lactase deficiency or glucose-galactose malabsorption) should not use LEXOTAN.

Medicine Abuse and Dependence

Dependence

There is a potential for abuse, and the development of physical and psychological dependence. 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.

Withdrawal

Once physical dependence has developed, termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability.

Initial: _____

In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. See SIDE EFFECTS.

Chronic use (even at therapeutic doses), may lead to the development of physical dependence: discontinuation of therapy may result in withdrawal or rebound phenomena, see WARNINGS AND SPECIAL PRECAUTIONS - Medicine Abuse and Dependence. Psychological dependence may also occur. Abuse of benzodiazepines such as LEXOTAN has been reported.

Rebound effect

Rebound anxiety and insomnia, 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 and restlessness.

Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually.

Effects on the ability to drive or to use machines

Sedation, amnesia and impaired muscular function may adversely affect the ability to drive or use machinery, and therefore, patients receiving LEXOTAN should be advised not to drive motor vehicles, or operate dangerous machinery, or climb dangerous heights until it is established that they do not become drowsy or dizzy while receiving LEXOTAN therapy. In these situations impaired decision making could lead to accidents. These effects are increased if the patient has taken alcohol.

Special precautions

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.

When LEXOTAN is used, withdrawal symptoms may develop when changing to a benzodiazepine with a considerably shorter elimination half-life. See WARNINGS AND SPECIAL PRECAUTIONS - Medicine Abuse and Dependence.

Monitoring of the blood count and of liver function is recommended during prolonged therapy

Initial: _____

INTERACTIONS

The effect of LEXOTAN may be intensified by alcohol. Concomitant intake with alcohol should be avoided.

If LEXOTAN is combined with other sedatives, its central-sedative effect may be enhanced. These medicines may include antidepressants, hypnotics, narcotic analgesics, antipsychotics, anxiolytics/sedatives, antiepileptic drugs, sedative antihistamines and anaesthetics.

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

Compounds which inhibit certain hepatic enzymes (particularly, cytochrome P450) may enhance the activity of LEXOTAN. Co-administration of cimetidine may prolong the elimination half-life of LEXOTAN.

PREGNANCY AND LACTATION

There is no evidence as to LEXOTAN's safe use in human pregnancy, nor is there evidence from animal work that is free from hazard. Do not use during pregnancy, especially during the first and last trimesters, unless there are compelling reasons.

If LEXOTAN 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.

The administration of high doses or prolonged administration of low doses of benzodiazepines such as LEXOTAN in the last trimester of pregnancy has been reported to produce irregularities in the foetal heart rate, and hypotonia, poor sucking, hypothermia and moderate respiratory depression in the neonate.

Moreover, infants born to mothers who took benzodiazepines such as LEXOTAN chronically during the latter stages of pregnancy may develop physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

Benzodiazepines have been detected in breast milk; therefore the use of LEXOTAN should be avoided during lactation.

DOSAGE AND DIRECTIONS FOR USE

Initial: _____

Standard dosage

Average dose for outpatient therapy: 1,5 3 mg three times daily.

Severe cases, 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 the lowest dosage, gradually increasing, if necessary, to the optimum level. The maximum dose should not be exceeded.

Elderly patients and those with impaired hepatic and/or renal function require lower doses because of individual variations in sensitivity and pharmacokinetics. 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. Doses should not exceed half the dose normally recommended for healthy adults.

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 duration of treatment generally should not be more than 8 - 12 weeks, including a tapering-off process.

The patient should be informed when treatment is started, that it will be of limited duration, and be explained precisely how the dosage will be progressively decreased. It is important that the patient be aware of the possibility of rebound phenomena that may occur while the medicine is being discontinued. See WARNINGS AND SPECIAL PRECAUTIONS - Medicine Abuse and Dependence.

SIDE EFFECTS

Psychiatric disorders: Confusional state, emotional disorder, libido disorder

Pre-existing depression may be unmasked during LEXOTAN use.

Paradoxical reactions like restlessness, agitation, irritability, aggression, delusion, anger, nightmare, hallucination, psychotic disorder and abnormal behaviour are known to occur when using benzodiazepines or benzodiazepine-like agents, see WARNINGS AND SPECIAL PRECAUTIONS -

Medicine Abuse and Dependence. Should this occur, the use of LEXOTAN should be discontinued. They are more likely to occur in children and elderly patients than in other patients.

Chronic use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of therapy may result in withdrawal or rebound phenomena (see WARNINGS AND SPECIAL PRECAUTIONS - Medicine Abuse and Dependence). Psychological dependence may occur. Abuse of benzodiazepines such as LEXOTAN has been reported.

Nervous system disorders: Somnolence, depressed level of consciousness, headache, dizziness, ataxia, anterograde amnesia.

Eye disorders: Diplopia.

Gastrointestinal disorders: Gastrointestinal disorder.

Skin and subcutaneous tissue disorders: Skin reaction.

Musculoskeletal, connective tissue and bone disorders: Muscular weakness. An increased risk for falls and fractures has been recorded in elderly benzodiazepine users.

General disorders and administration site conditions: Fatigue.

These phenomena occur predominantly at the start of therapy and may disappear with prolonged administration.

Social circumstances: Drug abuse.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdose of LEXOTAN is usually manifested by central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, and lethargy. In most cases it is sufficient to monitor the vital functions and await recovery. Higher overdoses, especially in combination with other centrally acting medicines, including alcohol, can result in ataxia, hypotonia, hypotension, respiratory depression, coma, and death. In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

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.

Initial: _____

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 , a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is contraindicated in the presence of medicines that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of this drug.

IDENTIFICATION

LEXOTAN 3 mg tablets: scored pale red, slightly speckled tablet, imprinted "Roche 3".

LEXOTAN 6 mg tablets: scored pale green, slightly speckled tablet, imprinted "Roche 6".

PRESENTATION

LEXOTAN 3: Blister packs or amber glass bottles containing 30, 90 or 100 tablets.

LEXOTAN 6: Blister packs or amber glass bottles containing 30, 90 or 100 tablets.

STORAGE INSTRUCTIONS

Store at or below 30 °C.

Protect from light and moisture.

Store in outer container until required for use.

Store out of reach of children.

REGISTRATION NUMBERS

LEXOTAN 3 - G/2.6/86

LEXOTAN 6 - G/2.6/87

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharmaco Distribution (Pty) Ltd

Initial: _____

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Sandton 2196

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South Africa

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DATE OF PUBLICATION OF THE PACKAGE INSERT

Registration: 03 March 1976

Last revision: To be provided

Initial: _____