SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Medocriptine 2.5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Medocriptine contain 2.5 mg bromocriptine as bromocriptine mesilate.

Excipient with known effect: lactose monohydrate. Each tablet contains 100.0mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White, round, flat, scored tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Prolactinomas
Treatment of prolactin-secreting pituitary micro- or macro-adenomas. Bromocriptine may be used prior to surgery in order to reduce tumour size and to facilitate removal.

Acromegaly
Bromocriptine has been used as an adjunct to surgery and/or radiotherapy, or in management of acromegalic patients with a contraindication to or for whom surgery is not suitable.

Hyperprolactinemia
For the treatment of hyperprolactinemia:
In male patients with hypogonadism (oligospermia, loss of libido, impotence) and or galactorrhea.
In female patients with hypogonadism (amenorrhea, hot flushes, and vaginal dryness), menstrual irregularity, female infertility and or galactorrhea.

Inhibition of lactation for medical reasons

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

Parkinson's disease

Treatment of the signs and symptoms of idiopathic Parkinson disease; bromocriptine is indicated as adjunctive treatment to levodopa (alone or in combination with other antiparkinsonian drugs) in patients with motor complications and those disabled by "on/off" phenomena. Bromocriptine may be useful in patients who are unable to tolerate levodopa's adverse effects or when levodopa is ineffective.

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.

4.2. Posology and method of administration

Posology

Adults

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 dosage the optimum response with the minimum of side-effects is best achieved by gradual introduction of bromocriptine. The following scheme is suggested.
Initially half a tablet (1.25 mg) at bedtime, increasing after 2 to 3 days to 2.5 mg at bedtime. Dosage may then be increased by half to one tablet 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.

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, 5mg six-hourly. Patients have responded to up to 30 mg daily.

Acromegaly

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, increasing to 10 to 20 mg daily, depending on clinical response and side effects.

Hyperprolactinemia

Women: Introduce bromocriptine gradually according to the suggested scheme increasing to 5 to 10 mg per day. Most patients with hyperprolactinemia have responded to 7.5 mg daily, in divided doses. Treatment is continued until breast secretion has completely ceased, and in association with amenorrhea, until the menstrual cycle normalized.

Men: Introduce bromocriptine gradually according to the suggested scheme. Doses up to 15 mg daily have been studied clinically.
Treatment is continued until an optimal therapeutic response is achieved.

Inhabitation of lactation for medical reasons

Prevention or suppression of lactation: On the first day of delivery, 1.25 mg (½ tablet 2.5 mg) with food in the morning and evening followed by 2.5 mg twice daily for 14 days. Gradual introduction of bromocriptine is not necessary in this indication.
To prevent the onset of lactation, treatment should be instituted within a few hours of parturition or abortion, but not before vital signs have stabilized. Slight milk secretion occasionally occurs 2 or 3 days after treatment has been withdrawn. This can be stopped by resuming treatment at the same dosage for a further week.

Parkinson's disease

In order to ensure optimal tolerability, bromocriptine should be introduced gradually.
Week 1: 1.25 mg at bedtime.
Week 2: 2.5 mg at bedtime.
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.
Bromocriptine should be titrated slowly in order to arrive at the minimal effective dose for each patient. An adequate therapeutic response may be reached within 6 to 8 weeks; if it is not, the daily dose may be further increased by 2.5 mg/day each week.
Continue until the optimum dose is reached. The usual therapeutic range for monotherapy or combined therapy is 10-30 mg bromocriptine per day. Daily doses should not exceed 30 mg.

In patients already receiving levodopa the dosage of this drug may be gradually decreased while the dosage of bromocriptine is increased until the optimum balance is determined. In certain patients, levodopa may be withdrawn completely.

Paediatric population

Children and adolescents (7-17 years)

The safety and efficacy of bromocriptine in pediatric patients has only been established for prolactinomas and acromegaly indications in patients older than 7 years of age (see sections 4.4 and 5.1).

Elderly

There is no clinical evidence that bromocriptine poses a special risk to older people.

Method of administration

Medocriptine tablets are for oral administration. They should be taken with a meal.

4.3. Contraindications

Hypersensitivity to the active substance, to other ergot alkaloids or to any of the excipients listed in section 6.1

Uncontrolled hypertension, hypertensive disorders of pregnancy (including eclampsia, pre-eclampsia or pregnancy induced hypertension), hypertension post partum and in the puerperium.

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.

For long-term treatment: Evidence of cardiac valvulopathy as determined by pre-treatment echocardiography.

4.4. Special warnings and precautions for use

General

If women with conditions not associated with hyperprolactinemia are treated with bromocriptine, the drug should be given in the lowest effective dose necessary to relieve the symptoms; this is in order to avoid the possibility of suppressing plasma prolactin below normal levels, with a consequent impairment of luteal function.

A few cases of gastrointestinal bleeding and gastric ulcer have been reported. If this occurs, bromocriptine should be withdrawn. Patients with a history or evidence of peptic ulceration should be closely monitored when receiving the treatment.

Since, especially during the first 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.

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 not to drive or operate machines during treatment with bromocriptine.

Patients who have experienced somnolence and/or an episode of sudden sleep onset must not drive or operate machines (see section 4.7). Furthermore, a reduction of dosage or termination of therapy may be considered.

In 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 considered In a few patients treated 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.

Use in postpartum women

In rare cases serious adverse events, including hypertension, myocardial infarction, seizures, stroke, or psychic 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. Blood pressure should be carefully monitored, especially during the first days of therapy. If hypertension, suggestive chest pain, severe, progressive, or unremitting headache (with or without visual disturbances), or evidence of central nervous system (CNS) toxicity develop, the administration of bromocriptine should be discontinued and the patient should be evaluated promptly.

Particular caution is required in patients who have recently been treated or are on concomitant therapy with drugs that can alter blood pressure, e.g., vasoconstrictors such as sympathomimetics or ergot alkaloids including ergometrine or methylergometrine. Although there is no conclusive evidence of an interaction between bromocriptine and these drugs, their concomitant use in the puerperium is not recommended.

Use in prolactin-secreting adenoma patients

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 field 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 hyperprolactinemia and often to a resolution of the visual impairment. In some patients, however, a secondary deterioration of visual fields may subsequently develop despite normalized 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 the 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.

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

Use for Parkinson's disease

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 to 17)

The safety and effectiveness of bromocriptine in pediatric patients has only been established for the prolactinomas and acromegaly indications, in patients aged 7 or above. Only isolated data are available for bromocriptine use in pediatric patients under the age of 7 years. However, other reported clinical experiences, including post-marketing reporting of adverse events, have not identified differences in tolerability between adults and adolescents or children. Even though no variation in adverse reaction profile in pediatric patients taking bromocriptine has been observed, greater sensitivity in some younger individuals cannot be categorically ruled out, and it is recommended that dose titration in pediatric patients should be cautious.

Prescribing of bromocriptine in children and adolescents should be limited to Pediatric Endocrinologists.

Elderly

Clinical studies for bromocriptine did not include sufficient numbers of subjects aged 65 and above to determine whether older people 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 older people and younger patients.

Even though no variation in efficacy or adverse reaction profile in older people patients taking bromocriptine has been observed, greater sensitivity in some older individuals cannot be categorically ruled out. In general, dose selection for an older 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.

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

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

4.5. Interactions with other medicinal products and other forms of interaction

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 use of macrolide antibiotics such as erythromycin or josamycin, was shown to increase the plasma levels of bromocriptine. The concomitant treatment of acromegalic patients with bromocriptine and octreotide led to increased plasma levels of bromocriptine. Since bromocriptine exerts its therapeutic effect by stimulating central dopamine receptors, dopamine antagonists such as antipsychotics (phenothiazines, butyrophenones and thioxanthenes), but also metoclopramide and domperidone may reduce its activity.

The tolerability to bromocriptine may be reduced by alcohol.

4.6. Fertility, pregnancy and lactation

Pregnancy

In patients wishing to conceive, bromocriptine, like all other drugs, should be discontinued when pregnancy is confirmed, unless there is a medical reason for continuing therapy. No increased incidence of abortion has been observed following withdrawal of bromocriptine at this point. Clinical experience indicated that bromocriptine, administered during pregnancy, does not adversely affect its course or outcome.

If pregnancy occurs in the presence of a pituitary adenoma and bromocriptine treatment has been stopped, close supervision throughout pregnancy is essential. In patients who show symptoms of a pronounced enlargement of a prolactinoma, e.g. headache or visual field deterioration, bromocriptine treatment may be re-instituted or surgery may be appropriate.

Breast-feeding

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

Fertility

Fertility may be restored by treatment with Medocriptine. 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

Since, especially during the first days of treatment, hypotensive reactions may occasionally occur and result in reduced alertness 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 (e.g., operating machines) until such recurrent episodes and somnolence have resolved (see section 4.4).

4.8. Undesirable effects

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Psychiatric Disorders
Uncommon: Confusion, Psychomotor agitation, Hallucinations
Rare: Psychotic disorders, Insomnia
Very rare: Libido increased, hypersexuality, pathological gambling, compulsive spending or buying, binge eating, compulsive eating

Nervous System Disorders
Common: Headache, Drowsiness, Dizziness
Uncommon: Dyskinesia
Rare: Somnolence, Paresthesia
Very Rare: Excess daytime somnolence, sudden onset of sleep

Eye Disorders
Rare: Visual disturbances, vision blurred

Ear and Labyrinth Disorders
Rare: Tinnitus

Cardiac Disorders
Rare: Pericardial effusion, Constrictive pericarditis, tachycardia, bradycardia, arrhthymia
Very rare: cardiac valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion), Cardiac valve fibrosis

Vascular Disorders
Uncommon: Hypotension, orthostatic hypotension (very rarely leading to syncope)
Very Rare: Reversible pallor of fingers and toes induced by cold (especially in patients with history of Raynaud's phenomenon)

Respiratory, thoracic and mediastinal disorders

Common: Nasal congestion

Rare: Pleural effusion, Pleural fibrosis, Pleurisy, Pulmonary fibrosis, dyspnea

Gastrointestinal Disorders

Common: Nausea, Constipation, Vomiting

Uncommon: 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 on withdrawal of Medocriptine.

Not known: Drug withdrawal syndrome* including 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.

The use of bromocriptine for the inhibition of physiological lactation post partum has been associated with the rare occurrence of hypertension, myocardial infarction, seizures, stroke or psychic disorders (see section 4.4).

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).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorization 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 national reporting system.

4.9. Overdose

Symptoms

All patients who have taken an overdose of bromocriptine alone have survived; the maximum single dose so far ingested is 325 mg. The observed symptoms were nausea, vomiting, dizziness, hypotension, postural hypotension, tachycardia, drowsiness, somnolence, lethargy and hallucinations.
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 appropriate management.

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 agonists, ATC code: N04BC01; Prolactin inhibitors, ATC code: G02CB01.

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 are discussed under each indication.
The safety and effectiveness of bromocriptine in pediatric patients has only been established for the prolactinomas and acromegaly indications, in patients aged 7 years or above (see sections 4.2 and 4.4).

Children and adolescents (7-17 years)

The use of bromocriptine in the treatment of prolactinomas and acromegaly in children is described in published case studies and retrospective cohort studies. In the age group of under 7 years, however, only a few isolated case reports are available. Bromocriptine is described as an effective non-invasive

treatment of prolactinomas and acromegaly in children and adolescents. In acromegaly, bromocriptine treatment resulted in an inhibition of growth hormone (IGF-1 concentration) release.
In hyperprolactinemia, bromocriptine was effective in inhibiting serum prolactin levels, allowing normal growth and puberty to be achieved. The used dosage of bromocriptine in children and adolescents ranged from 1.25 to 20 mg per day. It will be recommended that the dose titration in children be initiated with caution. Safety in the group adolescents appears to be comparable to the adult population in these indications. In younger patients, especially in the age group of under 7 years, however, the data are insufficient to assess the safety and determine effectiveness.

Endocrinological Properties

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 (galactorrhea) 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 amenorrhea and/or anovulation (with or without galactorrhea), 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 thrombo-embolism. 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 properties

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 characterized 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 along 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 (choreo-athetoid dyskinesia and/or painful dystonia), end-of-dose failure, and "on/off" phenomenon.
Bromocriptine improves the depressive symptomatology often observed in Parkinsonians. 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

Absorption

Following oral administration, bromocriptine is well absorbed. When using in healthy volunteers, the absorption half-life is 0.2 - 0.5 h, and peak plasma levels of bromocriptine are reached within 1 – 3 hours. An oral dose of 5mg of bromocriptine results in a Cmax of 0.465 ng/mL.

Distribution

The prolactin-lowering effect sets in within 1 - 2 h after ingestion, reaches its maximum, i.e. a reduction of prolactin in the plasma by more than 80%, within 5 - 10 h and remains close to maximum for 8 - 12 hours.

Elimination

The elimination of the parent drug from plasma is biphasic, with a terminal half-life of about 15 h (range 8 - 20 h). 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%.

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 and the clearance of bromocriptine and lead to increased levels. Bromocriptine is also a potent inhibitor of CYP3A4 with a calculated IC50 value of 1.6 μM. However, given the low therapeutic concentrations of free Bromocriptine in patients, a significant alteration of metabolism of a second drug whose clearance is mediated by CYP3A4 should not be expected.

Characteristics in patients

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.

5.3. Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycollate
Magnesium stearate
Maleic acid
Disodium edetate

6.2. Incompatibilities

None known.

6.3. Shelf life

5 years.

6.4. Special precautions for storage

Store below 25^{o}C, in the original package, in order to protect from light and moisture.

6.5. Nature and contents of container

Polyvinylchloride and aluminium combination blisters. Blisters and leaflet in an outer carton.
Medocriptine 2.5 mg tablets are available in packs of 30, 100 or 500 tablets.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

MEDOCHEMIE LTD, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER

05751/07611/NMR/2019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09/03/2021
Date of latest renewal: N/A

10. DATE OF REVISION OF THE TEXT

11/2022