1. Name of the medicinal product

Bromocriptine Tablet

2. Qualitative and Quantitative

S/N	Ingredients	Qty/tablet	Function
1	Bromocriptine	2.5mg	Active
2	Lactose monohydrate 200 Mesh	41mg	Diluent
3	Microcrystalline Cellulose (Avicel pH 102)	40mg	Diluent & Disintegrant
4	Maize Starch	35.08mg	Diluent & Disintegrant
5	Povidone K 30	5.20mg	Binder
6	Purified talc	3.90mg	Lubricant
7	Magnesium Stearate	1.3mg	Lubricant
8	Colloidal Anhydrous Silica (Aerosil 200)	0.65mg	Glidant

3. Pharmaceutical Form

White, round flat tablets plain from both sides.

4. CLINICAL PARTICULAS

4.1 Therapeutical Indications

Inhibition of lactation for medical reasons

The inhibition or suppression of puerperal lactation where medically indicated such as after intrapartum loss or neonatal death. **Bromocriptine** is not recommended for the routine suppression of lactation or for the relief of symptoms of post-partum pain and engorgement which can be adequately treated with simple analgesics and breast support.

Hyperprolactinaemia

The treatment of hyperprolactinaemia in men and women with hypogonadism and/or galactorrhoea.Amenorrhoea and oligomenorrhoea, with or without galactorrhoea. Drug-induced hyperprolactinaemic disorders. Polycystic ovary syndrome. Some infertile women with oligomenorrhoea or amenorrhoea and galactorrhoea may be unduly sensitive to prolactin.
Bromocriptine has been used successfully in the treatment of a number of infertile women with galactorrhoea who do not have demonstrable hyperprolactinaemia. To reduce tumour size, particularly in those at risk of optic nerve compression. **Bromocriptine** has been used in a number of specialised units, as an adjunct to surgery and/or radiotherapy to reduce circulating growth hormone in the management of acromegalic patients. In the treatment of idiopathic Parkinson's Disease, **Bromocriptine** has been used both alone and in combination with Levodopa in the management of previously untreated patients and those disabled by 'on-off' phenomena. **Bromocriptine** has been used with occasional benefit in patients who do not respond to or are unable to tolerate Levodopa and those whose response to Levodopa is declining.
Premenstrual symptoms and benign breast disease drug.

4.2 **Posology and method of administration**

Generally, the dose of Bromocriptine should be limited to 30 mg a day. Bromocriptine should always be taken with food.
A number of disparate conditions are amenable to treatment with Bromocriptine and for this reason,the recommended dosage regimens are variabl In most indications, irrespective of the final dose, the optimum response with the minimum of side effects is best achieved by gradual introduction of Bromocriptine. The following scheme is suggested: Initially,1 mg to 1.25 mg at bed time, increasing after 2 to 3 days to 2 mg to 2.5 mg at bed time. Dosage may then be increased by 1 mg at 2 to 3 day intervals, until a dosage of 2.5 mg twice daily is achieved. Further dosage increments, if necessary, should be added in a similar manner.

Prevention of Lactation

2.5 mg on the day of delivery, followed by 2.5 mg twice daily for 14 days. Treatment should be instituted within a few hours of parturition once vital signs have been stabilised. Gradual introduction of Bromocriptine is not necessary in this indication.

Suppression of Lactation for Medical Reasons

2.5 mg on first day, increasing after 2 to 3 days to 2.5 mg twice daily for 14 days. Gradual introduction of Bromocriptine is not necessary in this indication.

Hypogonadism/Galactorrhea syndromes/Infertility

Introduce Bromocriptine gradually according to the suggested scheme. Most patients with hyperprolactinaemia have responded 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 dose is 2.5 mg twice daily.

Prolactinomas

Introduce Bromocriptine gradually according to the suggested scheme. Dosage may then be increased by 2.5 mg daily at 2 to 3 day intervals,as follows:- 2.5 mg eight hourly, 2.5 mg six hourly, 5 mg six hourly. Daily doses should not exceed 30mg.

Acromegaly

Introduce Bromocriptine gradually, according to the suggested scheme. Dosage may then be increased by 2.5 mg at 2 to 3 day intervals as follows:-

2.5 mg eight-hourly, 2.5 mg six-hourly, 5 mg six-hourly. Parkinson's Disease

Introduce Bromocriptine gradually, as follows: Week 1: 1 mg to 1.25 mg at bed time. Week 2: 2 mg to 2.5 mg at bed time. Week 3: 2.5 mg twice daily. Week 4: 2.5 mg three times daily. Thereafter take three times a day increasing by 2.5 mg every 3 to 14 days, depending on the patient's response. Continue until the optimum dose is reached. This will usually be between 10 mg and 30 mg daily. Daily doses should not exceed 30 mg. In patients already receiving Levodopa the dosage of this drug may gradually be decreased, while the dosage of **Bromocriptine** is increased until the optimum balance is determined. **Use in Children:** Administration of **Bromocriptine** is not appropriate for children less than 15 years old.

Use in Elderly

There is no clinical evidence that **Bromocriptine** poses a special risk to the elderly.

Use in Patients with Hepatic Impairment

In patients with impaired hepatic function, the speed of elimination may be retarded and plasma levels may increase, requiring dose adjustment.

4.2 Contraindications

Hypersensitive to **Bromocriptine** or to any of the excipients of **Bromocriptine**

(see Section 2 Qualitative and Quantitative composition and 6.1 List of excipients) or other ergot alkaloids. Uncontrolled hypertension, hypertensive disorders of pregnancy (including eclampsia, pre eclampsia or pregnancy-induced hypertension), hypertension post partum and in the puerperium.

Bromocriptine is contraindicated for patients with pre-existing valve problems & for use in the suppression of lactation or other non-life threatening indications in patients with a history of coronary artery disease, or other severe cardiovascular conditions, or symptoms / history of severe psychiatric disorders. Patients with these underlying conditions taking **Bromocriptine** for the indication of macro-adenomas should only take it if the perceived benefits outweigh the potential risks (see Section 4.4 Special Warnings and Precautions). For long-term treatment: Evidence of cardiac valvulopathy as determined by pre-treatment echocardiography.

4,4 Special warnings and precautions for use

Bromocriptine is contraindicated for use in the suppression of lactation or other non-life threatening indications in patients with severe coronary artery disease, or symptoms and/or a history of serious mental disorders (see Section 4.3 Contraindications).

Other

There is insufficient evidence of efficacy of **Bromocriptine** in the treatment of premenstrual symptoms and benign breast disease. The use of **Bromocriptine** in patients with these conditions is therefore not recommended. In rare cases, serious adverse events, including hypertension, myocardial infarction, seizures, stroke or psychiatric disorders have been reported in postpartum women treated with **Bromocriptine** for inhibition of lactation. In some patients the development of seizures or stroke was preceded by severe headache and/or transient visual disturbances (see Section 4.8, Undesirable Effects). Patients with severe cardiovascular disorders or psychiatric disorders taking **Bromocriptine** for the indication of macro-adenomas should only take it if the perceived benefits outweigh the potential risks (see Section 4.3 Contraindications). Blood pressure should be carefully monitored, especially during the first days of therapy. Particular caution is required in patients who are on concomitant therapy with, or have recently been treated with drugs that can alter blood pressure. Concomitant use of **Bromocriptine** with vasoconstrictors such as sympathomimetics or ergot alkaloids including ergometrine or methylergometrine during the puerperium is not recommended. If hypertension, unremitting headache, or any signs of CNS toxicity develop, treatment should be discontinued immediately. Hyperprolactinaemia may be idiopathic, drug-induced, or due to hypothalamic or pituitary disease. The possibility that hyperprolactinaemic patients may have a pituitary tumour should be recognised and complete investigation at specialised units to identify such patients is advisable.

Bromocriptine will effectively lower prolactin levels in patients with pituitary tumours but does not obviate the necessity for radiotherapy or surgical intervention where appropriate in acromegaly. Since patients with macro-adenomas of the pituitary might have accompanying hypopituitarism due to compression or destruction of pituitary tissue, one should make a complete evaluation of pituitary functions and institute appropriate substitution therapy prior to administration of **Bromocriptine**. In patients with secondary adrenal insufficiency, substitution with corticosteroids is essential.

The evolution of tumour size in patients with pituitary macro-adenomas should be carefully monitored and if evidence of tumour expansion develops, surgical procedures must be considered. If in adenoma patients,pregnancy occurs after the administration of **Bromocriptine**, careful observation is mandatory. Prolactin-secreting adenomas may expand during pregnancy. In these patients, treatment with **Bromocriptine** often results in tumour shrinkage and rapid improvement of the visual fields defects. In severe cases, compression of the optic or other cranial nerves may necessitate emergency pituitary surgery. Visual field impairment is a known complication of macroprolactinoma. Effective treatment with **Bromocriptine** leads to a reduction in hyperprolactinaemia and often to resolution of the visual impairment. In some patients, however, a secondary deterioration of visual fields may subsequently develop despite normalised prolactin levels and tumour shrinkage, which may result from traction on the optic chiasm which is pulled down into the now partially empty sella. In these cases the visual field defect may improve on reduction of **Bromocriptine** re-expansion. Monitoring of visual fields in patients with macroprolactinoma is therefore recommended for an early recognition of secondary field loss due to chiasmal herniation and adaptation of drug dosage. In some patients with prolactin-secreting adenomas treated with **Bromocriptine**, cerebrospinal fluid rhinorrhea has been observed. The data available suggest that this may result from shrinkage of invasive tumours. **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 (see Section 4.7 Effects on ability to drive and use machines). Furthermore, a reduction of dosage or termination of therapy may be considered. When women of child-bearing age are treated with **Bromocriptine** for conditions not as ociated 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. Gynaecological assessment, preferably including cervical and endometrial cytology, is recommended for women receiving **Bromocriptine** for extensive periods. Six monthly assessment is suggested for post-menopausal women and annual assessment for women with regular menstruation. A few cases of gastrointestinal bleeding and gastric ulcer have been reported. If this occurs, **Bromocriptine** should be withdrawn. Patients with a history of evidence of peptic ulceration should be closely monitored when receiving the treatment. Since, especially during the first few days of treatment, hypotensive reactions may occasionally occur and result in reduced alertness, particular care should be exercised when driving a vehicle or operating machinery. 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 manifestations (e.g. back pain, oedema of the lower limbs, impaired kidney function) should be watched in this category of patients. Possible risk of fibrosis in patients taking **Bromocriptine** st high doses forlong period, 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. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including **Bromocriptine**.

Elderly

Clinical studies for **Bromocriptine** did not include sufficient numbers of subjects ages 65 and above to determine whether the elderly respond differently from younger subjects. However, other reported clinical experiences, including post-marketing reporting of adverse events have identified no differenced in response or tolerability between elderly and younger patients. Even though no variation in efficacy or adverse reaction profile in elderly patients taking **Bromocriptine** has been observed, greater sensitivity in some elderly individuals cannot be categorically ruled out. In general, dose selection for an elderly patient should be cautious, starting at the lower end of the dose range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy in this population.

Effect on ability to drive and use machines

Hypotensive reactions may be disturbing in some patients during the first few days of treatment and particular care should be exercised when driving vehicles or operating 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 (eg. Operating machines) until such recurrent episodes and somnolence have resolved.

4.5 Interactions with other medicines and other forms of interactions

Tolerance to **Bromocriptine** may be reduced by alcohol. Caution is required in patients who are on concomitant therapy with, or have recently been treated with drugs that can alter blood pressure. Although there is no conclusive evidence of an interaction between **Bromocriptine** and other ergot alkaloids concomitant use of **Bromocriptine** with these medications during the puerperium is not recommended (see also Section 4.4, Special Warnings and Precautions). The concomitant use of erythromycin and other macrolide antibiotics may increase **Bromocriptine** plasma levels. **Bromocriptine** is both a substrate and an inhibitor of CYP3A4 (see Section 5.2 Pharmacokinetic properties). Caution should therefore be used when co-administering drugs which are strong inhibitors and/or substrates of this enzyme (azole antimycotics, HIV protease inhibitors). The concomitant treatment of acromegalic patients with **Bromocriptine** and octreotide led to increased plasma levels of **Bromocriptine**. Dopamine antagonists such as antipsychotics (phenothiazines, butyrophenones and thioxanthenes) may reduce the prolactin-lowering and antiparkinsonian effects of **Bromocriptine**. Metoclopramide and domperidone may reduce the prolactin-lowering effect.

4.6 Pregnancy and Lactation

If pregnancy occurs it is generally advisable to withdraw **Bromocriptine** after the first missed menstrual period. Rapid expansion of pituitary tumours sometimes occurs during pregnancy and this may also occur in patients who have been able to conceive as a result of **Bromocriptine** therapy. As a precautionary measure, patients should be monitored to detect signs of pituitary enlargement so that **Bromocriptine** may be reintroduced if necessary. Based on the outcome of more than 2,000 pregnancies, the use of **Bromocriptine** to restore fertility has not been associated with an increased risk of abortion, premature delivery, multiple pregnancy or malformation in infants. Because this accumulated evidencesuggests

a lack of teratogenic or embryopathic effects in humans, maintenance of **Bromocriptine** treatment during pregnancy may be considered where there is a large tumour or evidence of expansion.

Lactation

Since **Bromocriptine** inhibits lactation, it should not be administered to mothers who elect to breast-feed.

Women of child-bearing potential

Fertility may be restored by treatment with **Bromocriptine**. Women of child bearing age who do not wish to conceive should therefore be advised to practice a reliable method of contraception.

4.7 Effects on ability to drive and use machine.

Hypotensive reactions may be disturbing in some patients during the first few days of treatment and particular care should be exercised when driving vehicles or operating 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 (eg. Operating machines) 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 (1/10,000to <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, seizures, stroke or mental disorders have been reported, although the causal relationship is uncertain. In some patients the occurrence of seizures or stroke was preceded by severe headache and/or transient visual disturbances (see Section 4.4 Special warnings and precautions for use). **Class effects**
Patients treated with dopamine agonists for treatment with Parkinson's disease, including **Bromocriptine**, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

4.9 Overdose

Signs and Symptoms

Overdosage with **Bromocriptine** is likely to result in vomiting and other symptoms which could be due to over stimulation of dopaminergic receptors and might include nausea, dizziness, hypotension, postural hypotension, tachycardia, drowsiness, somnolence, lethargy, confusion and hallucinations. General supportive measures should be undertaken to remove any unabsorbed material and maintain blood pressure if necessary.

Overdose management

In the case of overdose, administration of activated charcoal is recommended and in the case of very recent oral intake, gastric lavage may be considered.

5 PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopamine agonist (ATC code N04B C01), prolactin inhibitor (ATC code G02C B01)
Bromocriptine

active ingredient **Bromocriptine**, is an inhibitor of prolactin secretion and a stimulator of dopamine receptors. The areas of application of **Bromocriptine** are divided into endocrinological and neurological indications. The pharmacological particulars will be discussed under each indication.

Endocrinological indications

Bromocriptine inhibits the secretion of the anterior pituitary hormone prolactin without affecting normal levels of other pituitary hormones. However, **Bromocriptine** is capable of reducing elevated levels of growth hormone (GH) in patients with acromegaly. These effects are due to stimulation of dopamine receptors. In the puerperium prolactin is necessary for the initiation and maintenance of puerperal lactation. At other times increased prolactin secretion gives rise to pathological lactation (galactorrhoea) and/or disorders of ovulation and menstruation. As a specific inhibitor of prolactin secretion, **Bromocriptine** can be used to prevent or suppress physiological lactation as well as to treat prolactin-induced pathological states. In amenorrhoea and/or anovulation (with or without galactorrhoea), **Bromocriptine** can be used to restore menstrual cycles and ovulation. The customary measures taken during lactation suppression, such as the restriction of fluid intake are not necessary with **Bromocriptine**. In addition, **Bromocriptine** does not impair the puerperal involution of the uterus and does not increase the risk of thromboembolism. **Bromocriptine** has been shown to arrest the growth or to reduce the size of prolactin secreting pituitary adenomas (prolactinomas). In acromegalic patients - apart from lowering the plasma levels of growth hormone and prolactin - **Bromocriptine** has a beneficial effect on clinical symptoms and on glucose tolerance. **Bromocriptine** improves the clinical symptoms of the polycystic ovary syndrome by restoring a normal pattern of LH secretion.

Neurological Indications

Because of its dopaminergic activity, **Bromocriptine**, in doses usually higher than those for endocrinological indications, is effective in the treatment of Parkinson's Disease, which is characterised by a specific nigrostriatal dopamine deficiency. The stimulation of dopamine receptors by **Bromocriptine** can in this condition restore the neurochemical balance within the striatum. Clinically, **Bromocriptine** improves tremor, rigidity, bradykinesia and other Parkinsonian symptoms at all stages of the disease. Usually the therapeutic effect lasts over years (so far, good results have been reported in patients treated up to eight years). **Bromocriptine** can be given either alone or - at early as well as advanced stages – combined with other anti-Parkinsonian drugs. Combination with Levodopa treatment results in enhanced anti-Parkinsonian effects, often making possible a reduction of the Levodopa dose. **Bromocriptine** offers particular benefit to patients on Levodopa treatment exhibiting a deteriorating therapeutic response or complications such as abnormal involuntary movements (choreoatoid dykinesia and/or painful dystonia), end-of-dose failure, and 'on-off' phenomenon. **Bromocriptine** improves

the depressive symptomatology often observed in Parkinsonian patients. This is due to its inherent antidepressant properties as substantiated by controlled studies in non-Parkinsonian patients with endogenous or psychogenic depression.

5.2 **Pharmacokinetic properties**

Following oral administration, **Bromocriptine** (**Bromocriptine**) is rapidly and well absorbed. Peak plasma levels are reached within 1-3 hours. An oral dose of 5 mg of **Bromocriptine** results in a Cmax 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 CYP3A4 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 _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.

Bromocriptine is contraindicated for use in the suppression of lactation or other non-life threatening indications in patients with severe coronary artery disease, or symptoms and/or a history of serious mental disorders (see Section 4.3 Contraindications).

Other

There is insufficient evidence of efficacy of **Bromocriptine** in the treatment of premenstrual symptoms and benign breast disease. The use of **Bromocriptine** in patients with these conditions is therefore not recommended. In rare cases, serious adverse events, including hypertension, myocardial infarction, seizures, stroke or psychiatric disorders have been reported in postpartum women treated with **Bromocriptine** for inhibition of lactation. In some patients the development of seizures or stroke was preceded by severe headache and/or transient visual disturbances (see Section 4.8, Undesirable Effects). Patients with severe cardiovascular disorders or psychiatric disorders taking **Bromocriptine** for the indication of macro-adenomas should only take it if the perceived benefits outweigh the potential risks (see Section 4.3 Contraindications). Blood pressure should be carefully monitored, especially during the first days of therapy. Particular caution is required in patients who are on concomitant therapy with, or have recently been treated with drugs that can alter blood pressure. Concomitant use of **Bromocriptine** with vasoconstrictors such as sympathomimetics or ergot alkaloids including ergometrine or methylergometrine during the puerperium is not recommended. If hypertension, unremitting headache, or any signs of

CNS toxicity develop, treatment should be discontinued immediately. Hyperprolactinaemia may be idiopathic, drug-induced, or due to hypothalamic or pituitary disease. The possibility that hyperprolactinaemic patients may have a pituitary tumour should be recognised and complete investigation at specialised units to identify such patients is advisable.

Bromocriptine will effectively lower prolactin levels in patients with pituitary tumours but does not obviate the necessity for radiotherapy or surgical intervention where appropriate in acromegaly. Since patients with macro-adenomas of the pituitary might have accompanying hypopituitarism due to compression or destruction of pituitary tissue, one should make a complete evaluation of pituitary functions and institute appropriate substitution therapy prior to administration of **Bromocriptine**. In patients with secondary adrenal insufficiency, substitution with corticosteroids is essential.

The evolution of tumour size in patients with pituitary macro-adenomas should be carefully monitored and if evidence of tumour expansion develops, surgical procedures must be considered. If in adenoma patients,

pregnancy occurs after the administration of **Bromocriptine**, careful observation is mandatory. Prolactin-secreting adenomas may expand during pregnancy. In these patients, treatment with **Bromocriptine** often results in tumour shrinkage and

rapid improvement of the visual fields defects. In severe cases, compression of the optic or other cranial nerves may necessitate emergency pituitary surgery. Visual field impairment is a known complication of macroprolactinoma. Effective treatment with **Bromocriptine** leads to a reduction in hyperprolactinaemia and often to resolution of the visual impairment. In some patients, however, a secondary deterioration of visual fields may subsequently develop

despite normalised prolactin levels and tumour shrinkage, which may result from traction on the optic chiasm which is

pulled down into the now partially empty sella. In these cases the visual field defect may improve on reduction of **Bromocriptine** re-expansion. Monitoring of visual fields in patients with macroprolactinoma is therefore recommended for an early recognition of secondary field loss due to chiasmal herniation and adaptation of drug dosage. In some patients with

prolactin-secreting adenomas treated with **Bromocriptine**, cerebrospinal fluid rhinorrhea has been observed. The data

available suggest that this may result from shrinkage of invasive tumours. **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 (see Section 4.7 Effects on ability to drive and use machines). Furthermore, a reduction of dosage or termination of therapy may be considered. When women of child-bearing age are treated with **Bromocriptine** for conditions not as ociated 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. Gynaecological assessment, preferably including cervical and endometrial cytology, is recommended for women receiving **Bromocriptine** for extensive periods. Six monthly assessment is suggested for post-menopausal women and annual assessment for women with regular menstruation. A few cases of gastrointestinal bleeding and gastric ulcer have been reported. If this occurs, **Bromocriptine** should be withdrawn. Patients with a history of evidence of peptic ulceration should be closely monitored when receiving the treatment. Since, especially during the first few days of treatment, hypotensive reactions may occasionally occur and result in reduced alertness, particular care should be exercised when driving a vehicle or operating machinery. 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 manifestations (e.g. back pain, oedema of the lower limbs, impaired kidney function) should be watched in this category of patients. Possible risk of fibrosis in patients taking **Bromocriptine** st high doses forlong period, 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. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including **Bromocriptine**.

Elderly

Clinical studies for **Bromocriptine** did not include sufficient numbers of subjects ages 65 and above to determine whether the elderly respond differently from younger subjects. However, other reported clinical experiences, including post-marketing reporting of adverse events have identified no differenced in response or tolerability between elderly and younger patients. Even though no variation in efficacy or adverse reaction profile in elderly patients taking **Bromocriptine** has been observed, greater sensitivity in some elderly individuals cannot be categorically ruled out. In general, dose selection for an elderly patient should be cautious, starting at the lower end of the dose range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy in this population.

6 Pharmaceutical Particulars

6.1 List of Excipients

S/N	Ingredients	Qty/tablet	Function
1	Lactose monohydrate 200 Mesh	41mg	Diluent
2	Microcrystalline Cellulose (Avicel pH 102)	40mg	Diluent & Disintegrant
3	Maize Starch	35.08mg	Diluent & Disintegrant
4	Povidone K 30	5.20mg	Binder
5	Purified talc	3.90mg	Lubricant
6	Magnesium Stearate	1.3mg	Lubricant
7	Colloidal Anhydrous Silica (Aerosil 200)	0.65mg	Glidant

6.2 Incompatibilities

6.3 Shelf life: 24Months

6.4 Special Precautions for storage

Store at temperature not exceeding 30˚C in dry place .

6.5 Nature and contents of container

Carton box contains 1, 2 or 3 Al./PVC opaque white strips each of 10tablets & insert leaflet.

Manufactured by

OCTOBER PHARMA S.A.E.

6 - October City - EGYPT

Marketed by

Smart Way Pharma Ltd

61, Thomas Animasaun Street, Aguda.