SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bromocriptine 1 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg bromocriptine (as mesilate).

Excipient with known effect:

Each tablet contains 78.51 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White to off-white, round, uncoated, flat faced beveled edge tablets debossed with "1" and "MG" on either side of break line on one face and plain on the other face. The score line is not intended for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Inhibition of lactation for medical reasons

Prevention or suppression of post-partum physiological lactation only where medically indicated (such as in case of intrapartum loss, neonatal death, HIV infection of the mother).

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 non-pharmacological intervention (such as firm breast support, ice application) and/or simple analgesics.

Hyperprolactinaemia

The treatment of hyperprolactinaemia in men and women with hypogonadism and/or galactorrhoea.

Menstrual cycle disorders and female infertility

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.

Prolactinomas

To reduce tumour size, particularly in those at risk of optic nerve compression.

Acromegaly

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.

Parkinson's Disease

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

(See section 4.4 Special warnings and precautions for use).

4.2 Posology and method of administration

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 variable.

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, 1mg to 1.25mg at bed time, increasing after 2 to 3 days to 2mg to 2.5mg at bed time. Dosage may then be increased by 1mg at 2 to 3 day intervals, until a dosage of 2.5mg twice daily is achieved. Further dosage increments, if necessary, should be added in a similar manner.

Prevention of Lactation

2.5mg on the day of delivery, followed by 2.5mg 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

2.5mg on first day, increasing after 2 to 3 days to 2.5mg 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 7.5mg daily, in divided doses, but doses of up to 30mg daily have been used. In infertile patients without demonstrably elevated serum prolactin levels, the usual dose is 2.5mg twice daily.

Prolactinomas

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

Acromegaly

Introduce Bromocriptine gradually, according to the suggested scheme.

Dosage may then be increased by 2.5mg at 2 to 3 day intervals as follows: - 2.5mg eight-hourly, 2.5mg six-hourly, 5mg six-hourly.

Parkinson’s Disease

Introduce Bromocriptine gradually, as follows: Week 1: 1mg to 1.25mg at bed time. Week 2: 2mg to 2.5mg at bed time. Week 3: 2.5mg twice daily. Week 4: 2.5mg three times daily. Thereafter take three times a day increasing by 2.5mg every 3 to 14 days, depending on the patient’s response. Continue until the optimum dose is reached. This will usually be between 10mg and 30mg 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 and adolescents (aged 7-17)

Prescribing of bromocriptine in children and adolescents (aged 7-17) should be limited to Paediatric Endocrinologists.

Prolactinomas: Paediatric population 7 years and older: 1 mg 2 or 3 times daily, gradually increasing to several tablets daily as required to keep plasma prolactin adequately suppressed. Maximum daily dose recommended in children aged 7 to 12 years is 5 mg. Maximum daily dose recommended in adolescent patients (13-17 years) is 20 mg.

Gigantism (acromegaly): Paediatric population 7 years and older: The starting dose should be titrated in response to Growth Hormone levels. Maximum daily dose recommended in children ages 7 to 12 years is 10 mg. Maximum daily dose recommended in adolescent patients (13-17 years) is 20 mg.

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.

4.3 Contraindications

Hypersensitivity 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.

Bromocriptine is contraindicated in patients with uncontrolled hypertension, hypertensive disorders of pregnancy (including eclampsia, pre-eclampsia or pregnancy-induced hypertension), hypertension postpartum and in the puerperium.

Bromocriptine is contraindicated 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 the 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, suggestive chest pain, severe progressive or unremitting headache or any signs of central nervous system toxicity develop, treatment should be discontinued immediately and the patient should be evaluated promptly. 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 dosage while there is some elevation of prolactin and some tumour 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 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.

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. 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 bromocriptine. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Important Precautions

When dose reduction or discontinuation of this drug is necessary, the dose should be gradually reduced. Rapid dose reduction or discontinuation may cause a neuroleptic malignant syndrome. In addition, rapid dose reduction or discontinuation of dopamine receptor agonists may cause drug withdrawal syndrome (characterized by apathy, anxiety, depression, fatigue, sweating, pain, etc.).

Children and Adolescents (aged 7-17)

Bromocriptine has been used to treat prolactinomas and gigantism (acromegaly) indications in patients aged 7 or above and case series have been documented in the literature. Only isolated data are available for bromocriptine use in paediatric patients under the age of 7 years. Data on safety are limited, particularly in the long term. Prescribing is restricted to Paediatric Endocrinologists.

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 differences 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.

Bromocriptine tablets contain lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Bromocriptine tablets contain sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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 Fertility, pregnancy and lactation

Pregnancy

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 evidence suggests 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 childbearing 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 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 (see also Section 4.4 Special Warnings and Precautions).

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, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000), very rare (<1/10,000), including isolated reports.

MedDRA system organ class	**Frequency**	**Undesirable Effects**
Psychiatric disorders	Uncommon	Confusion, Psychomotor agitation, Hallucinations
	Rare	Psychotic disorders, Insomnia
Nervous system disorders	Common	Headache, Drowsiness
	Uncommon	Dizziness, Dyskinesia
	Rare	Somnolence, Paraesthesia
	Very Rare	Excess daytime somnolence and sudden sleep onset
Eye disorders	Rare	Visual disturbances, vision blurred
Ear and labyrinth disorders	Rare	Tinnitus
Cardiac disorders	Rare	Tachycardia, bradycardia, arrhythmia
	Very rare	Cardiac valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion)
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)

Respiratory, thoracic and mediastinal disorders	Common	Nasal congestion
	Rare	Pleural effusion, pleural and pulmonary fibrosis, pleuritis, dyspneoa
Gastrointestinal disorders	Common	Nausea, Constipation
	Uncommon:	Vomiting, dry mouth
	Rare	Diarrhoea, Abdominal pain, Retroperitoneal fibrosis, Gastrointestinal ulcer, Gastrointestinal haemorrhage
Skin and subcutaneous tissue disorders	Uncommon	Allergic skin reactions, Hair loss
Musculoskeletal and connective tissue disorders	Uncommon	Leg cramps
General disorders and administration site conditions	Uncommon	Fatigue
	Rare	Peripheral oedema
	Very Rare	A syndrome resembling Neuroleptic Malignant Syndrome has been reported on withdrawal of bromocriptine

Other Adverse Reactions

Drug withdrawal syndrome*
Apathy, anxiety, depression, fatigue, sweating, pain, etc

*When any abnormalities are observed, appropriate measures should be taken such as resuming administration or returning the dose to the level prior to reduction.

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 (see Section 4.4 Special warnings and precautions for use).

Impulse control disorders

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including BROMOCRIPTINE. (see section 4.4 'Special warnings and precautions for use').

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

There have been isolated reports of children who accidentally ingested BROMOCRIPTINE. Vomiting, somnolence and fever were reported as adverse events. Patients recovered either spontaneously within a few hours or after symptomatic treatment.

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.

The management of acute intoxication is symptomatic; Metoclopramide may be indicated for the treatment of emesis or hallucinations.

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 antiParkinsonian drugs. Combination with Levodopa treatment results in enhanced antiparkinsonian 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 is rapidly and well absorbed. Peak plasma levels are reached within 1-3 hours. An oral dose of 5mg 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 CYP3A and hydroxylations at the proline ring of the cyclopeptide moiety constitute a main metabolic pathway. Inhibitors and/or potent substrates for CYP3A4 might therefore be expected to inhibit the clearance of bromocriptine and lead to increased levels. Bromocriptine is also a potent inhibitor of CYP3A4 with a calculated IC50 value of 1.69 μM. 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.

5.3 Preclinical safety data

Pre-clinical data for BROMOCRIPTINE reveal no special hazard for humans based on conventional studies of single and repeat dose toxicity, genotoxicity, mutagenicity, carcinogenic potential, or toxicity to reproduction.

Endometrial carcinomas were observed in pre-clinical rat studies at high dosages only. They are considered to be due to the species-specific sensitivity of the test animals to the pharmacological activity of bromocriptine.

Other effects in pre-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Maize starch
Citric acid monohydrate
Disodium edetate
Maleic acid
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Bromocriptine tablets are available in Alu-Alu blister pack.

Pack size:
Blister pack: 7, 10, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100, 112 and 120 tablets

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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Hounslow
TW4 5DQ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 25298/0270

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/02/2022

10 DATE OF REVISION OF THE TEXT

14/02/2022