

New Zealand Data Sheet

APO-BROMOCRIPTINE

Bromocriptine 5mg capsules as Bromocriptine mesylate.

Presentation

APO-BROMOCRIPTINE 5mg hard gelatine capsules have a white opaque body, caramel opaque cap (5.1 x 13.8mm). Imprinted "APO 5", with white powder fill. Each capsule contains Bromocriptine mesylate which provides 5mg of Bromocriptine and typically weighs 157mg.

The Apo-Bromocriptine capsules are not capable of fulfilling all the dose regimes by themselves as they are not divisible and exist only in the 5 mg strength.

This medicine has been granted provisional consent under section 23 of the Medicines Act 1981.

This product is not interchangeable with any other bromocriptine products on the New Zealand market and bioequivalence has not been demonstrated with the Apo-Bromocriptine tablets.

Uses

Actions

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 tubero-infundibular region of the hypothalamus which 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 Parkinsons Disease.

Pharmacokinetics

Bromocriptine is rapidly absorbed after oral administration, but only 6% of the dose reaches the systemic circulation due to the high hepatic extraction rate and first pass metabolism. Maximum peak concentrations are obtained within 1 to 1.5 hours; serum prolactin decreases within 2 hours and is maximally decreased at 8 hours. Bromocriptine is highly distributed in the liver, stomach, and intestine, and plasma protein binding amounts to 96%.

Bromocriptine is extensively metabolised by the liver. The fate of bromocriptine primarily involves biliary excretion with renal excretion of two major metabolites accounting for only 6% of the total dose. It is not known whether these metabolites (2-bromolysergic acid and 2-bromoisolysergic acid) are pharmacologically active in humans. The elimination of the parent drug from plasma is biphasic, with a terminal half life of about 15 hours (range 8-20 hours). Multiple dosing may result in accumulation of bromocriptine to the extent that plasma levels may be almost double those observed following single doses.

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Indications

Prolactin dependent Menstrual Cycle disorders (Amenorrhoea, oligomenorrhoea, galactorrhoea), and/or female infertility associated with hyperprolactinaemia or luteal phase deficiency:

Bromocriptine may normalise the menstrual cycle and/or induce ovulation without ovarian overstimulation. Treatment with bromocriptine is not curative and it is not effective in treating ovarian failure.

Pre-menstrual symptoms:

Mood disturbances, bloating, cyclical oedema and breast tenderness.

Hyperprolactinaemia in man:

Prolactin-related hypogonadism (oligospermia, loss of libido, impotence) and galactorrhoea.

Prolactinomas:

Bromocriptine may result in a reduction in size of pituitary prolactin-secreting micro- or macro-adenomas. It can be used alone or prior to radiation or surgery for excision of the tumour. It can also be used post surgery if prolactin levels are still elevated.

Acromegaly:

Used as an adjunct to, or as an alternative to radiation or surgery.

Inhibition of lactation:

Bromocriptine can be used to prevent lactation after an abortion or still-birth, or to suppress puerperal lactation. It should not be used to suppress established lactation.

Benign breast disease:

Cyclical mastalgia with pre-menstrual syndrome with or without benign nodular or cystic conditions.

Parkinsons Disease:

Bromocriptine is used to treat idiopathic or post-encephalitic parkinsonian syndrome either as monotherapy or in combination with other anti-parkinsonian agents.

Dosage and Administration

Bromocriptine capsules should always be taken with food.

Patients being transferred from Apo-Bromocriptine tablets to Apo-Bromocriptine capsules must be titrated to an effective dose and monitored.

Dosage of bromocriptine mesylate is expressed in terms of bromocriptine, and should be individualised.

Menstrual cycle disorders, Galactorrhoea, Female Infertility:

Usual therapeutic dosage is 5 to 7.5 mg daily in divided doses, but may range from 2.5 mg to 30 mg daily. Initial doses should be low (1.25 to 2.5 mg) and slowly increased at 5 to 7 day intervals, as tolerated. The lowest dose possible, that controls symptoms, should be used. Treatment is continued until menstruation and/or ovulation has normalised.

Pre-menstrual symptoms:

Treatment should begin on the 14th day of the cycle taking 1.25mg per day. Increase the dosage in steps of 1.25mg daily up to 2.5mg twice a day until menstruation begins.

Male hypogonadism:

Initial dosage 1.25mg 2 or 3 times a day gradually increasing to 5-10mg a day.

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Prolactinomas:

1.25mg 2 or 3 times daily; this can be gradually increased as needed to suppress prolactin secretion.

Acromegaly:

Initially 1.25mg 2 or 3 times a day gradually increasing to 10-20mg a day, depending on side effects and clinical response.

Inhibition of lactation:

On day one take 1.25mg morning and night with food, increasing on day two to 2.5 mg twice daily. Therapy should be continued for 14 days to prevent rebound lactation. Treatment should be started as soon as possible after parturition or abortion.

Benign breast disease:

1.25mg 2 to 3 times a day which may be increased to 5-7.5mg a day.

Parkinson's Disease:

Starting doses must be low initially (1.25mg daily), preferably at bedtime, and dosage increases must be gradual e.g. at intervals of 5 to 7 days. Dosages should be individually titrated according to therapeutic response and tolerability and given in 2 to 3 divided doses. If an undesirable reaction occurs, the dosage should be reduced for at least a week. Titration upwards may then be cautiously re-tried. An adequate therapeutic response may be reached in 6 to 8 weeks. When bromocriptine is added to regimens of levodopa where patients are experiencing motor difficulties or side-effects, it is recommended that the dose of levodopa is reduced prior to the addition of bromocriptine. As the dosage of bromocriptine is titrated upwards, the dose of levodopa may be reduced further.

The usual range of bromocriptine when used as monotherapy or as an adjunct to levodopa therapy is 10 to 40 mg a day in divided doses, taken with food.

Hepatic dysfunction:

Dosage may have to be reduced in patients with impaired hepatic function.

Contraindications

1. Hypersensitivity to ergot alkaloids.
2. Uncontrolled hypertension, hypertensive disorders of pregnancy, hypertension postpartum and in puerperium.
3. Coronary artery disease and other severe cardiovascular conditions.
4. Symptoms and/or history of serious psychiatric disorders.
5. Bromocriptine is contraindicated in patients with pre-existing valve problems.

Warnings and Precautions**Hypotension:**

Blood pressure should be monitored periodically in all patients receiving bromocriptine. When used by women post-partum, it may induce hypotension, or more rarely hypertension, and should not be given for at least 4 hours post partum. Blood pressure must be monitored on several occasions initially, as development of hypertension may be delayed. Particular attention should be paid to patients who have used other drugs that can alter blood pressure.

Inhibition of Lactation:

Occasionally serious adverse reactions have been reported. These include seizures, strokes, myocardial infarction, hypertension and psychic disorders. Constant or progressively severe headache, which can be accompanied by visual disturbances, often precede by hours or days the occurrence of a seizure and/or stroke. Periodic monitoring of blood pressure is recommended in postpartum women receiving bromocriptine for the inhibition of lactation. Lactation inhibition therapy should not begin until the vital signs have stabilised and not before 4 hours after delivery, as bromocriptine may cause hypotension or sometimes hypertension in some patients. If hypertension, a severe progressive or unremitting headache (with or without visual disturbance),

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or the evidence of CNS toxicity develops, the drug therapy should be discontinued and the patient evaluated promptly.

Psychiatric disorders:

Bromocriptine should be used with caution in patients with a history of dementia or other psychiatric disorders, as high dosages (20 to 40 mg) may be associated with confusion and mental disturbances. May also cause visual or auditory hallucinations alone or combined with levodopa therapy.

Female patients:

Bromocriptine may restore fertility when used in the lowest dose possible to control symptoms, and if pregnancy is not desired during therapy, barrier contraceptive measures should be used. Oral contraceptives are contra-indicated since they may cause amenorrhoea or galactorrhoea. A pregnancy test should be performed every 4 weeks in amenorrhoeic women. If pregnancy occurs, the drug should be discontinued.

Although there is no evidence of uterine tumour development in women receiving Bromocriptine, it is recommended that patients on long-term therapy should have regular gynaecological assessments.

In patients treated for hyperprolactinaemia, or nodular and/or cystic breast disorders, malignancy of the pituitary or breast, respectively, should be excluded.

Peptic Ulcer:

Patients with known or suspected peptic ulcers should be treated with caution in respect of several reports of fatal gastric haemorrhage in acromegalic patients who received high doses of bromocriptine. If bromocriptine must be used in acromegalic patients, they should be instructed to report any gastrointestinal side effects immediately.

Parkinsons Disease:

Long-term treatment with bromocriptine for Parkinson's disease has been associated with pleural and pericardial effusions, as well as pleural and pulmonary fibrosis and constrictive pericarditis. During long term treatment regular monitoring with chest x-rays should be considered. Patients with unexplained pleuropulmonary signs should be examined thoroughly and discontinuation of treatment considered.

Retroperitoneal fibrosis has been reported in a few sufferers of Parkinsons Disease, who received daily doses of more than 30mg for a number of years. To recognise retroperitoneal fibrosis at an early and reversible stage its manifestations (e.g. Impaired renal function, back pain, and oedema of the lower limbs), should be looked for in such patients. Bromocriptine should be withdrawn if fibrotic changes in the peritoneum are diagnosed or suspected.

Pathological Gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's Disease. Health care professionals should inform patients to seek help from their doctor if they, their family or their carer notice that their behaviour is unusual.

Diabetic Retinopathy:

Bromocriptine may cause a release of growth hormone in normal and diabetic patients. Growth hormone has been implicated in the acceleration and maintenance of diabetic retinopathy. Bromocriptine should therefore be used with caution in diabetic patients.

Effect on ability to drive or operate machinery:

Patients should be warned that bromocriptine may cause dizziness and fainting during the first few days, and may impair their ability to drive a car or operate machinery.

Impaired liver, renal or severe cardiovascular dysfunction:

Bromocriptine should be used with caution in patients with impaired liver, renal or severe cardiovascular dysfunction.

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Usage in Pregnancy

Category A

Bromocriptine should be discontinued immediately if pregnancy occurs during therapy, unless there is a definite indication for its continuation. No increased risk of abortion has been observed following the withdrawal of bromocriptine. If patients with prolactinomas show signs of tumour enlargement e.g. headaches and/or visual deterioration following the withdrawal of bromocriptine, they may have therapy re-instituted. In other cases surgery may be appropriate.

There is no evidence that the use of bromocriptine is associated with an increased risk of congenital abnormalities.

Use in Lactation

Bromocriptine inhibits lactation and should not be used by women who elect to breast-feed.

Adverse Reactions

Nausea is the most common side effect at the beginning of therapy with bromocriptine, but vomiting, dizziness, postural hypotension and fainting sometimes occur. Initial doses must be low, taken preferably at bedtime, and blood pressure should be monitored initially.

Gastrointestinal effects include abdominal cramps, epigastric pain, indigestion, constipation or diarrhoea. Occasionally, acromegalic patients on doses 10 to 60 mg bromocriptine have developed a peptic ulcer or gastrointestinal haemorrhage.

Temporary reduction of dose or administration with food may relieve these effects.

Additional side-effects include headache, nasal congestion or watery rhinorrhoea, dryness of mouth, and drowsiness,

Dyskinesias have occurred in patients with Parkinsonism as well as psychosis, nightmares, anxiety, mania, hallucinations, confusion and erythromelalgia. These are more likely at higher doses, but may also occur at low doses. Mania has also been reported when bromocriptine has been used post-partum.

Episodes of reversible vasoconstriction in the extremities induced by cold, and leg cramps have been reported during prolonged therapy or with high doses.

Other adverse effects reported include depression, anxiety and extreme agitation, paraesthesias, fatigue, arrhythmias or exacerbation of angina.

Pleuropulmonary changes (pleural and pericardial effusions, pleural and pulmonary fibrosis), constrictive pericarditis, and retroperitoneal fibrosis have occurred in patients on long-term therapy (see Warnings and Precautions).

In several acromegalic patients treated with high doses, fatal gastric haemorrhage has been reported (see Warnings and Precautions).

The use of bromocriptine for the inhibition of physiological lactation postpartum has been associated with the rare occurrence of hypertension, myocardial infarction, seizures, strokes and psychiatric disorders (see Contraindications and Warnings and Precautions).

Patients treated with dopamine agonists for treatment of Parkinson's Disease, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality. These effects are generally reversible upon reduction of the dose or treatment discontinuation.

Interactions

The concomitant administration of erythromycin or other macrolides or octreotide may increase plasma bromocriptine levels.

Drugs which can increase prolactin levels, e.g. butyrophenones, phenothiazines, tricyclic antidepressants, reserpine, metoclopramide, methyl dopa, pimozide, oestrogens and TRF, may reduce the efficacy of bromocriptine.

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Conversely, levodopa, clonidine, pargyline, and iproniazid may synergise the prolactin inhibitory effect of bromocriptine.

The hypotensive effects of bromocriptine may be additive with those of anti-hypertensive agents.

Concomitant use of bromocriptine and other ergot alkaloids is not recommended since the combination may cause potentially serious side effects such as myocardial infarction and hypertension.

Alcohol may decrease tolerability to bromocriptine.

Overdosage

Overdose of bromocriptine may cause nausea, vomiting, dizziness, postural hypotension, sweating, drowsiness, and hallucinations. The management of acute intoxication is symptomatic. Metoclopramide may be indicated for the treatment of emesis or hallucinations.

Pharmaceutical Precautions

Store at or below 25°C. Protect from heat, light and moisture.

Keep container tightly closed.

Shelf Life: 24 months

Medicine Classification

Prescription Only Medicine.

Package Quantities

APO-BROMOCRIPTINE 5mg capsules:

Bottles of 100.

Further Information

Contain lactose.

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