AA PHARMA BROMOCRIPTINE
Bromocriptine Mesylate Tablets USP
AA Pharma Inc
Prolactin Inhibitor
Growth Hormone Suppressant in Acromegaly
Adjunctive Medication in Parkinson's Disease
Date of Revision: 16 August 2021

ACTIONS AND CLINICAL PHARMACOLOGY:

AA PHARMA BROMOCRIPTINE (bromocriptine mesylate) is a dopaminomimetic ergot derivative with D_2 type domain receptor agonist activity, and has also D_1 dopamine receptor antagonist properties. The dopaminomimetic activity of bromocriptine in the striatum is considered responsible for the clinical benefits seen in selected patients with Parkinson's Disease, when low doses of the drug are gradually added to levodopa therapy in patients on long-term treatment who develop late side effects of levodopa or no longer respond to the medication.

Excessive dopaminomimetic drive may, however, provoke psychotic and other adverse reactions. It inhibits the release and synthesis of prolactin y acting directly on the prolactin secreting cells of the anterior pituitary.

In patients with acromegaly, apart from lowering prolactin and elevated levels of growth hormone, bromocriptine has a beneficial effect on clinical symptoms and on glucose tolerance.

In man, bromocriptine is rapidly absorbed after oral administration with an absorption half-life of approximately 0.3 hours. The amount absorbed is about 65-95% of the oral dose. About 7% of the dose reaches the systemic circulation unchanged, due to a high hepatic extraction rate and first pass metabolism. The plasma protein binding amounts to 96%. Bromocriptine is extensively metabolized by the liver. Only traces of the unchanged compound are found in urine, together with 2 major metabolites. Unchanged drug represents about 10-15% of peak levels of radioactivity in plasma measured after a single dose of labelled drug. The active parent drug and the metabolites are primarily excreted via the liver, with only 6% being eliminated via the kidney. In plasma, the elimination half-life was between 2 to 8 hours for the parent drug and 50 to 70 hours for the metabolite after single oral doses.

The extreme variability in GI tract absorption and the extensive and individually variable first-pass metabolism are responsible for the broad variability in plasma concentrations of bromocriptine and, in part, for the variability in dose response.

A comparative bioavailability study was performed using normal healthy volunteers. The rate and extent of absorption after a single 7.5mg dose of AA PHARMA BROMOCRIPTINE 2.5 mg tablets and PARLODEL 2.5mg tablets was measured and compared. The results are summarized as follows:

	AA PHARMA BROMOCRIPTINE	Parlodel	Precentage of Parlodel
AUC_T*(ng hr/mL)	5.66 (16)	5.46 (23)	+3.7
AUC_1*(ng hr/mL)	7.00 (15)	6.72 (22)	+4.2
C_{max}*(ng/mL)	0.99 (14)	0.99 (16)	0.0
T_{max}**(hr)	1.18 (0.33)	1.18 (0.35)	0.0
$T_{½}$**(hr)	6.09 (1.00)	5.95 (1.44)	+2.4

*Geometric means (CV) **Arithmetic means (SD)

INDICATIONS:

Galactorrhea with or with amenorrhea due to hyperprolactinemia.

Prolactin-dependent menstrual disorders and infertility: e.g. secondary amenorrhea, ovulatory insufficiency and short luteal phase.

Prolactin-secretin adenomas: as a treatment for inoperable macroadenomas or prior to surgery in order to facilitate removal, and as an alternative to surgery in patients with microadenomas.

Prolactin-dependent male hypogonadism.

Acromegaly: the first line-treatment of this condition is by surgery or radiotherapy. AA PHARMA BROMOCRIPTINE (bromocriptine mesylate) may be a useful adjunct to such treatment and can be used as monotherapy in special cases.

Parkinson's Disease: AA PHARMA BROMOCRIPTINE has been found to be clinically useful as an adjunct to levodopa (usually with a decarboxylate inhibitor) in the symptomatic management of selected patients with Parkinson's Disease who experience prominent dyskinesia or wearing off reactions on long-term levodopa therapy.

Patients on long-term treatment who are beginning to deteriorate on levodopa therapy may be controlled by reducing the dose of levodopa and adjusting the frequency and schedule of drug administration. Patients maintained on optimal dosages of levodopa who still experience prominent dyskinesia and/or end-of-dose failure may benefit from the concomitant use of bromocriptine, by decreasing the occurrence and/or severity of these manifestations. Since rapid escalation of bromocriptine doses causes severe adverse reactions, it is usually recommended to combine a slow increase of bromocriptine, with a concomitant, gradual and limited reduction of levodopa dosage. Continued efficacy of bromocriptine for more than two years has not been established and there is some evidence that its efficacy tends to wane. Evidence available indicates that there is no consistent benefit from bromocriptine in patients who have not responded previously to levodopa, and studies have shown significantly more adverse reactions in bromocriptine treated patients than in patients treated with levodopa. AA PHARMA BROMOCRIPTINE is not recommended in the treatment of newly diagnosed patients or as the sole medication in Parkinson's Disease.

CONTRA-INDICATIONS: Uncontrolled hypertension of pregnancy, toxemia of pregnancy, sensitivity to ergot alkaloids. For procedure during pregnancy see "Use in Pregnancy" under PRECAUTIONS.

WARNINGS: In women with non-puerperal galactorrhea, reduction of prolactin levels may lead to resumption of normal menses. Following discontinuation of medication, galactorrhea returns in some patients and leads to suspicions of pituitary adenomas, a complete investigation at specialized units to identify these patients is advisable. Treatment with specialized units to identify these patients is advisable. Treatment with AA PHARMA BROMOCRIPTINE (bromocriptine mesylate) may effectively lower prolactin levels in patients with pituitary tumors but does not obviate the necessity for radiotherapy or surgical intervention where appropriate.

Long-term treatment (6-36 months) with bromocriptine 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 in which bromocriptine treatment was terminated, the changes slowly reverted towards normal.

To date, there have been seven (7) reported cases of retroperitoneal fibrosis occurring in parkinsonian patients on long-term treatment (15 months-10 years) with bromocriptine at daily

doses higher than 30mg. to recognize retroperitoneal fibrosis at an early, reversible stage it is recommended to look for its manifestations (e.g. back pain, oedema of the lower limbs, impaired kidney function) in this category of patients. AA PHARMA BROMOCRIPTINE medication should be withdrawn immediately if fibrotic changes in the retroperitoneum are diagnosed or suspected.

Bromocriptine is known to cause hypotension in some patients and rarely may cause hypertension in selected patients.

While hypotension during the start of therapy with bromocriptine occurs in some patients, 50 cases of hypertension have been reported, sometimes at the initiation of therapy, but often developing in the second week of therapy. Seizures have been reported in 38 cases (including 4 cases of status epilepticus), both with and without the prior development of hypertension. Fifteen cases of stroke during bromocriptine therapy have been reported. Many of these patients experiencing seizures and/or strokes reported developing a constant and often progressively severe headache hours to days prior to the acute event. Some cases of strokes and seizures during therapy with bromocriptine were also preceded by visual disturbances (blurred vision, and transient cortical blindness) Four cases of acute myocardial infarction have been reported. The relationship of these adverse reactions to bromocriptine administration is not certain. The use of AA PHARMA BROMOCRIPTINE (bromocriptine mesylate) is not recommended for patients with uncontrolled hypertension or toxemia of pregnancy.

Although there is no conclusive evidence which demonstrates the interaction between bromocriptine and other ergot alkaloids, the concomitant use of these medications is not recommended. Particular attention should be paid to patients who have recently received other drugs that can alter the blood pressure.

Periodic monitoring of the blood pressure particularly during the first few days of therapy is advisable. If severe progressive or unremitting headache, other signs of CNS toxicity, or hypertension develop, AA PHARMA BROMOCRIPTINE therapy should be discontinued immediately and the patient should be evaluated promptly.

DOSAGE AND DIRECTIONS FOR USE:

AA PHARMA BROMOCRIPTINE (bromocriptine mesylate) should always be taken with food. In order to establish tolerance, the first dose of 1.25-2.5mg (½ - 1 tablet), depending on the indication should be given at bedtime with food. Please consult the detailed dosage recommendations for each indication.

Galactorrhea with or without amenorrhea due to hyperprolactinemia: 1.25-2.5mg (½ - 1 tablet) at bedtime to establish tolerance; gradually increase after 2-3 days to 2.5mg (1 tablet) twice daily with meals. If required the dose may be increased to 2.5mg (1 tablet) t.i.d. Continue treatment until milk secretion has ceased completely or, in the case of menstrual dysfunction, until the menstrual cycle has returned to normal.

Prolactin-dependent menstrual disorders and infertility: 1.25-2.5mg (½ - 1 tablet) at bedtime to establish tolerance. Gradually increase after 2-3 days to one tablet twice daily with meals. If required the dose may be increased to 2.5mg (1 tablet) t.i.d.

Prolactin secreting adenomas: 1.25mg (½ a tablet) 2 or 3 times daily, increasing gradually (average maintenance dose: 5-7.5 mg (2 to 3 tablets) daily). If necessary to jeep plasma protein adequately suppressed, dosage may be increased gradually over a period of several weeks to 10-20mg (4 to 8 tablets daily with meals.

Prolactin dependent male hypogonadism: 1.25-2.5mg (½ - 1 tablet) at bedtime to establish tolerance. Gradually increase after 2-3 days to one tablet twice daily with meals or more, as required to 2.5mg (1 tablet) three times per day with meals.

Acromegaly: A starting dose of 1.25-2.5mg (½ - 1 tablet) at bedtime to establish tolerance is recommended, increasing gradually over a period of 2 to 4 weeks to 10-20mg (4 to 8 tablets) daily with meals, depending on clinical response. Daily requirements of 20mg should be taken in four equally divided doses.

The maximum recommended daily dose is 20mg (eight 2.5mg tablets).

In the event of serious or persistent adverse effects, the dosage should be reduced to 1.25mg (½ tablet) and increased again gradually to the recommended dose. If reactions such as nausea, vomiting, vertigo or headaches continue to be severe, AA PHARMA BROMOCRIPTINE should be discontinued.

Parkinson's Disease: Although bromocriptine has been clinically useful in decreasing the severity and frequency of "on-off" fluctuations of late levodopa therapy, the decision to use bromocriptine as adjunctive treatment and the selection of dosage must be individualized in each case. A low dose is recommended. The initial dose of AA PHARMA BROMOCRIPTINE is one half of a 2.5mg tablet (1.25mg) at bedtime, with food, to establish tolerance. Thereafter, the recommended dosage is 2.5mg daily in two divided doses, with meals, (half a 2.5mg tablet twice daily).

The dosage may be increased very gradually, if necessary, by adding an additional 2.5mg per day, once every 2 to 4 weeks, to be taken always in divided doses with meals. Increments should usually never exceed 2.5mg. Clinical assessments are recommended at two week intervals or less during titration, to ensure that the lowest effective dosage is not exceeded. The usual dosage range is from a few milligrams to 40mg daily in two or three divided doses with meals. The median dose varies with the experience of individual investigators, but can be around 10mg daily or higher. During initial titration, it is recommended that the dosage of levodopa should be maintained, if possible. Subsequently, it might be desirable to combine a slow increase of bromocriptine with a concomitant, limited and gradual reduction of levodopa.

PRECAUTIONS: AA PHARMA BROMOCRIPTINE (bromocriptine mesylate) may cause hypotension, primarily postural; periodic monitoring of the blood pressure, particularly during the first days of therapy, is advisable. In some patients, dizziness (vertigo) may occur with bromocriptine; patients should therefore be cautioned against activities requiring rapid and precise responses such as driving an automobile or operating dangerous machinery until their response has been determined.

Care should be exercised when administering AA PHARMA BROMOCRIPTINE concomitantly with phenothiazines or with other medications known to lower blood pressure. Dosage should be adjusted accordingly.

Alcohol should be avoided during treatment with bromocriptine. In some patients the concomitant use of bromocriptine and alcohol has given rise to alcohol intolerance and an increase in the severity and incidence of bromocriptine's possible adverse reactions.

Although there is no conclusive evidence demonstrating interactions between bromocriptine and other ergot derivatives, it is not recommended to administer AA PHARMA BROMOCRIPTINE and any drug with potentially vasoconstrictor activity concomitantly.

In patients being treated with AA PHARMA BROMOCRIPTINE for galactorrhea, prolactin induced amenorrhea, menstrual disorders or acromegaly, infertility might be reversed by restoration of normal menses and ovulation. Women who do not wish to conceive should, therefore, use a reliable method of contraception. Since pregnancy may occur prior to initiation of menses it is recommended that a pregnancy test be conducted at least every four weeks during the amenorrheic period, and, once menses are reinitiated, every time a patient misses a menstrual period.

There have been occasional reports of gastrointestinal bleeding in acromegalic patients, both in those treated with bromocriptine and those given a different or no medication. Until further data are available, therefore, acromegalic patients with a history or evidence of peptic ulceration should preferably be given alternative treatment. If bromocriptine must be used in such patients they should be instructed to report promptly any gastrointestinal reactions.

Safety and efficacy of bromocriptine has not been established in patients with severe renal or hepatic disease.

Bromocriptine therapy has been demonstrated to be effective in the short-term management of amenorrhea/galactorrhea. Data are not available on the safety or effectiveness of its use in long-term continuous dosage in this indication or in patients given repeated courses of treatment following recurrence of amenorrhea/galactorrhea after initial treatment. Recurrence rates are reportedly very high, ranging from 70% to 80%.

Bromocriptine should always be taken with food. In cases where adverse effects, such as nausea, vomiting and vertigo are severe or persisting, the therapeutic dosage of AA PHARMA BROMOCRIPTINE should be reduced to half of one tablet daily (1.25mg) and increased gradually to the recommended dose. The dopamine antagonist domperidone may be useful in the control of severe gastrointestinal side effects in Parkinsonian patients receiving bromocriptine (see Drug Interactions).

Use in Pregnancy: In patients receiving AA PHARMA BROMOCRIPTINE, immunological confirmation of suspected conception should be performed as soon as possible and treatment stopped unless, in the opinion of the treating physician, the possible benefit to the patient outweighs the potential risk to the fetus. In any event, the patient must be monitored closely throughout pregnancy for signs and symptoms which may develop if a previously undetected prolactin-secreting tumour enlarges.

In human studies with bromocriptine, there were 1410 reported pregnancies, which yielded 1236 live and 5 stillborn infants from women who took bromocriptine during early pregnancy. Among the 1241 infants, 43 cases (31 minor and 12 major) of congenital anomalies were reported. The incidence (3.46%) and type of congenital malformations and the incidence of spontaneous abortions (11.13%) in this group of pregnancies does not exceed that generally reported for such occurrences in the population at large.

Patients with pronounced enlargement of the sella turcica or a visual defect should, in the first instance, be treated by surgery and/or radiotherapy. If pregnancy occurs in the presence of a pituitary microadenoma, close supervision throughout pregnancy is essential. This includes regular checking of the visual fields.

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.

Use in Parkinson's Disease: Use of AA PHARMA BROMOCRIPTINE, particularly in high doses, may be associated with mental confusion and mental disturbances. Since patients with Parkinson's Disease may manifest varying degrees of dementia, caution should be exercised when treating such patients with bromocriptine.

AA PHARMA BROMOCRIPTINE administered alone or concomitantly with levodopa may cause visual or auditory hallucinations. These usually resolve with dosage reduction, but discontinuation of bromocriptine may be required in some cases. Rarely, after high doses, hallucinations have persisted for several weeks following discontinuation of bromocriptine. Caution should be exercised when administering AA PHARMA BROMOCRIPTINE to patients with a history of myocardial infarction, particularly if they have a residual, atrial, nodal or ventricular arrhythmia.

Symptomatic hypotension can occur and, therefore, caution should be exercised when administering AA PHARMA BROMOCRIPTINE, particularly in patients receiving antihypertensive medication. Periodic evaluation of hepatic, hematopoietic, cardiovascular and renal function is recommended.

Drug Interactions: The concomitant use of erythromycin may increase bromocriptine plasma levels.

Domperidone, a dopamine antagonist, may cause increases in serum prolactin. In so doing, domperidone may antagonize the therapeutically-relevant prolactin lowering effect of bromocriptine. It is possible that the anti-tumourigenic effect of bromocriptine in patients with prolactinomas may be partially blocked by domperidone administration.

ADVERSE REACTIONS:

The most frequently observed adverse reactions are nausea, vomiting, headache and gastrointestinal side effects such as abdominal pain, diarrhea and constipation. All these effects may be minimized or even prevented by giving small initial doses of bromocriptine and by taking it with food.

Postural hypotension can, on rare occasions, lead to fainting, and shock-like syndromes have been reported in sensitive patients. This is most likely to occur during the first few days of AA PHARMA BROMOCRIPTINE (bromocriptine mesylate) treatment.

In clinical studies to date, the incidences of adverse reactions were noted for the following indications:

Amenorrhea/Galactorrhea/Female Infertility/Acromegaly: The incidence of side effects in these indications is higher (68%), reflecting the larger doses required, but they are generally mild to moderate in degree. Therapy was discontinued in approximately 6% of patients because of adverse effects. In decreasing order of frequency these are: nausea 49%, headache 19%, dizziness 17%, fatigue 7%, abdominal cramps 4%, lightheadedness 5%, vomiting 5%, nasal congestion 3%, constipation 3%, diarrhea 3% and drowsiness 3%.

Parkinson's Disease: When bromocriptine is added to levodopa therapy, the incidence of adverse reactions may increase. The most common newly appearing adverse reactions in combination therapy 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.

General: Less common adverse reactions include: anorexia, anxiety, blepharospasm, epileptiform seizures, fatigue, headache, lethargia, 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.

Abnormalities in laboratory tests may include elevation of blood urea nitrogen, SGOT, SGPT, GGPT, CPK, alkaline phosphatase and uric acid, which are usually transient and not of clinical significance.

The occurrence of adverse reactions may be lessened by temporarily reducing the dosage to one half-tablet two or three times daily.

SYMPTOMS AND TREATMENT OF OVERDOSAGE:

There have been several reports of acute overdosage with bromocriptine in children and adults. No life threatening reactions have occurred. Symptoms reported have resulted from over-stimulation of dopaminergic receptors: they included nausea, vomiting, dizziness, drowsiness, hypotension, sweating and hallucinations. The management of acute intoxication is largely symptomatic. The cardiovascular system should be monitored. Metoclopramide can be used to antagonize the emesis and hallucinations in patients who have taken high doses.

STORAGE:

Store in a cool, dry place. Protect from light.

HOW SUPPLIED:

Each tablet contains Bromocriptine Mesylate 2.5mg. In bottles of 100's.

Date of last revision: 3 December 2021

Product Licence Holder: Pharmaforte Singapore Pte. Ltd., 6 Tagore Drive, #03-11 Tagore Building, Singapore 787623