PRODUCT MONOGRAPH

# LECTOPAM®

bromazepam

3 mg and 6 mg Tablets

Anxiolytic - Sedative

Hoffmann-La Roche Limited
7070 Mississauga Road
Mississauga, Ontario
L5N 5M8

www.rochecanada.com

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# LECTOPAM®

bromazepam

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Non-medicinal Ingredients |
|---|---|---|
| Oral | Tablets, 3 mg and 6 mg | **Tablets 3 mg**: iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, talc.<br><br>**Tablets 6 mg**: indigotine aluminum lake, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, talc. |

### INDICATIONS AND CLINICAL USE

LECTOPAM (bromazepam) is useful for the short-term, symptomatic relief of manifestations of excessive anxiety in patients with anxiety neurosis.

**Geriatrics**
Elderly and debilitated patients are especially susceptible to dose-related adverse events and a reduced dose is recommended (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics and DOSAGE AND ADMINISTRATION, Elderly and Debilitated Patients).

**Pediatrics**
LECTOPAM is not recommended for children under 18 years of age (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

### CONTRAINDICATIONS

- Patients who are hypersensitive to other benzodiazepines, this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Myasthenia gravis
- Severe hepatic insufficiency
- Severe respiratory insufficiency
- Sleep apnea syndrome
- Narrow angle glaucoma

## WARNINGS AND PRECAUTIONS

### General

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

LECTOPAM (bromazepam) is not recommended for use in patients with depressive disorders or psychosis.

Anterograde amnesia may occur with therapeutic doses of benzodiazepines and may be associated with inappropriate behaviour, the risk increasing with higher doses, (see ADVERSE REACTIONS).

### Concomitant use of alcohol / CNS depressants

The concomitant use of LECTOPAM with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of LECTOPAM possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression (see DRUG INTERACTIONS).

Patients should be advised against the concurrent use of alcohol and other CNS depressant drugs.

### Medical History of Alcohol or Drug Abuse

LECTOPAM should be used with extreme caution in patients with a medical history of alcohol or drug abuse.

Benzodiazepines have produced habituation, dependence and withdrawal symptoms similar to those noted with barbiturates and alcohol. The risk of dependence increases with dose and duration, and is greater in patients with a medical history of alcohol and drug).

### Dependence/Tolerance

**Dependence Liability and Withdrawal**

With long-term LECTOPAM treatment at the therapeutic doses, development of physical and psychic dependence may occur. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. The possibility that such effects may also occur following short-term use, especially at high doses, or if the daily dose is reduced rapidly or abruptly discontinued, should be considered. Symptoms of withdrawal include irritability, nervousness, insomnia, agitation, tremors, convulsions, diarrhea, abdominal cramps, vomiting, sweating, memory impairment, headache, muscle pain, extreme anxiety, tension, restlessness, and confusion. 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 epileptic seizures. Since these symptoms are similar to those for which the patient is being treated, it may appear that he/she has suffered a relapse upon discontinuation of the drug. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, abrupt withdrawal of the drug should be avoided and

treatment - even if only of short duration - should be terminated by gradually reducing the daily dose.

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

**Lactose Intolerance**
Lactose monohydrate is a non-medicinal ingredient in LECTOPAM. Therefore, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Neurologic**
**Driving and Hazardous Activities**
Since bromazepam has a central nervous system depressant effect, patients should be warned against driving, operating dangerous machinery, or engaging in other hazardous activities requiring mental alertness and physical coordination. Sedation, amnesia and impaired muscular function may adversely affect the ability to drive or operate machinery. This effect is increased if the patient has had alcohol.

Driving, operating machinery and other hazardous activities should be avoided altogether or at least during the first few days of treatment. The decision on this question rests with the patient's physician and should be based on the patient's response to treatment and the dosage involved. They also should be warned against the concomitant use of alcohol and other CNS depressant drugs.

**Psychiatric**
**Mental and Emotional Disorders**
It should be recognized that suicidal tendencies may be present in patients with emotional disorders and that protective measures and appropriate treatment may be necessary and should be instituted without delay.

Since excitement and other paradoxical reactions can result from the use of anxiolytic sedatives in psychotic patients, bromazepam should not be used in ambulatory patients suspected of having psychotic tendencies.

As with other benzodiazepines, bromazepam should not be used in individuals with physiological anxiety or normal stresses of daily living, but only in the presence of disabling manifestations of an appropriate pathological anxiety disorder.

These drugs are not effective in patients with characterological and personality disorders or those with obsessive-compulsive disorders. Bromazepam is also not recommended for management of depressive or psychotic disorders. Benzodiazepines should not be used to treat anxiety associated with depression, as suicide may be precipitated in these patients.

**Respiratory**

Respiratory depression may occur following administration of LECTOPAM. This effect may be aggravated by pre-existing airway obstruction or brain damage or if other medications which depress respiration have been given. As a rule, this effect can be avoided by careful adjustment of the dose to individual requirements.

LECTOPAM should be used with caution in patients with chronic respiratory diseases (see CONTRAINDICATIONS).

**Falls and fractures**

There have been reports of falls and fractures among benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

**Special Populations**

**Pregnant Women:** The safety of use of bromazepam in pregnancy has not been established. Therefore, bromazepam should not be used during pregnancy. Several studies have suggested an increased risk of congenital malformations (e.g., congenital malformations of the heart, cleft lip and/or palate) associated with the use of the benzodiazepines chlordiazepoxide and diazepam, and meprobamate, during the first trimester of pregnancies. Since bromazepam is also a benzodiazepine derivative, its administration is rarely justified in women of childbearing potential. Administration of bromazepam during the last three months of pregnancy or during labour is allowed only in the event of a strict medical indication, when the expected benefits to the patient outweigh the possible risks to the fetus. Due to the pharmacological action of the product, effects such as irregular heartbeat in the unborn child, hypothermia, hypotonia, moderate respiratory depression, and poor feeding in the neonate can be expected. Moreover, infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period. If the drug is prescribed to a woman of childbearing potential, she should be warned to consult her physician regarding discontinuation of the drug if she plans to become or suspects that she is pregnant.

**Nursing Women:** Bromazepam and its metabolites are probably excreted in human milk. Therefore, this drug should not be given to nursing mothers.

**Pediatrics:** Because of the lack of sufficient clinical experience, bromazepam is not recommended for use in patients less than 18 years of age.

**Geriatrics:** Elderly and debilitated patients, or those with organic brain syndrome, have been found to be prone to CNS depression after even low doses of benzodiazepines. Therefore, medication should be initiated in these patients with very low initial doses, and increments should be made gradually, depending on the response of the patient, in order to avoid over sedation or neurological impairment (see DOSAGE AND ADMINISTRATION).

There is an increased risk for falls and fractures among elderly and debilitated benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages).

**Impaired Hepatic or Renal Function**
In patients with impaired hepatic or renal function, it is recommended to initiate therapy, if necessary, at a very low dose and to increase the dosage only to the extent that such an increase is compatible with the degree of residual function of these organs. Such patients should be followed closely and have periodic laboratory assessments.

**Monitoring and Laboratory Tests**
If bromazepam should be administered for repeated cycles of therapy, periodic blood counts and liver function tests are advisable.

## ADVERSE REACTIONS

**Adverse Drug Reaction Overview**
**Most Frequent Adverse Reactions**
The most frequently reported adverse reactions with LECTOPAM (bromazepam) are related to CNS effects and include drowsiness, ataxia and dizziness. These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration.

**Serious and Important Adverse Reactions**
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.

Allergic reactions and a very few cases of anaphylaxis have been reported to occur with benzodiazepines.

Release of hostility and other paradoxical reactions such as irritability, excitability, restlessness, agitation, aggression, delusion, anger, nightmares, hallucinations, psychosis, inappropriate behaviour and other adverse behavioural effects are known to occur with the use of benzodiazepines. They are more likely to occur in children and elderly patients than in other patients. If these occur, use of the drug should be discontinued.

Anterograde amnesia may occur using therapeutic doses of benzodiazepines, the risk increasing with higher doses. Effects of anterograde amnesia may be associated with inappropriate behaviour.

Chronic use (even at therapeutic doses) may lead to the development of physical and psychic drug dependence: discontinuation of therapy may result in withdrawal or rebound phenomena (see WARNINGS and PRECAUTIONS).

Abuse of benzodiazepines has been reported.

**Post-Market Adverse Drug Reactions**
Other side effects which can occur, listed by body systems, include the following:

**Cardiovascular System**: Cardiac failure including cardiac arrest; hypotension, palpitations,

tachycardia.

**Digestive System:** Dry mouth, nausea, non-specific gastrointestinal disturbances, vomiting.

**Hemic and Lymphatic System:** Decreased hemoglobin and hematocrit, increased and decreased WBC.

**Metabolic and Nutritional Disorders:** increased and decreased blood sugar levels, elevations of alkaline phosphatase, bilirubin, SGOT, SGPT.

**Musculoskeletal System**: Muscle weakness, muscle spasm.

**Nervous System**: Drowsiness, headache, dizziness, decreased alertness, ataxia, fatigue, seizures, confusional state, emotional disorder, depression, euphoria, change in libido.

**Respiratory Disorders**: Respiratory depression.

**Skin and Subcutaneous Tissue Disorders Appendages**: Pruritus, rash.

**Special Senses**: Diplopia, blurred vision.

**Urogenital System:** Incontinence.

**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.

## DRUG INTERACTIONS

### Drug-Drug Interactions

**Pharmacokinetic Drug-Drug Interaction (DDI)**
The specific enzymes involved in the metabolism of bromazepam have not been fully elucidated. 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 propranolol 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 (2.4-fold increase in AUC) and elimination half-life (1.9-fold).

Bromazepam at therapeutic doses does not change the pharmacokinetics of co-administered antipyrine, a substrate of several CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C18, and CYP3A4).

**Pharmacodynamic Drug-Drug Interaction (DDI)**

*CNS-acting drugs*

Enhanced effects on sedation, respiration and hemodynamics may occur when LECTOPAM is co-administered with any centrally acting depressants including alcohol, narcotics, narcotic analgesics, barbiturates, non-barbiturate hypnotics, antihistamines, phenothiazines, thioxanthenes, butyrophenones classes of antipsychotics, anxiolytics/sedatives, anesthetics, monoamine oxidase inhibitors, tricyclic antidepressants and anticonvulsants (see WARNINGS AND PRECAUTIONS, Concomitant use of alcohol / CNS depressants, and OVERDOSAGE sections).

In the case of narcotic analgesics enhancement of euphoria may also occur, leading to an increase in psychic dependence. Because of the enhancement of effects that might occur, patients should be advised against the simultaneous use of other CNS depressant drugs and should be cautioned not to take alcohol during the administration of bromazepam.

**Drug-Lifestyle Interactions**

The concomitant use of LECTOPAM with alcohol should be avoided. Such concomitant use has the potential to increase the clinical effects of LECTOPAM possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression (see WARNINGS AND PRECAUTIONS, Concomitant use of alcohol / CNS depressants, and OVERDOSAGE sections).

## DOSAGE AND ADMINISTRATION

**Dosing Considerations**

Patients should be evaluated carefully at the start of treatment in order to minimize the dosage and/or the frequency of administration and to prevent overdose due to accumulation.

The dosage of LECTOPAM (bromazepam) must be individualized and carefully titrated in order to avoid excessive sedation or mental and motor impairment. Short course of treatment should usually be the rule for the symptomatic relief of excessive anxiety and the initial course of treatment should not last longer than one week without reassessment of the need for a limited extension. If necessary, drug dosage can be adjusted after one week of treatment. Initially, not more than one week's supply of the drug should be provided and automatic prescription renewals should not be allowed. Subsequent prescriptions, when required, should be limited to a short course of therapy.

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.

**Recommended Dose and Dosage Adjustment**

**Usual Adult Dosage**

The recommended initial adult daily dosage is 6 to 18 mg in equally divided doses, depending on the severity of symptoms and response of the patient. Treatment should be initiated by lower doses and adjusted as necessary. The optimal dosage may range from 6 to 30 mg daily in individual patients, in divided doses. There is limited experience with higher doses up to 60 mg daily.

**Elderly and Debilitated Patients**
The initial daily dose in these patients should not exceed 3 mg in divided doses. This dosage can be carefully adjusted, depending on tolerance and response of the patient (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics; ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

## OVERDOSAGE

| |
|---|
| For management of a suspected drug overdose, contact your regional Poison Control Centre. |

**Symptoms**
Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of LECTOPAM is seldom life-threatening if the drug is taken alone, but may lead to 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**
In managing overdosage, consider the possibility of multiple drug involvement.

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. Induction of vomiting is not generally recommended.

As in overdosage with other benzodiazepines, dialysis is of no known value in bromazepam overdosage.

If CNS depression is severe consider the use of flumazenil, a benzodiazepine receptor antagonist. The following should be kept in mind when flumazenil is used in the treatment of benzodiazepine overdosage:

- Flumazenil should only be administered under closely monitored conditions. In view of the short half-life (about 1 hour) and duration of action of flumazenil, and the possible need for repeat doses, the patient should be closely monitored until all possible central benzodiazepine effects (e.g., resedation) have subsided.
- Particular caution is necessary when using flumazenil in cases of multiple drug overdosage, since the toxic effects (cardiac arrhythmias and/or convulsions) of other psychotropic drugs, especially cyclic antidepressants, may increase as the effects of benzodiazepines subside. Flumazenil is contraindicated in patients who are showing signs of serious cyclic antidepressant overdose.

***Warning:*** The benzodiazepine receptor antagonist flumazenil is not indicated in patients with epilepsy who have been treated with benzodiazepines. Antagonism of the benzodiazepine effect in such patients may provoke seizures.

Refer to the product monograph for flumazenil for further information on the correct use of this drug.

## ACTION AND CLINICAL PHARMACOLOGY

### Pharmacokinetics

**Absorption:** The absolute bioavailability of unchanged, orally administered bromazepam is 60%, and peak blood levels are achieved within 2 hours after administration.

Food may decrease the bioavailability of bromazepam.

**Distribution:** On average, 70% of bromazepam is bound to plasma proteins.

**Metabolism:** Bromazepam is extensively metabolized in the liver. 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 points to co-involvement of CYP1A2 (see DRUG INTERACTIONS, Drug-Drug Interactions).

**Excretion:** Bromazepam has an elimination half-life of approximately 20 hours (the half-life may be longer in elderly patients). Over a 72-hour interval, 69% of a 12 mg oral dose was recovered in the urine, in the form of conjugated 3-hydroxybromazepam and conjugated 2-(2-amino-5-bromo-3-hydroxybenzoyl)-pyridine.

**Special Populations and Conditions**

**Elderly and Debilitated Patients:** 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 of bromazepam. 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 DOSAGE AND ADMINISTRATION: Recommended Dose and Dosage Adjustment, Elderly and Debilitated Patients).

## STORAGE AND STABILITY

Keep LECTOPAM in a cool dry place stored at room temperature (15-30°C).

## SPECIAL HANDLING INSTRUCTIONS

Keep this medicine out of sight and reach of children.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

LECTOPAM (bromazepam) is available as 3 mg (pale red in colour, slightly speckled, cylindrical and biplane in shape, single scored on one side and engraved with ROCHE over 3 on the other side) and 6 mg (greenish-grey to greyish-green in colour, slightly speckled, cylindrical and biplane in shape, single scored on one side and engraved with ROCHE over 6 on the other side) tablets in PVC blister packs. There are 10 tablets per blister card and 10 blister cards per carton, for a total of 100 tablets per unit.

The non-medicinal ingredients are as follows:

**Tablets 3 mg:** iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, talc.

**Tablets 6 mg:** indigotine aluminum lake, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, talc.

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

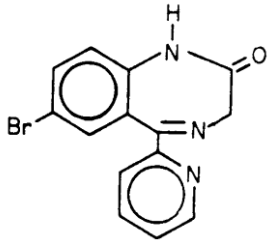
### Drug Substance

Proper name: Bromazepam

Chemical name: 7-bromo-1,3-dihydro-5-(2-pyridinyl)-2H-1,4-benzodiazepine-2-one

Molecular formula and molecular mass: $C_{14}H_{10}BrN_3O$, 316.2

Structural formula:




## DETAILED PHARMACOLOGY

Bromazepam is a benzodiazepine with CNS depressant properties. In laboratory animals, it has shown anti-anxiety, sedative, muscle relaxant and anticonvulsant properties. In a "conflict" test, bromazepam was active in restoring suppressed lever-pressing behaviour (punishment induced suppression) at a minimum effective dose (MED) of 0.16 mg/kg orally in rats. This activity was demonstrated over a dose range which did not involve either depression or stimulation of unpunished control patterns of lever-pressing behaviour. At 2.5 mg/kg, a dose 16 times greater than the MED, bromazepam produced the first decrease in unpunished lever-pressing. In rats, utilizing the Sidman continuous avoidance test, an MED of 1.7 mg/kg i.p. decreased the rate of avoidance of shock, and 5.6 mg/kg i.p. prevented the rat from turning off the shock.

A marked reduction in aggressive behaviour was observed in vicious cynomolgus monkeys after an oral dose of 1 mg/kg and a taming effect at a dose of 2.5 mg/kg p.o. In the inclined screen test in mice the ED50 for bromazepam was 30 mg/kg p.o. In cats, the minimal effective taming dose of bromazepam was 0.2 mg/kg p.o.

Doses of 0.72 to 0.94 mg/kg p.o. of bromazepam protected mice against metrazol (125 mg/kg) induced convulsions. Bromazepam administered at doses of 3.90 to 34.2 mg/kg and 65 to 133 mg/kg p.o. protected mice against maximal and minimal electroshock-induced convulsions, respectively. A single dose of bromazepam (0.25 to 0.50 mg/kg p.o.) produced sedation or ataxia and modified the sleep cycle in cats. An increase in the amplitude of the electrical patterns of the caudate nucleus was observed.

A decrease in blood pressure was observed after the intravenous administration of bromazepam to anesthetized cats (1 mg/kg) and dogs (5 mg/kg). However, in hypertensive rats, little or no antihypertensive effect was detected. Bromazepam exhibited no diuretic, anti-obesity, anti-diabetic or anti-emetic activity.

**Metabolism**

The metabolites of bromazepam were studied in the mouse, rat and dog using $^{14}C$ labelled drug. The quantitative determination of the metabolites indicates that marked differences in the excretion patterns exist in these species. In the mouse and dog, the major metabolite is 3-hydroxybromazepam, although it is only present as a minor metabolite in the rat. Both 2-(2-amino-5-bromobenzoyl) pyridine and its 3-hydroxy derivative are found as metabolites of bromazepam in all three species. In the dog, a separate biotransformation occurs, such that the nitrogen atom, at the 4-position of the diazepam ring, is oxidized to bromazepam 4-oxide. In rats, over 80% of an administered oral dose of bromazepam is excreted in four days, whereas in the dog, excretion is much slower. In rats, biliary excretion and in dogs, urinary excretion is the predominant route of elimination.

## TOXICOLOGY

**Acute Toxicity**

$LD_{50}$ (mg/kg):

| | **p.o.** | **i.p.** | **s.c.** | **i.v.** |
|---|---|---|---|---|
| Mice (CFI) | 2,350 | 550 | 7,400 | 13.7 |
| Rats - mature (Wistar) | 3,050 | 2,300 | - | - |
| Rats - neonatal (Wistar) | 110 | - | - | - |
| Rabbits (Wistar) | 1,690 | - | - | - |
| Dogs | $\geq$1,280 | - | - | - |

Signs of toxicity included decreased motor activity, ataxia, loss of righting reflex and lacrimation.

**Chronic Toxicity**

Bromazepam was administered in the diet to rats for a period of 18 months at doses of 0, 5, 20 and 80 mg/kg/day. No deviations from normal were observed except for an increase in the liver weight at necropsy at the time of the interim kill (18 months). Differences were not found in animals killed at the end of the study (24 months, after 6 months recovery) except for an increase in the ratio of liver to body weight. Histopathological examination revealed centrolobular hepatocellular hypertrophy in the treated groups

Daily doses of 0, 5, 20 and 80 mg/kg were administered in the diet to dogs for a period of one year. In the high-dose group, untoward effects were slight-to-moderate sedation and ataxia, which decreased as the study progressed. Isolated brief convulsive seizures were observed and an

occasional elevation in serum alkaline phosphatase, a borderline increase in SGPT and a slight increase in liver weights occurred in a few dogs in the 80 mg/kg dosage group.

**Reproductive Studies**

Reproductive, teratological, perinatal and postnatal studies in rats receiving bromazepam at levels of 5 and 50 mg/kg/day p.o. revealed an increase in fetal mortality in the 50 mg/kg group. However, a second reproductive study, in which rats were administered either 10 or 25 mg/kg/day, revealed an increase in the stillbirth rate and a reduction in pup survival at both doses during the first four days following delivery. In another rat study, the daily oral administration of 1 mg/kg, through two successive matings, did not affect the reproductive processes. Bromazepam, at doses of 10 mg/kg/day produced a slight decrease in the number of pregnancies and in the postpartum survival of the offsprings following the second matings. When 100 mg/kg/day was given through three successive matings, a decrease in the number of pregnancies in the parent generation and in the postpartum survivability of the offsprings was observed in all instances. Bromazepam was given to pregnant rabbits at doses of 5 and 50 mg/kg/day p.o. The following effects were noted: a reduction in maternal weight gain, a reduction in fetal weight and an increase in the incidence of resorptions in both treated groups. In a second study in rabbits, at dose levels of 5 and 80 mg/kg/day p.o., no teratogenic effects were observed. Pregnant mice were administered bromazepam orally, by stomach tube, from day 7 through 13 or 16 of pregnancy at dose levels of 5, 10, 50 and 125 mg/kg/day. No teratogenic effects were detected.

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**PART III: CONSUMER INFORMATION**

# LECTOPAM®
**bromazepam tablets**

**This leaflet is a part of the "Product Monograph" published for LECTOPAM and is designed specifically for Consumers.**

**Please read this information before you start to take your medicine. Keep this leaflet until you have finished all your tablets, as you may need to read it again. If you are helping someone else to take LECTOPAM, read this leaflet before you give the first tablet.**

**This leaflet is a summary and will not tell you everything about LECTOPAM. Contact your doctor or pharmacist if you have any questions about the drug.**

## ABOUT THIS MEDICATION

**What the medication is used for:**
The short-term treatment of severe anxiety.

**What it does:**
LECTOPAM contains the active ingredient bromazepam, which belongs to a group of medicines known as benzodiazepines. LECTOPAM has sedative properties which help in the treatment of severe anxiety.

**When it should not be used:**
- If you are allergic to the group of medicines known as benzodiazepines (examples: clonazepam, chlordiazepoxide, diazepam, or flurazepam).
- If you are allergic to the medicinal ingredient (bromazepam).
- If you are allergic to any of the other non-medicinal ingredients it contains (see '**What the non-medicinal ingredients are**').
- If you suffer from lung disease or from sleep apnea.
- If you have a liver condition.
- If you have glaucoma.
- If you have myasthenia gravis.
- If a child is less than 18 years of age.

**What the medicinal ingredient is:**
bromazepam

**What the non-medicinal ingredients are:**
**Tablets 3 mg**: iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, talc.
**Tablets 6 mg**: indigotine aluminum lake, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, talc.

**What dosage forms it comes in:**
LECTOPAM is available as:

3 mg tablet – pale red in colour, slightly speckled, cylindrical and biplane in shape, single scored on one side and engraved with ROCHE over 3 on the other side.

6 mg tablet - greenish-grey to greyish-green in colour, slightly speckled, cylindrical and biplane in shape, single scored on one side and engraved with ROCHE over 6 on the other side.

## WARNINGS AND PRECAUTIONS

- LECTOPAM may affect your ability to be alert. Driving, operating machinery and other hazardous activities should therefore be avoided altogether or at least during the first few days of treatment. This effect of LECTOPAM may be made worse if you take alcoholic drinks. If your doctor has increased your dose or if you have changed the timings of when you take your medication this may also modify your reactions.
- You must not consume alcohol or other drugs that affect your central nervous system while taking LECTOPAM (see INTERACTIONS WITH THIS MEDICATION below).
- Always contact your doctor before stopping or reducing your dosage of LECTOPAM, as suddenly stopping treatment or a large decrease in dose can cause withdrawal symptoms.
- Benzodiazepines such as LECTOPAM have produced dependence (addiction) and withdrawal symptoms can occur when treatment is stopped suddenly. The risk of dependence (addiction) increases with higher doses and longer duration of treatment. Symptoms of withdrawal may include shaking, convulsions (seizures), diarrhea, sweating, sleep disturbances, agitation/restlessness, headache, muscle pain, anxiety, confusion, and irritability. In severe cases of withdrawal, symptoms may include numbness and tingling of the extremities, hallucinations (see or hear things that are not there), increased sensitivity to light, noise and physical contact and seizures.
- There have been reports of falls and fractures in people who take benzodiazepines such as LECTOPAM. The risk is increased in those also taking other sedatives (including alcoholic beverages) and in the elderly.
- Memory loss may occur when LECTOPAM is used at therapeutic doses.
- If you develop any unusual or disturbing thoughts or behaviour while using LECTOPAM, discuss the matter immediately with your doctor.
- Do not take this medicine if you are pregnant, or might become pregnant, unless advised by your doctor. Contact your doctor if you think you may be pregnant, or are intending to become pregnant.
- LECTOPAM may pass into breast milk. Therefore, if you are breast feeding, this medicine should be avoided. Your doctor will discuss this with you.

**BEFORE you use LECTOPAM talk to your doctor or pharmacist if you:**
- Have a lung, liver or kidney condition.
- Are taking or plan on taking ANY other drugs (including herbal preparations, drugs you purchase without prescriptions, and those not prescribed by your doctor).

- Regularly drink alcohol or use recreational drugs or have a history of dependence /addiction to alcohol or drugs.
- Have a history of depression and/or suicide attempts.
- Have the rare hereditary problem of galactose intolerance.
- Are pregnant or plan to be pregnant.

## INTERACTIONS WITH THIS MEDICATION

**Tell your doctor if you are taking any other medicines including any that you have bought from a pharmacy, supermarket or health food store without a prescription.**

Some medicines may interfere with LECTOPAM. These medicines include:

- medicines to control seizures.
- narcotics and narcotic pain relievers.
- muscle relaxants.
- sleeping medication.
- antihistamines or allergy medications.
- medicines to treat your mood, such as monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazines.
- Cimetidine, propanolol and fluvoxamine

These medicines may be affected by LECTOPAM or may affect how well LECTOPAM works. Your doctor or pharmacist can tell you what to do if you are taking any of these medicines.

**If you have not told your doctor about any of the above, tell him/her before you start taking LECTOPAM.**

You must not consume alcohol while taking LECTOPAM as its effects may worsen side effects that some patients experience with LECTOPAM.

## PROPER USE OF THIS MEDICATION

**Usual dose:**
Always take the tablets exactly as your doctor tells you to. Your doctor will prescribe a suitable dose for you. The dose your doctor prescribes will depend on the nature of your illness, your reaction to the medicine, your age and body weight. The table below shows the different doses that your doctor may prescribe according to your age. Your doctor will start you on an initial low dose and gradually increase it until the desired effect is achieved.

| | Usual Daily Dose |
|---|---|
| Adults | Depending upon severity of symptoms - 6 mg to 18 mg, in equally divided doses. Treatment may be initiated at a lower dose. |
| Elderly | Maximum of 3 mg in equally divided doses. Dose can be increased gradually as needed and tolerated. |

The total daily dose should be taken as advised by your doctor.

Do not change the prescribed dose yourself. If you think the effect of your medicine is too weak or too strong, talk to your doctor.

Your doctor will advise you when to stop taking the medicine. Your doctor will slowly decrease the dosage as sudden discontinuation of treatment can cause the appearance of withdrawal symptoms.

**Overdose:**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications LECTOPAM can cause some side effects. For most patients these side effects are likely to be minor and temporary as your body adjusts to the medicine. However, some may be serious. Consult your doctor or pharmacist as soon as you can if you do not feel well while taking LECTOPAM.

The most common side effects are:
- Feeling drowsy or tired, especially at the start of treatment.
- Loss of some muscle coordination.
- Dizziness.

Less common possible side effects are:
- Rash, nausea, headache, blurred vision, tremors, hypotension (low blood pressure), urinary incontinence, and constipation.
- In rare cases changes in your blood and liver may occur and your doctor will monitor for these.
- Falls and fractures: The risk is increased in those also taking other sedatives (including alcoholic beverages) and in the elderly.

Withdrawal-related side effects:
- With sudden discontinuation of treatment with LECTOPAM symptoms of withdrawal may occur, including: headache, muscle pain, convulsions, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases of withdrawal, symptoms may include numbness and tingling of the extremities, hallucinations, increased sensitivity to light, noise and physical contact and seizures.

## SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom / effect | | Talk with your doctor or pharmacist | | Stop taking drug and and seek medical help |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| **Rare** | Unusual behavioural problems (aggression, rage), sudden anxiety or excitation; restlessness, agitation, irritability; hallucinations (see or hear things that are not there) or delusions; severe sleep disturbances, nightmares, inappropriate behaviour | | ✓ | |
| | Allergic reactions (red skin, hives, itching, swelling of the lips, face, tongue, throat, trouble breathing, wheezing, shortness of breath, skin rashes, blisters of the skin, sores or pain in the mouth or eyes) | | | ✓ Immediately. |
| | Depression. Symptoms may include: Difficulty sleeping, changes in weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family gatherings and activities with friends, reduced libido (sex drive), and thoughts of death or suicide. | | ✓ | |

**This is not a complete list of side effects. If you are concerned about these or any other unwanted side-effects, talk to your doctor or pharmacist.**

## HOW TO STORE IT

- Keep LECTOPAM in a cool dry place stored at room temperature (15-30°C).
- Keep this medicine out of sight and reach of children.

## REPORTING SUSPECTED SIDE EFFECTS

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

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- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  **- Fax toll-free to 1-866-678-6789, or**
  **- Mail to: Canada Vigilance Program**
  **Health Canada**
  **Postal Locator 0701E**
  **Ottawa, Ontario**
  **K1A 0K9**

**Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.**

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.rochecanada.com or by contacting the sponsor, Hoffmann-La Roche Limited, at 1-888-762-4388.

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Roche

Hoffmann-La Roche Limited
Mississauga, Ontario L5N 5M8