

## LACTOPAR

Tablets

### Composition

Each tablet contains Bromocriptine (as mesylate) 2.5 mg.

### Action

Bromocriptine is a brominated ergot derivative that functions as a dopamine D2 receptor agonist and a dopamine D1 receptor antagonist. It imposes a direct dopaminergic effect on cells located within the basal ganglia, mesolimbic system, and hypothalamus. It does not possess the uterotonic and vasoconstrictive properties associated with other ergot preparations.

Bromocriptine specifically inhibits the synthesis and secretion of prolactin from the anterior pituitary gland by dopaminergic stimulation of pituitary prolactin cells. Amenorrhoea, galactorrhoea and other endocrine processes associated with hyperprolactinaemia are consequently returned to physiological levels of activity. Bromocriptine also enhances the release of gonadotrophin and gonadal steroids that are suppressed in hyperprolactinaemia. Preclinical studies have reported that bromocriptine decreases dopamine turnover in the median eminence and dopaminergic tuberoinfundibular region of the hypothalamus that may further regulate the synthesis and secretion of prolactin.

Bromocriptine reduces the elevated levels of growth hormone (GH) in acromegaly and may alleviate the clinical symptoms and glucose intolerance presented in this condition.

The dopaminemimetic activity of bromocriptine in the striatum may be responsible for the beneficial effects observed in selected cases of Parkinson's disease.

### Pharmacokinetics

Following oral administration, bromocriptine is rapidly and well absorbed. Peak plasma levels are reached within 1-3 hours. An oral dose of 5mg of bromocriptine results in a  $C_{max}$  of 0.465ng/ml. The prolactin-lowering effect occurs 1-2 hours after ingestion, reaches its maximum within about 5 hours and lasts for 8-12 hours.

The substance is extensively metabolised in the liver. The elimination of parent drug from plasma occurs biphasically, with a terminal half-life of about 15 hours. Parent drug and metabolites are almost completely excreted via the liver, with only 6% being eliminated via the kidney. Plasma protein-binding amounts to 96%.

There is no evidence that the pharmacokinetic properties and tolerability of bromocriptine are directly affected by advanced age. However, in patients with impaired hepatic function, the speed of elimination may be retarded and plasma levels may increase, requiring dose adjustment.

### Biotransformation

Bromocriptine undergoes extensive first-pass biotransformation in the liver, reflected by complex metabolite profiles and by almost complete absence of parent drug in urine and faeces. It shows a high affinity for CYP3A and hydroxylations at the proline ring of the cyclopeptide moiety constitute a main metabolic pathway. Inhibitors and/or potent substrates for CYP3A4 might therefore be expected to inhibit the clearance of bromocriptine and lead to increased levels. Bromocriptine is also a potent inhibitor of CYP3A4 with a calculated IC50 value of 1.69  $\mu$ M. However, given the low therapeutic concentrations of free bromocriptine in patients, a significant alteration of the metabolism of a second drug whose clearance is mediated by CYP3A4 should not be expected.

### Indications

#### Inhibition of lactation

Lactopar can be used to prevent lactation after an abortion or stillbirth, or to suppress puerperal lactation. It should not be used to suppress established lactation.

#### Galactorrhoea/ Amenorrhoea

Lactopar is indicated for the short-term treatment of galactorrhoea/ amenorrhoea associated with hyperprolactinaemia due to various etiologies. It is not indicated in patients with normal prolactin levels.

#### **Female and Male Infertility**

Lactopar is indicated for the treatment of female and male infertility associated with hyperprolactinaemia.

#### **Acromegaly**

Alone or as an adjunct to surgery and/or radiotherapy, to reduce circulating growth hormone levels.

#### **Pituitary Prolactinoma**

In the treatment of prolactin-secreting pituitary tumours in males and females. This treatment is usually considered secondary to surgical excision of microadenomas, but may be the treatment of choice for macroadenomas in order to shrink the tumour prior to surgery. Bromocriptine mesylate may be used as an adjunct to radiotherapy when the tumour is inoperable.

Since the effects of external pituitary radiation may not become maximal for several years, adjunctive therapy with Lactopar offers potential benefit before the effects of irradiation are manifested.

#### **Parkinson's disease**

Lactopar is indicated in the treatment of the signs and symptoms of idiopathic or postencephalitic Parkinson's disease. As adjunctive treatment to levodopa (alone or with peripheral decarboxylase inhibitor), Bromocriptine mesylate therapy may provide additional therapeutic benefits in those patients who are currently maintained on optimal dosages of levodopa, and in those who are beginning to deteriorate on levodopa therapy by developing tolerance.

Bromocriptine mesylate may obviate the need to reduce the maintenance dose of levodopa. Therefore, it may ameliorate the occurrence and/or severity of adverse reactions associated with long-term levodopa therapy, such as abnormal involuntary movements (e.g. dyskinesias) and marked swings in motor function ("on-off" phenomenon). Continued efficacy of Bromocriptine mesylate during treatment of more than two years has not been established.

#### **Contraindications**

- Known hypersensitivity to any ergot alkaloid.
- Uncontrolled hypertension.
- Toxemia of pregnancy.

#### **Warnings**

Since hyperprolactinaemia with galactorrhoea/amenorrhoea and infertility has been found in patients with pituitary tumours (Forbes-Albright syndrome), a complete evaluation of the sella turcica is indicated prior to treatment with Bromocriptine mesylate. Although Bromocriptine mesylate therapy effectively lowers the plasma levels of prolactin in patients with pituitary tumours, this does not obviate the necessity for radiotherapy or surgical procedures, where appropriate.

Bromocriptine mesylate therapy is known to produce hypotension, and rarely hypertension in some patients. Because the development of hypertension may be delayed, it is prudent to monitor the blood pressure periodically during the first weeks of therapy. If hypertension, severe, progressive, or unremitting headache (with or without visual disturbance), or evidence of CNS toxicity develops, drug therapy should be discontinued and the patient should be evaluated promptly.

Symptomatic hypotension may occur in patients treated with Bromocriptine mesylate for any indication. Hypotension often develops during the second week of therapy, although it sometimes occurs at the start of therapy.

Cases of severe gastrointestinal bleeding from peptic ulcers, some fatal have been reported in acromegalic patients being treated with Bromocriptine mesylate. Although there is no evidence that Bromocriptine increases the incidence of peptic ulcers in acromegalic patients, symptoms suggestive of peptic ulcer should be investigated thoroughly and treated appropriately

Furthermore, care should be exercised when Bromocriptine mesylate is administered concomitantly with other medications known to lower blood pressure.

Long-term treatment (6-36 months) with Bromocriptine mesylate in doses ranging from 20-100 mg/day has been associated with pulmonary infiltrates, pleural effusion and thickening of the pleura in a few patients. In those instances where treatment was terminated, the changes slowly reverted to normal.

### **Pregnancy**

If pregnancy occurs during Bromocriptine mesylate therapy, treatment should be discontinued immediately. Careful observation of these patients throughout pregnancy is mandatory. Small prolactin-secreting adenomas not detected previously may rapidly increase in size during pregnancy. Optic nerve compression may occur, and emergency pituitary surgery or other appropriate measures may be necessary.

### **Nursing Mothers**

Bromocriptine mesylate prevents lactation. Therefore, it should not be administered to breastfeeding mothers.

### **Paediatric Use**

Safety and efficacy of Bromocriptine mesylate therapy have not been established in children under the age of 15 years.

## **Adverse Reactions**

### **Hyperprolactinaemia-associated Diseases**

Therapy was reported to have been discontinued in approximately 5% of patients because of adverse effects.

The most frequently occurring adverse reactions, in decreasing order of frequency, were nausea, headache, dizziness, fatigue, abdominal cramps, light-headedness, vomiting, nasal congestion, constipation and diarrhea. A slight hypotensive effect may accompany Bromocriptine mesylate treatment. The occurrence of adverse reactions may be lessened by the temporary reduction of dosage to 1/2 tablet, 2 or 3 times daily.

### **Acromegaly**

The most frequently occurring adverse reactions encountered in acromegalic patients treated with Bromocriptine mesylate, in decreasing order of frequency, were nausea, constipation, postural/orthostatic hypotension, anorexia, dry mouth/nasal stuffiness, indigestion/dyspepsia, digital vasospasm, drowsiness/tiredness, and vomiting.

### **Parkinson's disease**

The most common newly-appearing adverse reactions were nausea, abnormal involuntary movements, hallucinations, confusion, "on-off" phenomenon, dizziness, drowsiness, faintness/fainting, vomiting, asthenia, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, hypotension, shortness of breath, constipation and vertigo.

Less common adverse reactions that may be encountered include anorexia, anxiety, blepharospasm, dry mouth, and dysphagia, edema of the feet and ankles, erythromelalgia, epileptiform seizure, fatigue, headache, lethargy. Mottling of skin, nasal stuffiness, nervousness, nightmares, paresthesia, skin rash, urinary frequency, urinary incontinence, urinary retention and, rarely, signs and symptoms of ergotism such as tingling of fingers, cold feet, numbness, muscle cramps of feet and legs or exacerbation of Raynaud's syndrome.

## **Precautions**

The relative efficacy of Bromocriptine mesylate versus surgery in preserving visual fields unknown. Patients with rapidly progressive visual field loss should be evaluated by a neurosurgeon, to help decide on the most appropriate therapy.

Safety and efficacy of Bromocriptine mesylate have not been established in patients with renal or hepatic disease. Care should be exercised when administering Bromocriptine mesylate concomitantly with other medications known to lower blood pressure.

Patients should be warned that their ability to perform potentially hazardous tasks requiring mental alertness or physical coordination, such as driving a vehicle or operating machinery, may be impaired.

## **Galactorrhoea/ Amenorrhea**

The treatment of women suffering from galactorrhoea/amenorrhea with Bromocriptine mesylate may result in restoration of fertility. Therefore, women who do not desire pregnancy, or those harboring large adenomas, should be advised to adopt contraceptive measures (other than oral contraceptives) during treatment with Bromocriptine mesylate.

Since pregnancy may occur prior to re-initiation of menses, a pregnancy test is recommended as an additional precaution at least every 4 weeks during the amenorrheic period and, once menses are re-initiated, every time a patient misses a menstrual period.

## **Female Infertility**

Treatment of patients with Bromocriptine mesylate should be discontinued as soon as the diagnosis of pregnancy has been established. Patients must be monitored closely throughout pregnancy for signs and symptom which may develop if a previously undetected prolactin-secreting tumour enlarges.

## **Acromegaly**

Cold sensitive digital vasospasm has been observed in some acromegalic patients treated with Bromocriptine mesylate. The response, should it occur, can be reversed by reducing the dose of Bromocriptine mesylate, and may be prevented by keeping the fingers warm.

## **Parkinson's disease**

Safety during long-term use for more than 2 years at the doses required for the treatment of Parkinsonism has not been established.

As with any chronic therapy, periodic evaluation of hepatic, hematopoietic, cardiovascular and renal function is recommended. Symptomatic hypotension can occur, and therefore caution should be exercised when treating patients receiving antihypertensive drugs.

High doses of Bromocriptine mesylate may be associated with confusion and mental disturbances. Since patients suffering from Parkinsonism may manifest mild degrees of dementia, caution should be exercised in treatment.

Bromocriptine mesylate, administered alone or concomitantly with levodopa, may cause hallucinations (visual or auditory). Hallucinations usually resolve with dosage reduction; occasionally, discontinuation of Bromocriptine mesylate is required. Rarely, following high doses, hallucinations have persisted for several weeks following discontinuation of Bromocriptine mesylate.

As with levodopa, caution should be exercised when administering Bromocriptine mesylate to patients with a history of myocardial infarction who have a residual atrial, nodal, or ventricular arrhythmia.

## **Drug Interactions**

*Bromocriptine/ Dopamine-depleting Agents*

Bromocriptine has been administered concurrently to patients receiving phenothiazines, and has effectively lowered raised prolactin concentrations, apparently without interfering with the psychotropic effect. The antiparkinsonism effects of dopaminergic agents can, however, be antagonized by reserpine, phenothiazine and the butyrophenone.

#### *Bromocriptine/ Other Ergot Alkaloids*

Although there is no conclusive evidence that demonstrates an interaction between Bromocriptine mesylate and other ergot alkaloids, the concomitant use of these medications is not recommended.

#### **Diagnostic Interference**

Bromocriptine mesylate may affect laboratory test results. Blood urea nitrogen (BUN), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), gamma glutamyl transpeptidase (GGTP), creatinine phosphokinase (CPK), alkaline phosphatase and uric acid may be elevated. Such results are usually transient and not of clinical significance.

#### **Dosage and Administration**

Lactopar should always be taken with food.

Patients should be evaluated frequently during dose escalation to determine the lowest dosage that produces a therapeutic response.

#### **Galactorrhoea/ Amenorrhoea/ Male Infertility**

Most patients with hyperprolactinaemia respond to 7.5 mg daily, in divided doses, but doses of up to 30 mg daily have been used. In infertile patients without demonstrably elevated serum prolactin levels, the usual dosage is 2.5 mg twice daily.

#### **Female Infertility**

The initial dosage of Lactopar is 1.25-2.5 mg daily. An additional 2.5 mg may be added to the treatment regimen, as tolerated, every 3-7 days, until an optimal therapeutic response is achieved.

The therapeutic dosage is usually 5-7.5 mg, and ranges from 2.5 to 15 mg per day.

In order to reduce the likelihood of prolonged exposure to Lactopar in an unsuspected pregnancy, a mechanical contraceptive should be used in conjunction with Lactopar therapy, until normal ovulatory menstrual cycles have been restored. Contraception should then be discontinued. If menstruation does not occur within 3 days of the expected date, Lactopar therapy should be discontinued and a pregnancy test performed.

#### **Acromegaly**

Virtually all acromegalic patients receiving therapeutic benefit from Bromocriptine mesylate also have reductions in circulating levels of growth hormone. Therefore, periodic assessment of circulating levels of growth hormone will, in most cases, serve as a guide in determining the therapeutic potential of Bromocriptine mesylate. If, after a brief trial with Lactopar therapy, no significant reduction in growth hormone levels has taken place, careful assessment of the clinical features of the disease should be made, and if no change has occurred, dosage adjustment or discontinuation of therapy should be considered.

The initial recommended dosage is 1.25-2.5 mg on retiring (to be taken with food), for 3 days. An additional 1.25-2.5 mg should be added to the treatment regimen every 3-7 days, as tolerated, until the patient obtains optimal therapeutic benefit. Patients should be re-evaluated monthly, and the dosage adjusted according to reductions of growth hormone or clinical response. The usual optimal therapeutic dosage range of Bromocriptine mesylate varies from 20-30 mg per day in most patients. The maximal dosage should not exceed 100 mg per day.

Patients treated with pituitary irradiation should be withdrawn from Lactopar therapy on a yearly basis to assess both the clinical effects of radiation on the disease process as well as the effects of Lactopar therapy. Usually a 4-8 week withdrawal period is adequate for this purpose. Recurrence of

the signs/symptoms or increases in growth hormone indicate the disease process is still active and further courses of Lactopar should be considered.

### **Pituitary Prolactinoma**

Initially, 1.25 mg at bedtime, increasing after 2-3 days to 2.5 mg at bedtime. Dosage may then be increased by 1.25-2.5 mg at 2-3 day intervals until a dosage of 2.5 mg twice daily is achieved. The dosage may then be increased by 2.5 mg daily at 2-3 day intervals as follows: 2.5 mg 8-hourly, 2.5 mg 6-hourly, 5 mg 6-hourly. Patients have responded to doses of up to 30 mg daily.

### **Parkinson's disease**

The basic principle of Lactopar therapy is to initiate treatment at a low dosage and, on an individual basis, increase the daily dosage slowly until a maximum therapeutic response is achieved.

The initial dose is 1.25 mg twice daily with meals. Assessments are recommended at two-week intervals during dosage titration, to ensure that the lowest dosage producing an optimal therapeutic response is not exceeded. If necessary, the dosage may be increased every 14-28 days, by 2.5 mg per day. This should be continued until the optimum dosage is reached, which is usually between 10-40 mg daily.

For patients on levodopa therapy, the dosage of levodopa during the introductory period should be maintained, if possible. In the event that it is advisable to reduce the dosage of levodopa because of adverse reactions, the daily dosage of Bromocriptine mesylate, if increased, should be accomplished gradually in small (2.5 mg) increments.

The safety of Lactopar has not been demonstrated in dosages exceeding 100 mg per day.

### **Over Dosage**

Over Dosage with Bromocriptine is likely to result in vomiting and other symptoms that could be due to over-stimulation of the dopaminergic receptors and may include confusion, hallucinations and hypotension. General supportive measures should be undertaken to remove any unabsorbed material and if necessary, blood pressure should be maintained.

### **Presentation**

Box of 30 tablets