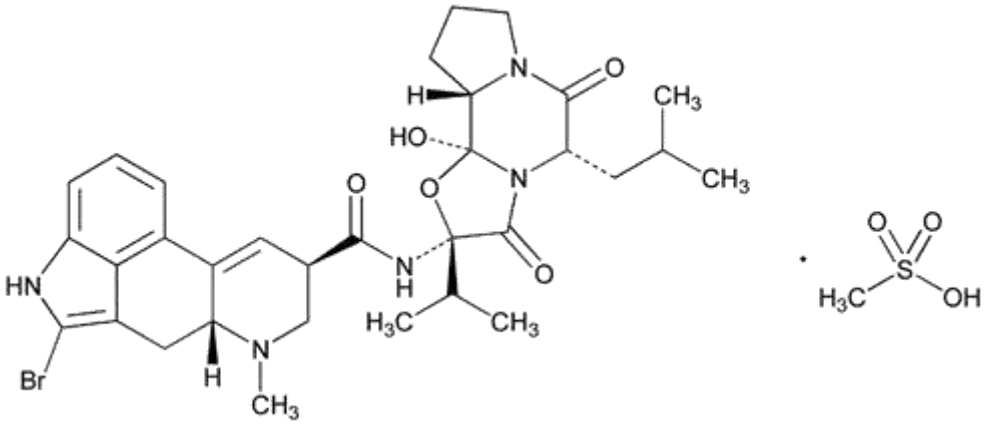
APO-BROMOCRIPTINE

1 APO-BROMOCRIPTINE (2.5mg tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bromocriptine mesylate 2.5mg tablets

Chemical Structure:



Excipient(s) of known effect

APO-BROMOCRIPTINE contains lactose.

If you have been told by your doctor that you have intolerance to some sugars contact your doctor before taking this medicinal product.

Contains 135 mg of lactose monohydrate per 50 mg and 85 mg of lactose monohydrate per 100 mg.

This should be taken into account in patients with diabetes mellitus.

APO-BROMOCRIPTINE does not contain gluten.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Bromocriptine 2.5mg tablets are white, oval, slope-faced & flat-faced tablets with bevelled edges. Scored and engraved 2.5 on the right side on slope side, plain on flat side. Each tablet contains 2.87mg bromocriptine mesylate which provides 2.5mg bromocriptine and typically weighs 140mg.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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.

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.

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

4.2 Dose and method of administration

Bromocriptine tablets should always be taken with food.

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.

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

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.

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.

Maximum Tolerated Daily Dose

The maximum dose is usually not more than 40mg per day in divided doses.

Method of administration

The tablets are to be administered orally.

4.3. 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.
6. Hypersensitivity to Bromocriptine mesylate, lactose or any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

Blood Pressure:

Blood pressure should be monitored periodically in all patients receiving bromocriptine. 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.

If hypertension, unremitting headache, or any signs of CNS toxicity develop, treatment should be discontinued immediately.

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.

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), or the evidence of CNS toxicity develops, the drug therapy should be discontinues 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.

Somnolence and sudden sleep onset

Bromocriptine has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with bromocriptine. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. A reduction of dose or termination of therapy may need to be considered.

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.

When women of child-bearing age are treated with BROMOCRIPTINE for conditions not associated with hyperprolactinaemia the lowest effective dose should be used. This is in order to avoid suppression of prolactin to below normal levels, with consequent impairment of luteal function.

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.

Fibrosis:

Among patients on bromocriptine, particularly on long-term and high-dose treatment, pleural and pericardial effusions, as well as pleural and pulmonary fibrosis and constrictive pericarditis have occasionally been reported. Patients with unexplained pleuropulmonary disorders should be examined thoroughly and discontinuation of bromocriptine therapy should be contemplated

In a few patients on bromocriptine, particularly on long-term and high-dose treatment, retroperitoneal fibrosis has been reported. To ensure recognition of retroperitoneal fibrosis at an early reversible stage it is recommended that its early manifestations (e.g. back pain, fever, weight loss, polyuria, haematuria, oliguria and anorexia) should be watched in this category of patients. Bromocriptine medication should be withdrawn if fibrotic changes in the retroperitoneum are diagnosed or suspected

Attention should be paid to the signs and symptoms of

- Pleuro-pulmonary disease such as dyspnoea, shortness of breath, persistent cough or chest pain
- Cardiac failure as cases of pericardial fibrosis have often manifested as cardiac failure. Constrictive pericarditis should be excluded if such symptoms appear.

Appropriate investigations such as erythrocyte sedimentation rate, chest X-ray and serum creatinine measurements should be performed if necessary to support a diagnosis of a fibrotic disorder. It is also appropriate to perform baseline investigations of erythrocyte sedimentation rate or other inflammatory markers, lung function/chest X-ray and renal function prior to initiation of therapy.

These disorders can have an insidious onset and patients should be regularly and carefully monitored while taking bromocriptine for manifestations of progressive fibrotic disorders.

bromocriptine should be withdrawn if fibrotic or serosal inflammatory changes are diagnosed or suspected.

Impulse Control Disorders

Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including APO-BROMOCRIPTINE. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

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.

Patients with impaired renal function

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

4.5. Interactions with other medicines and other forms of 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, methyldopa, pimozide, oestrogens and TRF, may reduce the efficacy of bromocriptine.

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.

4.6. Fertility, pregnancy and lactation

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.

Lactation

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

4.7. Effects on ability to drive and use machines

APO-BROMOCRIPTINE likely to produce minor or moderate adverse effects on the ability to drive or use 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.

Patients being treated with bromocriptine and presenting with somnolence and/or sudden sleep episodes must be advised not to drive or engage in activities where impaired alertness may put themselves or others at risk of serious injury or death until such recurrent episodes and somnolence have resolved.

4.8. Undesirable effects

The occurrence of side-effects can be minimised by gradual introduction of the dose or a dose reduction followed by a more gradual titration. If necessary, initial nausea and/or vomiting may be reduced by taking bromocriptine during a meal and by the intake of a peripheral dopamine antagonist, such as domperidone, for a few days, at least one hour prior to the administration of bromocriptine.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) including isolated reports.

Nervous System Disorders
Common: Headache, drowsiness
Uncommon: Dizziness, dyskinesia
Rare: Somnolence, paresthesia
Very Rare: Excess daytime somnolence and sudden sleep onset

Psychiatric Disorders
Uncommon: Confusion, psychomotor agitation, hallucinations
Rare: Psychotic disorders, insomnia

Gastrointestinal Disorders
Common: Nausea, constipation
Uncommon: Vomiting, dry mouth
Rare: Diarrhoea, abdominal pain, retroperitoneal fibrosis, gastrointestinal ulcer, gastrointestinal haemorrhage

Vascular Disorders
Uncommon: Hypotension including orthostatic hypotension (which may in very rare instances lead to collapse)
Very Rare: Reversible pallor of fingers and toes induced by cold (especially in patients who have a history of Raynaud's phenomenon)

Cardiac Disorders
Rare: Tachycardia, bradycardia, arrhthymia
Very rare: Cardiac valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion).

Respiratory, thoracic and mediastinal disorders
Common: Nasal congestion
Rare: Pleural effusion, pleural and pulmonary fibrosis, pleuritis, dyspneoa

Musculoskeletal and connective tissue disorders
Uncommon: Leg cramps

Skin and subcutaneous tissue disorders
Uncommon: Allergic skin reactions, hair loss

General disorders and administration site conditions
Uncommon: Fatigue
Rare: Peripheral oedema
Very Rarely: A syndrome resembling Neuroleptic Malignant Syndrome has been reported on withdrawal of BROMOCRIPTINE.

Eye Disorders
Rare: Visual disturbances, vision blurred

Ear and Labyrinth Disorders
Rare: Tinnitus

Post-partum women
In extremely rare cases (in postpartum women treated with bromocriptine for the prevention of lactation) serious adverse events including hypertension, myocardial infarction, convulsion, stroke or mental disorders have been reported, although the causal relationship is uncertain. In some patients the occurrence of convulsion or stroke was preceded by severe headache and/or transient visual disturbances.

Impulse control disorders
Pathological gambling, increased libido, hyper sexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including APO-BROMOCRIPTINE (See SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9. Overdose

Overdosage 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Gynecologicals – Prolactine inhibitors

ATC code: not yet assigned

Mechanism of 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 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.

5.2 Pharmacokinetic properties

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.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

APO-BROMOCRIPTINE tablets contain the following excipients:

- Lactose monohydrate
- Microcrystalline cellulose
- Croscarmellose sodium
- Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Bottles of 30 – 24M from date of manufacture
Bottles of 100 – 36M from date of manufacture

6.4 Special precautions for storage

Store at or below 25°C. Protect from heat, light and moisture.
Keep container tightly closed.

6.5 Nature and contents of container

APO-BROMOCRIPTINE 2.5mg tablets is available as:
Bottles (plastic Amber HDPE bottle with blue) of 30 or 100 tablets.

Not all pack types or pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Apotex NZ Ltd
32 Hillside Road
Glenfield
Private Bag 102-995
North Shore Mail Centre
Auckland
Telephone: (09) 444 2073
Fax: (09) 444 2951

9 DATE OF FIRST APPROVAL

03 March 1999

10 DATE OF REVISION OF THE TEXT

30 November 2016

Summary Table of Changes

Section changed	Summary of new information
Whole data sheet	Reformatted as per Medsafe new guideline for data sheet.
2	Added & moved information to align with new data sheet format
3	Change in tablet engraving due to market harmonization
4.1	Title updated as per new data sheet format
4.2	Title updated as per new data sheet format Additional title added and statement added to provide all required information in new data sheet format
4.3	Additional statement added to provide all information required in new data sheet format
4.4	Title updated as per new data sheet format
4.5	Title updated as per new data sheet format
4.6	Title updated as per new data sheet format
4.7	Title updated as per new data sheet format Added information to align with new data sheet format
4.8	Title updated as per new data sheet format Additional information based on new data sheet format.
4.9	Title updated as per new data sheet format Additional information based on new data sheet format.
5	Added information to align with new data sheet format

6	Title updated as per new data sheet format New section added to comply with new data sheet format
6.1	Title updated as per new data sheet format formatting changes to align with new data sheet format
6.3	Title updated as per new data sheet format
6.5	Title updated as per new data sheet format Added container material information as required by new data sheet format Added statement about marketed packs to align with required information in new data sheet format
6.6	New section and information required in new data sheet format
8	Title updated as per new data sheet format
9	New section and information required in new data sheet format
10	Title updated to Date of Revision of the text to align with new data sheet format Date of amendments to data sheet
Summary Table of Changes	New Section and information in new data sheet format.