NOVARTIS

Parlodel®

Composition

Active substance
Bromocriptine, as bromocriptine mesilate

Excipients
Tablets
Tableting excipients

Capsules containing 5 mg
Colouring agent E 132, capsule excipients

Capsules containing 10 mg
Capsule excipients

Pharmaceutical form and quantity of active substance per unit

Scored tablets containing 2.5 mg
Capsules containing 5 or 10 mg

Indications / Potential uses

Menstrual cycle disorders and female infertility
Prolactin-induced hyperprolactinaemic and apparently normoprolactinaemic conditions
Amenorrhoea (with or without galactorrhoea), oligomenorrhoea; luteal-phase deficiency; drug-induced hyperprolactinaemic disorders (e.g. due to certain psychotropic or antihypertensive agents).

Prolactin-independent female infertility
Polycystic ovary syndrome; anovulatory cycles (to supplement anti-oestrogens, e.g. clomifene).

Hyperprolactinaemia in males
Prolactin-induced hypogonadism (oligospermia, loss of libido, impotence)

Prolactinomas
Conservative treatment of pituitary micro- or macroprolactinomas; presurgical reduction of tumour size to facilitate resection; postsurgical inhibition of persistent hyperprolactinaemia

Acromegaly
As an adjunct to other therapy; as an alternative to surgery or radiotherapy in special cases

Inhibition of lactation for medical reasons
Prevention or suppression of puerperal lactation; prevention of lactation following abortion; treatment of incipient puerperal mastitis.
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.

Other indications
There is insufficient evidence of efficacy in the treatment of premenstrual symptoms and benign breast disease. Use of Parlodel is not recommended in the treatment of patients with these conditions.

Parkinson's disease
All stages of idiopathic and postencephalitic Parkinson's disease, either as monotherapy or in combination with other antiparkinsonian drugs.

Dosage and Administration

Parlodel should always be taken with food.

Disorders of the menstrual cycle and female infertility
1.25 mg (½ tablet) two or three times daily; if this proves inadequate, gradually increase to 2.5 mg (one tablet) two or three times daily. Treatment should be continued until the menstrual cycle is normalized and/or ovulation occurs and, if necessary, over several cycles to prevent relapse.

Hyperprolactinaemia in males
1.25 mg (½ tablet) two or three times daily, gradually increasing to 5–10 mg (2–4 tablets) daily.

Prolactinomas
1.25 mg (½ tablet) two or three times daily, gradually increasing to several tablets or capsules daily as required for control of plasma prolactin.

Acromegaly
1.25 mg (½ tablet) two or three times daily, gradually increasing to 10–20 mg daily depending on clinical response and adverse effects.

Incipient puerperal mastitis
Same dosage as for inhibition of lactation (see below). An antibiotic may be added to the regimen as required.

Inhibition of lactation for medical reasons
1.25 mg (½ tablet) with the morning meal and again with the evening meal on the first day of treatment, followed by 2.5 mg (one tablet) twice daily for 14 days. To prevent the onset of lactation, treatment should be instituted within a few hours after parturition or abortion, but not before vital signs have stabilized. Slight milk secretion occasionally occurs 2–3 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 optimum tolerability, treatment should be started at a small dose of 1.25 mg (½ tablet) daily. During the first week the dose should preferably be taken in the evening. The daily dosage should then be increased by 1.25 mg at weekly intervals until the lowest effective dose is established; it should be given in 2 or 3 divided doses. If a satisfactory therapeutic response is not achieved within 6–8 weeks, further dose increases of 2.5 mg/day at weekly intervals may be attempted.
If adverse effects occur during the dose-finding phase the daily dose should be reduced temporarily for at least one week. It may be increased again as soon as the adverse effects disappear.
In patients exhibiting levodopa-induced motor disturbances, the dosage of levodopa should be reduced before introducing Parlodel. Further gradual reduction of the levodopa dosage may be possible once a satisfactory response to Parlodel has been obtained, with the possibility of complete withdrawal of levodopa in some cases.
The total daily dose in monotherapy and combination therapy should not exceed 30 mg bromocriptine. The adverse pleuropulmonary effects mentioned under **Warnings and Precautions** were reported in connection with long-term treatment in which high doses exceeding 20 mg daily were given for 6 months.

Children and adolescents (between 7 and 18 years of age)

	Dosage / use in children over 7 years of age	Maximum recommended daily dose	
		7–12 years	13–18 years
Prolactinomas	1.25 mg (½ tablet) twice or three times daily; increase gradually to several tablets or capsules per day, as needed, to control plasma prolactin.	5 mg	10 mg
Acromegaly	Initially 1.25 mg (½ tablet) twice or three times daily; depending on clinical response and desired efficacy, increase gradually to several tablets or capsules per day.	10 mg	10 mg

Elderly patients
In general, dose selection for elderly patients should be cautious, starting at the lowest dose in the dose range in question, in view of the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Contraindications

Hypersensitivity to bromocriptine, to any of the excipients (see **Composition**) or to other ergot alkaloids.
Inadequately controlled arterial hypertension, hypertensive states of pregnancy (including eclampsia, preeclampsia and pregnancy-related hypertension). Postpartum and puerperal hypertension. Coronary heart disease and other severe cardiovascular disorders.
Symptoms of severe psychiatric disorder and/or a history of severe psychiatric disorder.
History of cerebrovascular accident; arterial occlusive disease, Raynaud's phenomenon, temporal arteritis and nicotine abuse.
Peptic ulcers and gastrointestinal bleeding.
Severe hepatic dysfunction and sepsis.
Treatment with methylergometrine or other ergot alkaloids. In addition, Parlodel should not be given concomitantly with certain cytochrome P450 inhibitors (see **Interactions**).

Warnings and Precautions

Infertility may be reversed by treatment with Parlodel. Women of childbearing age who do not wish to conceive should therefore be advised to use a reliable method of contraception.
Treatment should be discontinued immediately if vasospastic or thrombotic symptoms, persistent headache or any other sign of CNS toxicity develop.
There have been a few reports of gastrointestinal bleeding and gastric ulcer. In the event of such reactions, Parlodel should be discontinued. Patients presenting with an active ulcer or with a history of ulcer should be closely monitored during treatment with Parlodel.
Caution is required when using Parlodel in patients with severe renal impairment.
Hypotensive reactions due to a fall in blood pressure occasionally occur during the first few days of treatment and may cause decreased mental alertness (see **Effects on ability to drive and use machines**).
Parlodel has been associated with drowsiness and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. There have been very rare reports of sudden onset of sleep during daily activities, without warning signs. Patients must be informed of this. Dosage reduction or termination of treatment must be considered if drowsiness or episodes of sudden sleep onset occur (see **Effects on ability to drive and use machines**).
In a few instances pleural effusions, pleural and pulmonary fibrosis, retroperitoneal fibrosis and constrictive pericarditis have been reported in parkinsonian patients receiving long-term treatment with high-doses of Parlodel. Fibrotic changes cannot be ruled out even when Parlodel is used in indications other than Parkinson's disease.
Parkinsonian patients with a history of such conditions should not be treated with Parlodel.
Unexplained pleuropulmonary changes should therefore be investigated, and consideration given to discontinuing Parlodel. It is advisable to bear in mind the relevant manifestations of retroperitoneal fibrosis (e.g. back pain, peripheral oedema, renal dysfunction) in order to ensure detection of this condition at its early, reversible stage. Parlodel should be withdrawn if retroperitoneal fibrotic changes are diagnosed or suspected. The pleuropulmonary fibrotic changes that have been observed may be associated with fibrotic thickening of the heart valves, as has been the case in patients treated with other ergot alkaloid derivatives.
There have been reports of pathological / compulsive gambling, increased libido and hypersexuality in patients who have used dopamine agonists (including Parlodel) to treat Parkinson's disease. These adverse effects generally subsided following dose reduction or withdrawal of treatment.

Postpartum and puerperal use
In rare cases, serious adverse drug reactions – such as hypertension, myocardial infarction, seizures, stroke and psychiatric disorders – have been reported in postpartum women treated with Parlodel for the inhibition of lactation.
In some patients, seizure or stroke was preceded by severe headache and/or transient visual disturbances. Although there is no conclusive evidence of a causal connection, regular blood pressure monitoring is essential in these patients and in patients receiving Parlodel in other indications. In the event of hypertension, severe, increasing or persistent headache (with or without visual disturbances) or signs of CNS toxicity, treatment should be discontinued immediately and the patient's condition assessed without delay.
Particular caution is required in patients either recently treated with – or concurrently using – drugs that can alter blood pressure, e.g. vasoconstrictors such as sympathomimetics or ergot alkaloids, including ergometrine or methylergometrine. Concomitant use of such drugs in the puerperium is not recommended.
Parlodel tablets/capsules contain lactose. Patients with rare hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take Parlodel.

Hyperprolactinaemia (micro- and macroadenoma) / Infertility / Amenorrhoea / Galactorrhoea
Non-hyperprolactinaemic women should be given Parlodel at the lowest dose necessary to achieve relief of symptoms in order to avoid the possibility of **hypo**prolactinaemia, with the risk of luteal function impairment.
Since patients with pituitary macroadenoma resulting from compression or destruction of pituitary tissue may also suffer from hypopituitarism, introduction of Parlodel should be preceded by a thorough examination of pituitary function and appropriate substitution therapy. In patients with secondary adrenocortical insufficiency, corticosteroid substitution is essential.
Tumour growth must be closely monitored in patients with pituitary macroadenoma. Surgery should be considered at the first sign of progression.
Close monitoring is necessary in adenoma patients who become pregnant during Parlodel therapy. Prolactin-secreting adenomas may grow during pregnancy. In such patients Parlodel therapy often results in tumour shrinkage and rapid improvement of visual field deterioration. In severe cases compression of the optic or other cerebral 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 improvement of the visual field. In some patients, however, secondary visual field impairment may develop despite normalized prolactin levels and tumour shrinkage. This is due to mechanical stress exerted on the optic chiasm, which is pulled down into the now partially empty sella when the tumour shrinks. In such cases the visual field defect may improve on reduction of the dose of Parlodel due to a rise in prolactin levels and some renewed tumour growth. Regular monitoring of visual fields in patients with macroprolactinoma is therefore indicated in order to allow early recognition of secondary visual field loss due to chiasmal herniation and adaptation of the dose of Parlodel, if necessary.
Cerebrospinal fluid rhinorrhoea has been observed in some patients with prolactin-secreting adenomas treated with Parlodel. The available data suggest that this may result from shrinkage of invasive tumours.

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Interactions
Bromocriptine is both a substrate and an inhibitor of cytochrome P450 (CYP3A). Caution is therefore required when co-administering drugs which are strong inhibitors and/or substrates of this enzyme: azole antifungals, HIV protease inhibitors. Concomitant use of macrolide antibiotics (e.g. erythromycin, clarithromycin, troleandomycin, spiramycin or josamycin), resulted in elevated plasma levels of bromocriptine.
Concomitant use of bromocriptine and octreotide in acromegalic patients resulted in elevated plasma levels of bromocriptine, and an increased incidence of adverse effects is likely.
Concomitant treatment with methylergometrine or other ergot alkaloids should be avoided due to the increased risk of adverse effects (see **Contraindications**).
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 of Parlodel may be reduced by alcohol.

Pregnancy and Lactation
Data on exposure in pregnant women have shown no adverse effects of bromocriptine on pregnancy or on the health of the fetus or neonate. Data from studies are not available.
Animal studies have not shown any direct or indirect toxicity affecting pregnancy, embryonic development, fetal development and/or postnatal development (see **Preclinical data**).
Caution is required when using the product during pregnancy.

Pregnancy
Women wishing to conceive should be told to stop taking Parlodel – and all other drugs – as soon as pregnancy is confirmed, unless there is a medical reason for continuing treatment. No increased incidence of abortion has been reported following withdrawal of Parlodel.
Clinical experience shows that administration of Parlodel does not adversely affect the course or outcome of pregnancy.
Women with a pituitary adenoma who become pregnant and discontinue Parlodel must be closely monitored throughout the pregnancy. Treatment may be resumed, or surgery considered, if evidence of pronounced prolactinoma enlargement (e.g. headache or visual field deterioration) is found.

Lactation
Parlodel inhibits lactation and should therefore not be given to women who are breastfeeding unless there are medical reasons for its use (see **Indications / Potential uses**).

Effects on ability to drive and use machines
Hypotensive reactions due to a fall in blood pressure may occasionally occur during the first few days of treatment, causing reduced alertness, and particular caution is therefore necessary when driving a vehicle or operating machinery.
Patients being treated with Parlodel who have experienced drowsiness and/or episodes of sudden sleep onset must be advised not to drive or engage in activities such as operating machines since they may endanger themselves or others. Patients should be informed of this problem, and should avoid such activities until the extent to which they are affected by the symptoms in question has become sufficiently clear.

Adverse effects
Frequency
Very common (≥ 10%), common (≥ 1% to < 10%), uncommon (≥ 0.1% to < 1%), rare (≥ 0.01% to < 0.1%), very rare (< 0.01%, including isolated reports).

Psychiatric disorders
Uncommon: Depressive mood, confusion, psychomotor agitation, hallucinations, anxiety.
Rare: Disturbed sleep, psychoses.
Very rare: Increased libido, hypersexuality, pathological / compulsive gambling (see **Warnings and Precautions**).

Nervous system disorders
Common: Headache, dizziness, fatigue.
Uncommon: Dyskinesia
Rare: Paraesthesia, drowsiness.
Very rare: Excessive daytime drowsiness, episodes of sudden sleep onset (see **Warnings and Precautions**).

Eye disorders
Rare: Visual disturbances, blurred vision.

Ear and labyrinth disorders
Rare: Tinnitus.

Cardiac disorders
Rare: Pericardial effusion, constrictive pericarditis, arrhythmia, tachycardia, bradycardia.
Very rare: Cardiac valvular fibrosis.
Parlodel has been associated with aggravation of angina pectoris.

Vascular disorders
Uncommon: Hypotension, orthostatic hypotension (very rarely leading to syncope).
Very rare: Pallor of the fingers and toes induced by cold (particularly in patients with a history of Raynaud's phenomenon).

Respiratory disorders
Common: Nasal congestion.
Rare: Pleural effusion, pleural and pulmonary fibrosis, pleurisy, dyspnoea.

Gastrointestinal disorders
Common: Nausea, vomiting, constipation.
Uncommon: Dry mouth.
Rare: Diarrhoea, abdominal pain, retroperitoneal fibrosis, peptic ulcer, gastrointestinal haemorrhage.

Skin disorders
Uncommon: Allergic skin reactions, hair loss.

Musculoskeletal disorders
Uncommon: Leg cramps.

Kidney and urinary tract
Uncommon: Urinary incontinence.

General disorders
Rare: Peripheral oedema.
Very rare: Occurrence of a syndrome, resembling neuroleptic malignant syndrome, when Parlodel is abruptly withdrawn.
There have been rare reports of hypertension, myocardial infarction, seizures, stroke or psychiatric disorders (in postpartum women treated with Parlodel to prevent lactation; see **Warnings and Precautions**).

Overdose
Signs and symptoms
No fatalities have been reported among patients taking an overdose of Parlodel alone. The highest single oral dose ingested to date has been 325 mg. The symptoms reported were nausea, vomiting, dizziness, hypotension, orthostatic hypotension, tachycardia, light-headedness, drowsiness, lethargy and hallucinations.

Management
Administration of activated charcoal is recommended in case of overdose. Gastric evacuation may be considered if only a very short time has elapsed since oral ingestion. Management of acute intoxication is symptomatic. Metoclopramide may be given to control vomiting and hallucinations.

Properties and Actions
Dopamine agonist
ATC code: N04BC01

Prolactin inhibitor
ATC code: G02CB01

Mechanism of action / Pharmacodynamics
Effect on the adenohypophysis
Parlodel inhibits secretion of the anterior pituitary hormone, prolactin, without affecting normal levels of other pituitary hormones, although it does reduce elevated levels of growth hormone (GH) in patients with acromegaly. These effects are due to stimulation of dopamine receptors.
Following childbirth prolactin is necessary for the initiation and maintenance of lactation. At other times, however, 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. Normalization of the menstrual cycle and ovulation occurs in patients with amenorrhoea and/or anovulation (with or without galactorrhoea).
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 puerperal involution of the uterus or increase the risk of thromboembolism.
Parlodel has also been shown to arrest the growth or reduce the size of prolactin-secreting pituitary adenomas (prolactinomas).
In acromegalic patients Parlodel has a beneficial effect on clinical symptoms and glucose tolerance, as well as lowering plasma GH and prolactin.
Parlodel induces a normal pattern of luteinizing hormone secretion, thereby improving the clinical symptoms in polycystic ovary syndrome.

Dopaminergic effects
On account of its dopaminergic activity, Parlodel is effective in the treatment of Parkinson's disease, although normally at higher doses than those given for its endocrinological indications. By stimulating the dopamine receptors it reverses the specific nigrostriatal dopamine deficiency that characterizes this condition.
Clinically, Parlodel improves tremor, rigidity, bradykinesia and other manifestations of the disease in all stages. Its therapeutic effect is normally maintained over long periods (up to 8 years among cases so far reported). Parlodel can be given alone in both early- and advanced-stage disease, or in combination with other antiparkinsonian drugs. Combination with levodopa results in an enhanced antiparkinsonian effect and frequently enables the levodopa dose to be reduced. This is of particular benefit in levodopa patients experiencing deteriorating response or complications such as abnormal involuntary movements (choreoathetoid dyskinesia and/or painful dystonia), end-of-dose failure or "on-off" phenomenon.
Parlodel improves the depressive symptoms often observed in parkinsonian patients. This is due to its specific antidepressant properties, as substantiated by controlled studies in non-parkinsonian patients with endogenous or psychogenic depression.

Pharmacokinetics
Absorption
Parlodel (bromocriptine) is rapidly and readily absorbed following oral administration. The absorption half-life in healthy volunteers is 0.2–0.5 hours. A 5 mg oral dose of bromocriptine results in a C_{max} of 0.465 ng/ml.

Distribution
Plasma protein binding is 96%. Peak plasma levels are attained within 1–3 hours. The prolactin-lowering action begins to take effect 1–2 hours after ingestion, peaks (i.e. brings about reduction of > 80% in plasma prolactin) after 5–10 hours and is maintained for 8–12 hours.

Metabolism
Bromocriptine is almost completely metabolized in the liver. The metabolite profile is complex. Bromocriptine shows a high affinity for CYP3A4, and hydroxylation at the proline ring constitutes a major metabolic pathway.

Elimination
Bromocriptine is extensively metabolized, and the parent drug and metabolites are eliminated via the bile; only 6% of the drug is eliminated via the kidneys. The elimination half-life is 3-4 hours for the parent substance and 50 hours for the inactive metabolites.

Pharmacokinetics in special patient populations
There is no evidence that the pharmacokinetic properties or tolerability of Parlodel are altered in elderly patients.
However, in patients with impaired hepatic function elimination may be slower, giving rise to higher plasma levels and making dose adjustment necessary.

Preclinical data
Pre-clinical data for Parlodel (bromocriptine) reveal no evidence of any special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, genotoxicity, mutagenicity, carcinogenic potential, or reproductive toxicity (side effects in preclinical studies were observed only at doses 25 times higher than the maximum doses in humans).
In preclinical studies in rats, endometrial carcinoma was also observed only in association with high doses. Carcinomas are considered to be due to the species-specific sensitivity of the test animals to the pharmacological activity of bromocriptine.

Other information
Shelf-life
Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage
See folding box.

Pack sizes
Country specific pack sizes

Manufacturer
See folding box

Information last revised
May 2009

Approval date (text)
16 July 2009

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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