# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

PARLODEL 5mg Hard Capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Bromocriptine Mesilate equivalent to bromocriptine 5 mg.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Capsule, hard
Hard gelatin capsules with light blue cap and white opaque body printed “5mg” in ink on one side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

**Parkinson’s Disease:**
In the treatment of idiopathic Parkinson's disease. PARLODEL has been used both alone and in combination with levodopa in the management of previously untreated patients and those disabled by “on/off” phenomena. PARLODEL has been used with occasional benefit in patients who do not respond or are unable to tolerate levodopa and those whose response to levodopa is declining.

**Prolactinomas:**
In a number of specialised units, patients who have been shown to have prolactin secreting adenomas have been treated successfully with PARLODEL. In particular PARLODEL can be considered as a first choice of treatment in patients with macroadenomas and as an alternative to the surgical procedure transsphenoidal hypophysectomy in patients with microadenomas.

**Acrolmegaly:**
PARLODEL has been used in a number of specialized units as an adjunct to surgery and/or radiotherapy to reduce circulating growth hormone levels in the management of acromegalic patients.

**Hyperprolactinaemia:**
For the treatment of hyperprolactinaemia in patients with hypogonadism and/or galactorrhoea.

**Menstrual cycle disorders, female infertility:**
In the treatment of female infertility associated with normal basal gonadotrophin levels and hyperprolactinaemia (Absolute or relative).

**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.

### 4.2 Posology and method of administration

**Posology**

*Adults*

PARLODEL should always be taken during a meal.

A number of disparate conditions are amenable to treatment with PARLODEL, 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 PARLODEL. The following scheme is suggested.

Initially half a tablet (1.25mg) at bedtime, increasing after 2 to 3 days to 2.5mg at bedtime. Dosage may then be increased by half to one tablet 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.

1. Hypogonadism/galactorrhoea syndrome/infertility
Introduce PARLODEL 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 dosage is 2.5mg twice daily.

3. Prolactinomas
Introduce PARLODEL 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 sixhourly, 5mg six-hourly. Patients have responded to up to 30mg daily.

4. Acromegaly
Introduce PARLODEL 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. The final dose is usually 20 -60 mg daily.

5. Parkinson's disease
P ARLODEL should be introduced gradually.
Week 1: 1.25mg at bedtime.
Week 2: 2.5mg at bedtime.
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 10 and 40mg daily. In patients already receiving levodopa the dosage of this drug may be gradually decreased, while the dosage of PARLODEL is increased until the optimum balance is determined.

*Paediatric population*
PARLODEL should not be used children less than 15 years of age.

*Older people*

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

**Method of administration**

Oral.

**4.3 Contraindications**

- Hypersensitivity to bromocriptine or to any of the excipients of Parlodel Tablets *(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.
- 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**

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.

A few cases of gastrointestinal bleeding 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. Furthermore, a reduction of dosage or termination of therapy may be considered.

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 Parlodel; dose reduction/tapered discontinuation should be considered if such symptoms develop

**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 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 porlactin-secreting adenomas treated with Parlodel, cerebrospinal fluid rhinorrhea has been observed. The data available suggest that this may result from shrinkage of invasive tumours.

**Use in parkinsonian patients**

Among patients on Parlodel 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 Parlodel therapy should be contemplated.

In a few patients treated on Parlodel, 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. Parlodel medication should be withdrawn if fibrotic changes in the retroperitoneum are diagnosed or suspected.

**Children and Adolescents ( aged 7 to 17)**

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.

**Older people**

Clinical studies for Parlodel 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 taking Parlodel 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.

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

**4.5 Interaction with other medicinal products and other forms of interactions**

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 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.

The tolerability to PARLODEL may be reduced by alcohol.

**4.6 Fertility, 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 indicated that Parlodel, administered during pregnancy, does not adversely affect its course or outcome.

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.

**Fertility**

Fertility may be restored by treatment with Parlodel. 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 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 4.4 Special warnings andspecial precautions for use)*.

**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

| | |
|---|---|
| **Psychiatric disorders**<br>Uncommon<br>Rare:<br>Very rare: | <br>Confusion, psychomotor agitation, Hallucinations,<br>Psychotic disorders, Insomnia<br>Libido increased, hypersexuality, pathological gambling, compulsive spending or buying, binge eating, compulsive eating |
| **Nervous system disorders**<br>Common:<br>Uncommon:<br>Rare:<br>Very rare: | Headache, Drowsiness, Dizziness<br>Dyskinesia<br>Somnolence, Paresthesia<br>Excess daytime somnolence, Sudden onset of sleep |
| **Eye Disorders**<br>Rare: | Visual disturbance, Vision blurred |
| **Ear and Labyrinth disorders**<br>Rare: | Tinnitus |
| **Cardiac disorders**<br>Rare:<br><br>Very rare: | <br>Pericardial effusion, constrictive pericarditis, Tachycardia, Bradycardia, Arrhythmia<br>Cardiac valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion), cardiac valve fibrosis |
| **Vascular disorders**<br>Uncommon:<br><br>Very Rare : | <br>Hypotension, Orthostatic hypotension (very rarely leading to syncope)<br>Reversible pallor of fingers and toes induced by cold (especially in patients with history of Raynaud's phenomenon. |
| **Respiratory, thoracic and mediastinal disorders**<br>Common:<br>Rare: | <br>Nasal congestion<br>Pleural effusion, Pleural fibrosis, Pleurisy, Plumonary fibrosis, Dyspneoa |
| **Gastrointestinal disorders**<br>Common:<br>Uncommon:<br>Rare: | <br>Nausea, Constipation, Vomiting<br>Dry Mouth<br>Diarrhoea, Abdominal pain, Retroperitoneal fibrosis, Gastrointestinal ulcer, Gastrointestinal haemorrhage |
| **Skin and subcutaneous tissue disorders**<br>Uncommon: | Allergic skin reactions, Hair loss |
| **Musculoskeletal and connective tissue disorders** | Leg cramps |

| | |
|---|---|
| Uncommon: | |
| **General disorders and administration site conditions** | Fatigue |
| Uncommon: | Peripheral oedema |
| Rare: | A syndrome resembling Neuroleptic Malignant Syndrome on abrupt withdrawal of Parlodel |
| Very Rare: | |

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 special 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 Parlodel (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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

**4.9 Overdose**

**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.

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.

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

Endocrinological Properties

PARLODEL inhibits the secretion of the anterior pituitary hormone prolactin without affecting normal levels of other pituitary hormones.However, PARLODEL 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, PARLODEL 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), PARLODEL 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 PARLODEL. In addition, PARLODEL does not impair the puerperal involution of the uterus and does not increase the risk of thrombo-embolism.

PARLODEL 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 - PARLODEL has a beneficial effect on clinical symptoms and on glucose tolerance.

PARLODEL improves the clinical symptoms of the polycystic ovary syndrome by restoring a normal pattern of LH secretion.

Neurological properties

Because of its dopaminergic activity, PARLODEL, 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 PARLODEL can in this condition restore the neurochemical balance within the striatum.

Clinically, PARLODEL 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). PARLODEL 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. 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.

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.

**5.2 Pharmacokinetic properties**

**Absorption**
Following oral administration, PARLODEL is well absorbed. When using tablets or standard capsules 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 $C_{max}$ of 0.465 ng/mL.

**Distribution**
The prolactin-lowering effect sets in within 1 - 2h after ingestion, reaches its maximum, i.e. a reduction of prolactin in the plasma by more than 80%, within 5 - 10h 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 clerance 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 PARLODEL 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**

Not applicable.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

**Capsule contents**

Lactose monohydrate
Maize starch
Maleic acid
Colloidal anhydrous silica
Magnesium stearate

**Capsule shell**

Gelatin
Titanium dioxide (E171)
Indigo carmine (E132)

**Printing Ink**

Iron Oxide Black (E172)
Shellac
Propylene Glycol

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

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

**6.5 Nature and contents of container**

AL/PVC/PVDC blister strips containing 30 or 100 capsules.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Mylan IRE Healthcare Limited
Unit 35/36
Grange Parade
Baldoyle Industrial Estate
Dublin 13
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA2010/042/002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

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