NOVARTIS

Drug Regulatory Affairs

PARLODEL® / PARLODEL® SRO®

(bromocriptine mesylate)

2.5 mg Tablets

5.0 mg or 10.0 mg Capsules

2.5 mg, 5.0 mg or 10.0 mg SRO Capsules

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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1 Name of the medicinal product

PARLODEL® / PARLODEL® SRO®

2 Qualitative and quantitative composition

Active substance: Ergotaman-3',6',18-trione, 2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl-), monomethanesulfonate (salt), (5'alpha).

One scored tablet contains bromocriptine mesylate 2.87 mg (corresponding to 2.5 mg bromocriptine base).

One capsule contains bromocriptine mesylate 5.74 mg or 11.47 mg (corresponding to 5.0 mg or 10.0 mg bromocriptine base).

One capsule SRO contains bromocriptine mesylate 2.87 mg, 5.74 mg or 11.47 mg (corresponding to 2.5 mg, 5.0 mg or 10.0 mg bromocriptine base).

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Tablets (scored), Capsules and Capsules SRO.

4 Clinical particulars

4.1 Therapeutic indications

Parkinson's disease

All stages of idiopathic and postencephalitic Parkinson's disease, either as monotherapy or in combination with other antiparkinsonian drugs [39-47,80].

Prolactinomas [4,68-72]

Conservative treatment of prolactin-secreting pituitary micro- or macro-adenomas.

Prior to surgery in order to reduce tumour size and to facilitate removal.

After surgery if prolactin level is still elevated.

Acromegaly

As an adjunct, or in special cases as an alternative, to surgery or radiotherapy [18-20,24,52].

Hyperprolactinaemia in men

Prolactin-related hypogonadism (oligospermia, loss of libido, impotence) [11,62-66].

Menstrual cycle disorders, female infertility

Prolactin-dependent hyperprolactinaemic or apparently normoprolactinaemic conditions

- amenorrhoea (with or without galactorrhoea) [8-12], oligomenorrhoea [83,88,100],
- luteal phase deficiency [36-38],

- drug-induced hyperprolactinaemic disorders (e.g. induced by certain psychotropic or antihypertensive agents).

Prolactin-independent female infertility

- polycystic ovary syndrome [83-88],
- anovulatory cycles [35] (supplementary to anti-estrogens, e.g. clomiphene).

Inhibition of lactation for medical reasons [109,158]

Prevention or suppression of puerperal lactation [13-15].

Prevention of lactation after abortion [57-59].

Incipient puerperal mastitis [60,61].

Parlodel® is not recommended for the routine prevention or suppression of puerperal breast engorgement which can be adequately treated with simple analgesics and breast support [158].

Other

There is insufficient evidence of efficacy of Parlodel in the treatment of premenstrual symptoms and benign breast disease. The use of Parlodel in patients with these conditions is therefore not recommended [158].

4.2 Posology and method of administration

Parlodel should always be taken with food.

Tablets or capsules (standard forms)

Parkinson's disease

In order to ensure optimal tolerability, treatment should be started with a low dose of 1.25 mg (½ tablet) per day, given preferably in the evening, for the first week. Parlodel should be titrated slowly in order to arrive at the minimal effective dose for each patient. The daily dosage should be increased gradually by 1.25 mg/day each week, and given as 2 to 3 divided doses. 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.

The usual therapeutic range for monotherapy or combined therapy is 10-40 mg bromocriptine per day, but higher doses may be required in some patients.

Should undesirable reactions occur during the titration phase, the daily dose should be reduced and maintained at the lower level for at least a week. If the adverse reactions disappear, the dose can be increased again.

For patients exhibiting motor disorders on levodopa therapy, it is suggested that the levodopa dosage should be reduced before Parlodel treatment is initiated. When a satisfactory response to Parlodel has been obtained, a further stepwise reduction in levodopa dosage can be made. In certain patients, levodopa may be withdrawn completely.

Prolactinomas

1.25 mg (½ tablet) 2 or 3 times daily, gradually increasing to several tablets or capsules daily as required to keep plasma prolactin adequately suppressed.

Acromegaly

Initially 1.25 mg (½ tablet) 2 or 3 times daily, gradually increasing to 10 to 20 mg daily, depending on clinical response and side effects.

Hyperprolactinaemia in men

1.25 mg (½ tablet) 2 or 3 times daily, gradually increasing to 5 to 10 mg per day.

Menstrual cycle disorders, female infertility

1.25 mg (½ tablet) 2 or 3 times daily; if this proves inadequate, gradually increase to 2.5 mg 2 or 3 times daily. Continue treatment until the menstrual cycle has returned to normal and/or ovulation is restored. If required, treatment may be continued over several cycles to prevent relapse.

Inhibition of lactation for medical reasons

On the first day, ½ tablet with food in the morning and evening, followed by 1 tablet twice a day for 14 days. To prevent the onset of lactation, treatment should be instituted within a few hours of parturition or abortion, but not before vital signs have stabilised. 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.

Incipient puerperal mastitis

Same dosage as for inhibition of lactation. An antibiotic should be added to the regimen, as required.

Children and Adolescents (aged 7 – 17) [162]

Prolactinomas: Paediatric population older than 7 years: 1.25 mg (½ tablet) 2 or 3 times daily, gradually increasing to several tablets or capsules daily as required to keep plasma prolactin adequately suppressed. Maximum daily dose recommended in children aged 7 to 12 years is 5mg. Maximum daily dose recommended in adolescent patients (13-17 years) is 20mg.

Acromegaly: Paediatric population older than 7 years: Initially 1.25 mg (½ tablet) 2 or 3 times daily, gradually increasing to several tablets or capsules daily, depending on clinical response and side effects. Maximum daily dose recommended in children aged 7 to 12 years is 10mg. Maximum daily dose recommended in adolescent patients (13-17 years) is 20mg.

SRO capsules [118-120]

As experience with Parlodel SRO in the treatment of Parkinson's disease is limited, its use in Parkinsonian patients is not recommended.

As experience with Parlodel SRO in the treatment of children and adolescents is limited, its use in these patients is not recommended [162].

In the other indications listed above, the appropriate once-a-day doses are similar to the daily doses recommended for the standard forms. Parlodel SRO should preferably be taken after the evening meal and must be swallowed whole.

In patients not previously treated with Parlodel tablets or standard capsules, the usual starting daily dose is 1 capsule SRO 2.5 mg. After 3 to 7 days, the dose should be increased to 5 mg. If this proves insufficient, further gradual increases in steps of 2.5 or 5 mg up to the optimal dose are indicated.

In patients to be switched from Parlodel tablets or standard capsules to once-a-day treatment with Parlodel SRO, the preceding daily dose should be maintained.

If Parlodel SRO capsules are used for the inhibition of lactation, the recommended dose is 1 capsule of 2.5 mg on the first day followed by 2 capsules once a day (preferably after the evening meal) for 2 weeks.

4.3 Contraindications

Hypersensitivity to bromocriptine or to any of the excipients of Parlodel/Parlodel SRO (see section 2. Qualitative and quantitative composition and section 6.1. List of excipients) or to other ergot alkaloids.

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

Coronary artery disease and other severe cardiovascular conditions.

Symptoms and/or a history of serious psychic disorders [113].

4.4 Special warnings and precautions for use

General

If women with conditions not associated with hyperprolactinaemia are treated with Parlodel, 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 [53].

A few cases of gastrointestinal bleeding [28,29] and gastric ulcer have been reported. If this occurs, Parlodel 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.

Parlodel 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 Effects on ability to drive and use machines). Furthermore, a reduction of dosage or termination of therapy may be considered [156].

Among patients on Parlodel, particularly on long-term and high-dose treatment, pleural and pericardial effusions, as well as pleural and pulmonary fibrosis and constrictive pericarditis [79,126,155,159] have occasionally been reported. Patients with unexplained pleuropulmonary disorders should be examined thoroughly and discontinuation of Parlodel therapy should be contemplated.

In a few patients on Parlodel, particularly on long-term and high-dose treatment, retroperitoneal fibrosis has been reported [111,159]. 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. Parlodel medication should be withdrawn if fibrotic changes in the retroperitoneum are diagnosed or suspected.

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including Parlodel. These effects are generally reversible upon reduction of the dose or treatment discontinuation [166].

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

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 Parlodel for the inhibition of lactation. In some patients the development of seizures or stroke was preceded by severe headache and/or transient visual disturbances [112]. Although the causal relationship of these events to the drug is uncertain, periodic monitoring of blood pressure is advisable in postpartum women receiving Parlodel for the inhibition of lactation, as well as in patients treated for any other condition. If hypertension, severe, progressive, or unremitting headache (with or without visual disturbances), or evidence of CNS toxicity develop, the administration of Parlodel 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 [124,125] and their concomitant use in the puerperium is not recommended [161].

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 Parlodel. 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 Parlodel, careful observation is mandatory. Prolactin-secreting adenomas may expand during pregnancy. In these patients, treatment with Parlodel 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 Parlodel leads to a reduction in hyperprolactinaemia and often to a 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 [157].

In some patients with prolactin-secreting adenomas treated with Parlodel, cerebrospinal fluid rhinorrhea has been observed. The data available suggest that this may result from shrinkage of invasive tumours [159].

Children and Adolescents (aged 7 to 17) [162]

The safety and effectiveness of bromocriptine in paediatric 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 paediatric 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 paediatric patients taking Parlodel has been observed, greater sensitivity in some younger individuals cannot be categorically ruled out, and it is recommended that dose titration in paediatric patients should be cautious.

Elderly [162]

Clinical studies for Parlodel did not include sufficient numbers of subjects aged 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 Parlodel 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.

4.5 Interaction 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) [160]. The concomitant use of macrolide antibiotics such as erythromycin [102,160] or josamycin [160], 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 [127].

Since Parlodel 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 [159].The tolerability to Parlodel may be reduced by alcohol [77].

4.6 Pregnancy and lactation

Pregnancy

In patients wishing to conceive, Parlodel, 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 Parlodel at this point. Clinical experience indicates that Parlodel, administered during pregnancy, does not adversely affect its course or outcome [50, 78,106,159].

If pregnancy occurs in the presence of a pituitary adenoma and Parlodel 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, Parlodel treatment may be re-instituted or surgery may be appropriate.

Lactation

Since Parlodel 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 Parlodel. Women of childbearing age who do not wish to conceive should therefore be advised to practise a reliable method of contraception [82,99-101].

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 exercise when driving a vehicle or operating machinery [54,55].

Patients being treated with Parlodel 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 Special warnings and special precautions for use) [156].

4.8 Undesirable effects

Adverse reactions (Table 1) 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.

Table 1 Adverse drug reactions [159]

Psychiatric disorders	
Uncommon:	Confusion, psychomotor agitation [131], hallucinations [131].
Rare:	Psychotic disorders [159], insomnia [159].
Very rare:	Pathological gambling [166], libido increase [163], hypersexuality [163].
Nervous system disorders	
Common:	Headache [131], drowsiness, dizziness [131].
Uncommon:	Dyskinaesia [131].
Rare:	Somnolence, paraesthesia [159]
Very rare:	Excess daytime somnolence [156], sudden onset of sleep [156].
Eye disorders	
Rare:	Visual disturbance [159], vision blurred [159].
Ear and labyrinth disorders	
Rare:	Tinnitus [159].
Cardiac disorders	
Rare:	Pericardial effusion [155], constrictive pericarditis [155], tachycardia [159], bradycardia [159], arrhythmia [159].
Very rare:	Cardiac valve fibrosis [165].
Vascular disorders	
Uncommon:	Hypotension [27], orthostatic hypotension (very rarely leading to syncope) [104,105,131].
Very rare:	Reversible pallor of fingers and toes induced by cold (especially in patients with history of Raynaud's phenomenon) [25,26,56,131].
Respiratory, thoracic and mediastinal disorders	
Common:	Nasal congestion [128].
Rare:	Pleural effusion [79,126], pleural fibrosis [79,126], pleurisy [159], pulmonary fibrosis [79,126], dyspnoea [159].
Gastrointestinal disorders	
Common:	Nausea [131], constipation, vomiting [131].
Uncommon:	Dry mouth.
Rare:	Diarrhoea, abdominal pain, retroperitoneal fibrosis [111], gastrointestinal ulcer [159], gastrointestinal haemorrhage [28,29,159].
Skin and subcutaneous tissue disorders	
Uncommon:	Allergic skin reactions [122], hair loss [129,130].
Musculoskeletal and connective tissue disorders	
Uncommon:	Leg cramps [131].
General disorders and administration site conditions	
Uncommon:	Fatigue [131].
Rare:	Peripheral oedema [159].
Very rare:	A syndrome resembling Neuroleptic Malignant Syndrome on abrupt withdrawal of Parlodel [159].

Patients treated with dopamine agonists for Parkinson's disease, especially at high doses, have been reported as exhibiting pathological gambling [166], increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation. Very rarely, such reports have also been received for Parlodel [163,166].

The use of Parlodel 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. Special warnings and precautions for use) [123].

4.9 Overdose [103,132]

Signs and symptoms

All patients who have taken an overdose of Parlodel 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 [159].

There have been isolated reports of children who accidentally ingested Parlodel. Vomiting, somnolence and fever were reported as adverse events. Patients recovered either spontaneously within a few hours or after appropriate management [162].

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 [159].

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 N04B C01), prolactin inhibitors (ATC code G02C B01)

Parlodel inhibits the secretion of the anterior pituitary hormone prolactin without affecting normal levels of other pituitary hormones [1,2]. It can, however, reduce elevated levels of growth hormone (GH) in patients with acromegaly [3,17,18]. These effects are due to stimulation of dopamine receptors.

In the puerperium prolactin is necessary for the initiation and maintenance of puerperal lactation [3]. 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, Parlodel can be used to prevent or suppress physiological lactation [4,8] as well as to treat prolactin-induced pathological states. In amenorrhoea and/or anovulation (with or without galactorrhoea), Parlodel can be used to restore menstrual cycles and ovulation [8].

Customary measures taken during lactation suppression, such as the restriction of fluid intake, are not necessary with Parlodel [5]. In addition, Parlodel does not impair the puerperal involution of the uterus [5-7] and does not increase the risk of thromboembolism [16].

Parlodel has been shown to arrest the growth or to reduce the size of prolactin-secreting pituitary adenomas (prolactinomas) [68].

In acromegalic patients – in addition to lowering the plasma levels of growth hormone [17] and prolactin [18] – Parlodel has a beneficial effect on clinical symptoms and on glucose tolerance [21-24].

Parlodel improves the clinical symptoms of the polycystic ovary syndrome by restoring a normal pattern of LH secretion [84].

Because of its dopaminergic activity, Parlodel, at 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. In this condition, the stimulation of dopamine receptors by Parlodel can restore the neurochemical balance within the striatum [48].

Clinically, Parlodel improves tremor, rigidity, bradykinesia and other parkinsonian symptoms at all stages of the disease [45]. Usually the therapeutic effectiveness lasts over years (so far, good results have been reported in patients treated for up to 8 years). Parlodel can be given either alone or - at both early and advanced stages – combined with other antiparkinsonian drugs. Combination with levodopa treatment results in enhanced antiparkinsonian effects, often making possible a reduction of the levodopa dosage [43]. Parlodel 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 [49,121].

Parlodel 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 [107,108].

5.2 Pharmacokinetic properties

Absorption

Parlodel is well absorbed after oral administration [75]. When tablets or standard capsules are administered to healthy volunteers, the absorption half-life is 0.2 to 0.5 hours, and peak plasma levels of bromocriptine are reached within 1 to 3 hours [73-75]. An oral dose of 5 mg of bromocriptine results in a C_{max} of 0.465 ng/mL [160]. The prolactin-lowering effect begins within 1 to 2 hours of ingestion, reaches its maximum, i.e. a reduction of prolactin in the plasma by more than 80%, within 5 to 10 hours and remains close to maximum for 8 to 12 hours [74].

With Parlodel SRO capsules, a form designed for once-a-day administration, peak plasma levels are reached within 7 to 10 hours, and the maximal inhibitory effect on prolactin secretion, similar in magnitude to that achieved with tablets or standard capsules, occurs within 10 to 17 hours after the ingestion. As the period of time during which plasma concentrations higher than 50% of the maximal level are maintained for about 14.5 hours (compared with 3.5 hours with standard capsules), the duration of the prolactin-lowering effect is prolonged [115-117].

Distribution

With single-dose administration the bioavailability of SRO capsules relative to the standard capsules is more than 90%. Under steady-state conditions, a slight reduction in bioavailability (to about 80%) is observed, but there is no loss of therapeutic effectiveness. Plasma protein binding is 96% [76].

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 [81]. It shows a high affinity for CYP3A and hydroxylations at the proline ring of the

cyclopeptide moiety constitute a main metabolic pathway [81,160]. 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 microM. 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 [160].

Elimination

The elimination of the parent drug from plasma is biphasic, with a terminal half-life of about 15 hours (range 8 to 20 hours) [114]. Parent drug and metabolites are almost completely excreted via the liver [81], only 6% being eliminated via the kidney [72].

Characteristics in patients

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 Parlodel (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 [52,133-154,164].

Effects in pre-clinical studies were observed only at exposures considered sufficiently (25 times) in excess of the maximum human exposure indicating little relevance to clinical use [164].

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 [164].

6 Pharmaceutical particulars

6.1 List of excipients

Tablets 2.5 mg

2.5 mg bromocriptine (present as 2.87 mg mesylate):

One tablet contains as excipients silica colloidal anhydrous, disodium edetate, magnesium stearate maleic acid, maize starch and lactose.

Capsules 5 mg, 10 mg

5 mg bromocriptine (present as 5.74 mg mesylate) and 10 mg bromocriptine (present as 11.47 mg mesylate):

The 5 mg and the 10 mg capsule contain as excipients silica colloidal anhydrous, magnesium stearate, maleic acid, maize starch dried and lactose.

SRO capsules 2,5 mg, 5 mg, 10 mg

2.5 mg bromocriptine (present as 2.87mg mesylate), 5 mg bromocriptine (present at 5.74 mg mesylate) and 10 mg bromocriptine (present at 11.47 mg mesylate):

The 2.5 mg, the 5 mg and the 10 mg capsules contain as excipients silica colloidal anhydrous, cetylpalmitate; magnesium stearate, maleic acid, maize starch dried, hydroxypropylmethylcellulose.

Information might differ in some countries.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Formulation- and container-specific.

Information might differ in some countries.

6.4 Special precautions for storage

Tablets

Store below 25°C. Protect from light.

Capsules / SRO capsules

Store below 25°C.

Information might differ in some countries.

Parlodel/Parlodel SRO must be kept out of the reach and sight of children.

6.5 Nature and contents of container

Formulation- and country-specific.

Information might differ in some countries.

This is a non-referenced document.