

PARLODEL[®]
(bromocriptine mesylate)

NAME OF THE MEDICINE

Active ingredient: Bromocriptine mesylate

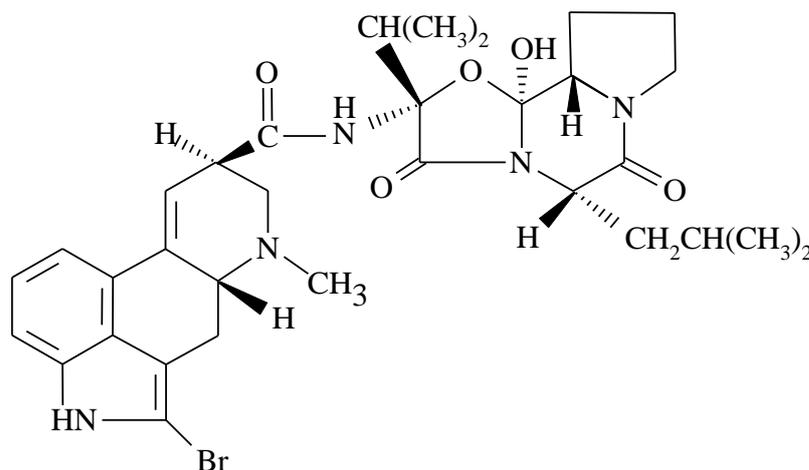
Chemical names: Ergotaman-3',6',18-trione, 2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)-, (5'α)-;

2-Bromoergocryptine monomethanesulphonate;

2-bromo-α- ergocryptine mesylate;

CAS Number: 22260-51-1

Chemical structure:



Chemical Formula: $C_{32}H_{40}BrN_5O_5CH_4O_3S$

Molecular weight: 750.7 (mesylate salt); 654.5 (free base)

DESCRIPTION

Bromocriptine mesylate is a peptide ergot alkaloid, poorly soluble in water (<0.1% at 20 - 25°C). Freely soluble in methanol. Solubility in ethanol (70% v/v) is 75%.

Parlodel tablets and capsules contain bromocriptine mesylate.

Excipients

Tablets: magnesium stearate, silica colloidal anhydrous, maize starch, disodium edetate, maleic acid, and lactose.

Capsules: magnesium stearate, silica colloidal anhydrous, maize starch, maleic acid, lactose, gelatin, and titanium dioxide. The 5 mg capsules also contain shellac, red iron oxide CI77491, and indigo carmine CI73015.

PHARMACOLOGY

Parlodel has a pharmacological spectrum unlike that of most classical ergot compounds, having no uterotonic and little vasoconstrictor activity. Its principal effects derive from dopaminergic receptor stimulant activity. It inhibits prolactin secretion and the effect can be demonstrated after single or repeated oral administration of the drug. Moreover, the effect is relatively specific in that doses necessary to produce inhibition of prolactin secretion do not interfere with release of gonadotrophins or thyrotrophin. However, Parlodel elevates growth hormone for a few hours after each dose in normal or diabetic persons. This may not be reflected by an elevation of basal levels during chronic administration. However, it may suppress the elevated growth hormone levels of acromegalic patients.

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

Pharmacological investigations in rodent brains show that, in addition to its effects at the hypothalamic - pituitary axis, Parlodel exerts CNS activity primarily via post-synaptic dopamine receptor activation in the corpus striatum. Parlodel can, therefore, be used in Parkinson's disease.

Clinical Effects

Hyperprolactinaemia:

Prolactin secretion is controlled by the hypothalamic tuberoinfundibular dopaminergic neurone system, which releases either dopamine or a prolactin inhibiting factor (PIF) into the hypothalamohypophyseal portal system to suppress the secretion of prolactin by the pituitary. Parlodel has been shown to mimic this action of dopamine on the pituitary prolactin cells and to act also at the hypothalamic level.

Prolactin is the crucial hormone for the preparation of the mammary gland for lactation and for the initiation and maintenance of milk secretion. During pregnancy and after childbirth (through suckling stimuli) prolactin levels are elevated. Reduction of circulating prolactin levels will thus prevent or suppress lactation. In some conditions, the secretion of prolactin may become elevated in situations unconnected with pregnancy and childbirth. Such nonphysiological hyperprolactinaemia may mimic the postpartum situation by inducing amenorrhoea and/or lactation (galactorrhoea). In healthy women, prolactin does not seem to be involved in the normal cycle of gonadotrophin secretion and ovarian functions but, in conditions favouring prolactin secretion, the regular cyclic gonadotrophin and gonadal steroid secretion become attenuated and are eventually suppressed. Bromocriptine, through its dopaminergic activity, returns prolactin levels towards normal and either enhances the release of gonadotrophic hormones or restores the sensitivity of the ovary to gonadotrophic stimulation. Hence, galactorrhoea and amenorrhoea are interrupted and menses return.

Apparent regression in tumour size has been documented in a number of patients with prolactin- secreting adenomas.

Acromegaly:

In about 50% of acromegalic patients, Parlodel reduced the elevated growth hormone level to half of pretreatment levels or below. In acromegaly, Parlodel has a beneficial effect on clinical symptoms such as headaches, sweating, acral features, ring and shoe size, hypertension and glucose tolerance, although this may not be clearly correlated with a change in growth hormone levels. Overall, about 50% of patients have shown clinical improvement to Parlodel. Of the remaining patients, many have a significant fall in growth hormone levels not associated with improvements in clinical symptoms.

There are no data on the effect of bromocriptine on tumour size in acromegaly or on the functional capacity of the tumour. There is some evidence that the acromegalic process resumes on cessation of therapy.

Parkinson's disease:

This disorder is characterised by progressive deficiency in dopamine synthesis in the substantia nigra. Parlodel produces its therapeutic effect by directly acting on dopamine receptors in the corpus striatum, mimicking an increased supply of endogenous dopamine. In clinical studies, Parlodel has been as effective as levodopa alone or in combination with decarboxylase inhibitors. Combination with levodopa may allow a reduction in the dosage of either compound. Bromocriptine is useful in patients with a deteriorating response to levodopa or suffering from the "on-off" phenomena. Parlodel may be given alone in mild, early cases or in combination with anticholinergic drugs and/or other antiparkinson drugs. However, data are not yet sufficient to evaluate the role of Parlodel in treating early Parkinsonism.

Pharmacokinetics

Absorption:

In rats, rabbits, monkeys and man, Parlodel has been shown to be rapidly absorbed after oral administration. In man, the absorption half-life from the oral tablet formulation determined by radioimmunoassay is approximately 0.3 hours. About 7% of the dose reaches the systemic circulation unchanged. This is due to a high hepatic extraction rate and first pass metabolism. The studies were done on fasting subjects. There are no studies on the effect of food on bioavailability but clinical experience suggests that absorption is satisfactory when bromocriptine is taken in the recommended way (i.e. with meals).

Distribution:

Two hours after oral administration of ³H-bromocriptine in the rat, radioactivity was found in all organs, with highest values in the liver, stomach and intestine. Plasma protein binding amounts to 96%.

Metabolism:

In man, the substance is extensively metabolised by the liver. Only traces of the unchanged compound were found in urine, with 2 major metabolites. Unchanged drug represents about 10-15% of peak levels of radioactivity in plasma, measured after single doses of labelled drug. It is not known whether the metabolites are pharmacologically active in man. However the two main urinary metabolites, 2-bromolysergic acid and 2-bromoisolysergic acid have negligible pharmacological activity in animals.

Excretion:

The active parent drug and the metabolites are excreted primarily via the liver into the bile; only 6% is eliminated via the kidney. After single oral doses, the mean elimination half-life from plasma varies from 2 to 8 hours for the parent drug and 50 to 73 hours for the metabolites.

On repeated dosing, bromocriptine accumulates to the extent that plasma concentrations may be about twice those observed after single doses. Although there are no data on the accumulation of metabolites, their much longer half-life indicates that steady state plasma concentrations, which are about ten times greater than those observed after single doses, should be reached in approximately 10 days.

INDICATIONS

- Prevention of onset of lactation in the puerperium for clearly defined medical reasons. Therapy should be continued for 14 days to prevent rebound lactation. Parlodel should not be used to suppress established lactation.
- Treatment of hyperprolactinaemia where surgery and/or radiotherapy are not indicated or have already been used with incomplete resolution. Precautions should be taken to ensure that the hyperprolactinaemia is not due to severe primary hypothyroidism. Where the cause of hyperprolactinaemia is a prolactin-secreting microadenoma or macroadenoma, Parlodel is indicated for conservative treatment; prior to surgery in order to reduce tumour size and to facilitate removal; after surgery if prolactin level is still elevated.
- Adjunctive therapy in the management of acromegaly when:
 - (1) The patient refuses surgery and/or radiotherapy
 - (2) Surgery and/or radiotherapy has been unsuccessful or full effects are not expected for some months
 - (3) A manifestation of the acromegaly needs to be brought under control pending surgery and/or radiotherapy.
- Idiopathic or post-encephalitic Parkinson's disease. It should be noted that data are not yet sufficient to evaluate the role of Parlodel in treating early Parkinsonism.

CONTRAINDICATIONS

- Hypersensitivity to bromocriptine or other ergot alkaloids, hypersensitivity to any other component of the formulations (see DESCRIPTION).
- Uncontrolled hypertension, toxæmia, hypertensive disorders of pregnancy (including eclampsia, pre-eclampsia or pregnancy-induced hypertension), hypertension postpartum and in the puerperium. For procedure during pregnancy see "Use in Pregnancy".
- Coronary artery disease and other severe cardiovascular conditions.
- Symptoms and/or history of serious psychiatric disorders.

PRECAUTIONS

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.

Use in Pregnancy (Category A)

Over 2,400 women are recorded as having taken bromocriptine during part of pregnancy. The reported incidence of congenital malformations and spontaneous abortions within this group of pregnancies did not exceed that generally reported in the population at large.

Postnatal development was studied in more than 900 children exposed to bromocriptine *in utero*. One hundred and five of these children were exposed throughout pregnancy. No specific pattern of abnormal postnatal development could be recognised.

In patients wishing to conceive however, Parlodel, like all drugs, should be discontinued when pregnancy is confirmed, unless there is a medical reason for continuing therapy.

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.

Fertility:

In patients being treated with Parlodel for hyperprolactinaemic conditions, fertility is commonly restored. The return of ovulation post-partum also may be hastened. Thus women who do not wish to conceive should take contraceptive measures in order to prevent an unintended pregnancy.

In women wishing to conceive, the cause of sterility and a search for pituitary adenoma should be made before starting Parlodel (bromocriptine) treatment. Pregnancy must be avoided if a significant or expanding pituitary adenoma is diagnosed. However, if pregnancy occurs in the presence of a pituitary adenoma and Parlodel treatment has 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 reinstated. In other cases, surgery may be considered appropriate.

In the absence of a significant or expanding pituitary adenoma and if the patient wishes to conceive, Parlodel should be stopped as soon as possible after conception.

Established pregnancy:

In cases of established pregnancy - as a precautionary measure - possible untoward effects of pituitary enlargement associated with pregnancy should be sought regularly, for instance, by checking the visual fields.

Use in Lactation

Since Parlodel prevents lactation, Parlodel should not be administered to mothers who wish to breast-feed.

Physiological lactation:

In rare cases, serious adverse reactions have been reported in postpartum women treated with Parlodel for the inhibition of lactation, including seizures, stroke, myocardial infarction, hypertension and psychic disorders. Seizures were not necessarily accompanied by the development of hypertension. An unremitting and often progressively severe headache, sometimes accompanied by visual disturbance (blurred vision and transient cortical blindness), often preceded by hours to days the occurrence of seizure and/or stroke. Most patients had shown no evidence of toxæmia during the pregnancy. Although the relationship of these adverse reactions to Parlodel administration is not certain, periodic monitoring of blood pressure is advisable in post-partum women receiving Parlodel for the inhibition of lactation as well as in patients treated for any other condition.

The use of Parlodel is contraindicated in patients with uncontrolled hypertension, coronary artery disease, toxæmia of pregnancy or symptoms and/or a history of serious psychic disorders.

Particular attention should be paid to patients who have recently received or are on concomitant therapy with other drugs that can alter the blood pressure, e.g. vasoconstrictors such as sympathomimetics or ergot alkaloids, including ergometrine. The concomitant use of these medications in the puerperium is not recommended.

Parlodel therapy for the inhibition of lactation should not be initiated until the vital signs have been stabilised and no sooner than four hours after delivery, as Parlodel is known to produce hypotension, and rarely hypertension, in some patients. Because the development of

hypertension may be delayed, the blood pressure should be monitored periodically during the first weeks of therapy. If hypertension, severe progressive or unremitting headache (with or without visual disturbance) or evidence of CNS toxicity develops, drug therapy should be discontinued and the patient should be evaluated promptly.

Use in patients with prolactin-secreting adenomas:

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.

In some patients with macroprolactinoma, secondary deterioration of the visual fields may develop despite normalised prolactin levels and tumour shrinkage. This 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 Parlodel dosage, while there is some elevation of prolactin and some tumour re-expansion. Monitoring of visual fields in patients with macroprolactinoma is recommended to allow early recognition of secondary loss of visual fields due to chiasmal herniation and adaptation of drug dosage.

If pregnancy occurs in patients with adenomas after the administration of Parlodel, careful observation is mandatory (see **PRECAUTIONS - Fertility**). Prolactin-secreting adenomas may expand during pregnancy. In severe cases, compression of the optic or other cranial nerves may necessitate emergency pituitary surgery.

In some patients with prolactin-secreting adenomas treated with Parlodel, cerebrospinal fluid rhinorrhea has been observed.

Psychiatric disturbances:

Parlodel, administered alone or concomitantly with levodopa for Parkinson's disease, may cause hallucinations (visual or auditory), which usually resolve with dosage reduction. Occasionally, discontinuation of Parlodel is required. Rarely after high doses, hallucinations have persisted for several weeks following discontinuation of Parlodel. High doses of Parlodel may be associated with confusion and mental disturbances. Since parkinsonian patients may manifest mild degrees of dementia, caution should be used when treating such patients.

Hypotension:

Parlodel is known to cause hypotension in some subjects. This usually manifests as postural hypotension and may be more common during initial dosing. Occasional reports have been made of collapse with hypotension and loss of consciousness within a few hours of taking initial doses of 1.25 to 2.5 mg.

For these reasons, treatment should be initiated with small doses and great care in all patients and especially in those with compromised cerebral or cardiac circulation. In post-partum patients, hypotension independent of drug therapy may already be present and Parlodel therapy for suppression of lactation should not be commenced until vital signs are stable, and no sooner than four hours after delivery.

Although there is no evidence of an interaction with antihypertensive agents, care should be exercised if Parlodel is administered with other medication known to lower blood pressure.

Tumourigenicity:

A lifetime rat study revealed that some animals developed uterine tumours and endometrial carcinoma, thought to be due to a state of induced oestrogen dominance. However, clinical experience in women with a variety of hyperprolactinaemic and other conditions, treated with bromocriptine for months and in some cases for years, failed to demonstrate abnormal trends in hormonal levels or in endometrial cytology.

Gynaecological supervision:

Although there is no evidence of uterine tumour development in women receiving Parlodel, in view of the above-mentioned lifetime rat study, it is recommended that female patients on long term therapy should have regular gynaecological assessments (see “PRECAUTIONS – Tumourigenicity”).

Peptic ulcer:

A few cases of gastrointestinal bleeding and gastric ulcer have been reported. Patients with a history or evidence of peptic ulceration should be closely monitored when receiving treatment in view of several reports of fatal gastric haemorrhage in acromegalic patients given high doses of bromocriptine. No causal relationship has been established between bromocriptine treatment and these findings and gastric haemorrhage is known to occur in acromegalic patients. If bromocriptine must be used in such patients, they should be instructed to report any gastrointestinal side effects. If gastrointestinal bleeding or gastric ulceration occurs, bromocriptine should be withdrawn.

CNS effects:

Parlodel can have unwanted central actions such as dizziness, syncope, confusion and hallucinations, and particular care should, therefore, be exercised by patients driving vehicles, operating dangerous machinery or being pedestrians in busy areas.

Bromocriptine has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with bromocriptine. Patients who have experienced somnolence and/or an

episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered.

Diabetic retinopathy:

Parlodel may cause a release of growth hormone in normal and diabetic patients, lasting 1-2 hours. Growth hormone has been implicated in the acceleration or maintenance of diabetic retinopathy and Parlodel should, therefore, be used with caution in patients with diabetes.

Fibrotic conditions:

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, have occasionally been reported. If long-term treatment is required, physicians should consider regular monitoring (e.g. chest x-rays). Patients presenting with unexplained pleuropulmonary signs or symptoms 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. 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) be looked for in this category of patient. Parlodel should be withdrawn if fibrotic changes in the peritoneum are diagnosed or suspected.

Liver function:

The extensive hepatic metabolism of bromocriptine suggests that patients with impaired hepatic function should be treated with care. Dose adjustment may be required.

Galactose intolerance:

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

Impulse control disorders:

Patients should be regularly monitored for the development of impulse control disorders. Patients with carers should be made aware that compulsive behaviour such as pathological gambling, increased libido, hypersexuality, compulsive spending or shopping, binge eating, compulsive eating, medication use and punding (repetitive purposeless activity) has been reported in patients treated with dopamine agonists including Parlodel, especially at high doses. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Prescribers, patients and caregivers should be alert to the possibility of such behaviour, which may have serious financial and social consequences.

Renal impairment

No studies have been performed in renally impaired patients.

Hepatic impairment

No studies have been performed in hepatically impaired patients.

Use in Geriatrics (aged 65 years and above)

Clinical studies for Parlodel did not include sufficient numbers of subjects aged 65 years and above to determine whether the elderly respond differently from younger subjects. 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.

Use in Children

The use of Parlodel is not recommended for children.

Effects on the ability to drive and use machinery

Since, especially during the first days of treatment, hypotensive reactions may occur and result in decreased alertness, particular care should be exercised when driving a vehicle or operating machinery (see **PRECAUTIONS - Hypotension**).

Bromocriptine has been associated with somnolence and/or 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, operate machines, or engage in activities where impaired alertness may put themselves or others at risk of serious injury or death until such recurrent episodes and somnolence have resolved (see **PRECAUTIONS - CNS effects**). Furthermore, a reduction of dosage and termination of therapy may be considered.

INTERACTIONS WITH OTHER MEDICINES

Pharmacological considerations indicate there are a number of theoretically possible drug interactions.

Alcohol

Tolerability to Parlodel (bromocriptine) may be reduced by alcohol.

Antihypertensives

The hypotensive effects of bromocriptine may be additive with those of drugs used to treat hypertension and other medication known to lower blood pressure.

CYP3A4 substrates/inhibitors

Bromocriptine is both a substrate and an inhibitor of CYP3A4 (see **PHARMACOLOGY**). 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 erythromycin, other macrolide antibiotics or octreotide has been shown to

increase bromocriptine plasma levels. The bioavailability of bromocriptine increased by approximately 40 % when it was administered together with octreotide.

Sympathomimetic drugs

Co-administration of sympathomimetics such as phenylpropanolamine and bromocriptine may lead to hypertension and severe headache (see **PRECAUTIONS**).

For the concomitant use of sympathomimetic drugs in post-partum women, see **PRECAUTIONS - Physiological lactation**.

Sumatriptan

Co-administration of sumatriptan may potentiate the risk of vasospastic reactions due to additive pharmacological effects.

Ergot alkaloids

Co-administration may increase the dopamine stimulant activity and lead to dopaminergic side effects such as headache, nausea, vomiting (see **PRECAUTIONS**).

Dopamine receptor agonists

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 following drugs may increase prolactin secretion and possibly may antagonise Parlodel in a dose dependent manner: phenothiazines, butyrophenones, metoclopramide, methyldopa, reserpine, tricyclic antidepressants, pimozide, oestrogens, TRF. Other drugs may inhibit prolactin release from the pituitary and may be synergistic with Parlodel: levodopa, clonidine, pargyline, iproniazid.

ADVERSE REACTIONS

The following adverse drug reactions with Parlodel have been derived from multiple sources including clinical trial and post-marketing experience via spontaneous case reports and literature cases (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$) very rare ($< 1/10,000$) and unknown.

Table 1 Adverse drug reactions**Psychiatric disorders**

Uncommon:	Confusional state, psychomotor hyperactivity, hallucinations.
Rare:	Psychotic disorders, insomnia.
Unknown:	Impulse control disorder*

Nervous system disorders

Common:	Headache, somnolence, dizziness.
Uncommon:	Dyskinesia.
Rare:	Paraesthesia
Very rare:	Sudden onset of sleep.

Eye disorders

Rare:	Visual impairment, vision blurred.
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Ear and labyrinth disorders

Rare:	Tinnitus.
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Cardiac disorders

Rare:	Pericardial effusion, constrictive pericarditis, tachycardia, bradycardia, arrhythmia.
Very rare:	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, dyspnoea.

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:	Dermatitis allergic, alopecia.
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Musculoskeletal and connective tissue disorders

Uncommon:	Muscle spasms.
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General disorders and administration site conditions

Uncommon:	Fatigue.
Rare:	Oedema peripheral.
Very rare:	A syndrome resembling Neuroleptic Malignant Syndrome on abrupt withdrawal of Parlodel.

**Impulse control disorders: pathological gambling, increased libido and hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Parlodel (see PRECAUTIONS).*

During the first days of treatment, patients commonly experience nausea, dizziness or headache and, less frequently, nasal congestion, fatigue or vomiting, not usually sufficiently serious to require treatment to be discontinued. Bromocriptine frequently causes a reduction in blood pressure manifested as postural hypotension (very rarely leading to syncope).

The spectrum and incidence of side effects occurring in Parkinson's patients differs somewhat from that found in patients being treated for endocrinological indications. It should be noted that, to date, clinical experience of bromocriptine in Parkinson's disease has generally followed or been associated with other therapy. Hallucinations, confusion and behavioural disturbances have been reported commonly in patients receiving doses above 15 mg/day. Delusions, psychotic episodes (including paranoia) and delirium are less frequent. Psychotic episodes have also occurred at 2.5 to 5.0 mg daily. Dyskinesias or abnormal involuntary movements and "on-off" effect have been reported in patients treated for Parkinson's disease but, to date, there is no adequate experience of patients who have been treated only with Parlodel. Pleuro-pulmonary changes (pleural and pericardial effusions, pleural and pulmonary fibrosis), constrictive pericarditis and retroperitoneal fibrosis have occurred in patients on long term therapy (see "PRECAUTIONS").

In several acromegalic patients treated with high doses, fatal gastric haemorrhage has been reported (see "PRECAUTIONS").

Episodes of reversible pallor of the fingers and toes induced by cold have occasionally been reported during prolonged treatment, particularly in patients previously exhibiting Raynaud's phenomenon.

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 and psychiatric disorders (see "CONTRAINDICATIONS" and "PRECAUTIONS").

Less frequently ataxia, depression, anorexia, dyskinesia, erythromelalgia, metallic taste, decreased alcohol tolerance, diplopia, eye discomfort, cardiac arrhythmias, epigastric pain, oedema, urticaria and other rashes, and a burning sensation in the breast have also been reported. These side effects are usually dose dependent and can in most cases be controlled by a reduction in dosage.

Bromocriptine has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes (see "PRECAUTIONS - CNS effects").

DOSAGE AND ADMINISTRATION

The drug should always be taken with food since the incidence of nausea is reduced.

Inhibition of physiological lactation

2.5 mg (1 tablet) twice daily with morning and evening meals for 14 days. To prevent the onset of lactation, treatment should be commenced as soon as possible after parturition but not until vital signs, especially blood pressure, have stabilised and not until four hours after delivery (see "PRECAUTIONS-Hypotension"). Secretion of milk may recur 2 to 3 days after the end of the

treatment period. This can be controlled by resuming treatment at the same dosage for a further week.

Hyperprolactinaemia

1.25 mg (½ tablet) 2 to 3 times daily. If this proves inadequate, gradually increase to 2.5 mg (1 tablet) 2 or 3 times daily with meals. If associated with galactorrhoea, continue treatment until breast secretion has completely disappeared and, if associated with amenorrhoea, until the menstrual cycle has returned to normal. If required, treatment may be continued over several menstrual cycles to prevent relapse. For the treatment of prolactinomas, Parlodel should be initiated at 1.25 mg (½ tablet) 2 times daily. If the dosage proves inadequate to reduce the serum prolactin level and reduce tumour size, gradually increase up to 15 mg daily in divided doses.

Adjunctive therapy in the management of acromegaly

Initially 1.25 mg (½ tablet) at night, increasing gradually over a period of 1 to 2 weeks to 10 mg daily. Most acromegalics able to derive benefit from Parlodel do so at doses of 10 to 30 mg daily. Dosage should be adjusted appropriately, depending on clinical response and side effects. The daily dose should be taken in four equally divided doses with meals. It is recommended that a daily dose of 40 mg is not exceeded.

Parkinson's disease

Anti-Parkinson effects can be obtained with doses as low as 5-10 mg daily. The therapeutic range in either mono- or combined therapy is 5-40 mg/day in divided doses, usually at 6-8 hourly intervals. The best results may be achieved if the dosage is increased slowly, starting with 1.25 mg (½ tablet) once or twice a day (with meals) for the first week, followed by increments of not more than 1.25 mg every week as monitored by therapeutic response and tolerability. When Parlodel is given in combination with levodopa, with or without decarboxylase inhibitor, it may be possible to reduce the dose of levodopa. Any reduction in the dosage should be gradual. In certain cases levodopa can be withdrawn completely.

The 10 mg capsule has yet to be established as bioequivalent with 4 x 2.5 mg tablets or 2 x 5 mg capsules.

OVERDOSAGE

Signs and symptoms

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.

Several reports have been made to the Company of acute overdosage with Parlodel which, however, were mainly within the therapeutic range. There were no life threatening reactions. Symptoms reported could have resulted from overstimulation of dopaminergic receptors. The

observed symptoms of overdose include nausea, vomiting, dizziness, drowsiness, lethargy, somnolence, tachycardia, hypotension and postural hypotension. In addition, psychotic reactions and hallucinations may also occur.

Treatment

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATIONS AND STORAGE CONDITIONS

Presentations

Oral tablets:

2.5 mg bromocriptine (present as 2.9 mg mesylate); white, coded XC with breakline one side, SANDOZ other side; 30's, 60's. The tablets contain as excipients silica-colloidal anhydrous, disodium edetate, magnesium stearate, maleic acid, starch-maize and lactose.

Oral capsules*:

10 mg bromocriptine (present as 11.5 mg mesylate); opaque white, 100's. The 10 mg capsules contain as excipients silica-colloidal anhydrous, magnesium stearate, maleic acid, starch-maize, lactose, titanium dioxide and gelatin.

5 mg bromocriptine (present at 5.735 mg mesylate); opaque white and opaque blue, marked PS, 60's. The 5 mg capsules contain as excipients silica-colloidal anhydrous, magnesium stearate, maleic acid, starch-maize, lactose, indigo carmine CI 73015, iron oxide red CI 77491, titanium dioxide, gelatin and shellac.

* Not all presentations are available

Storage Conditions

Tablets: Store below 25°C. Protect from light.

Capsules*: Store below 30°C.

* Not all presentations are available

POISON SCHEDULE

S4: Prescription Only Medicine

NAME AND ADDRESS OF SPONSOR

NOVARTIS Pharmaceuticals Australia Pty. Limited
ABN 18 004 244 160
54 Waterloo Road
NORTH RYDE NSW 2113

ARTG START DATES

21 Aug 1991 - PARLODEL bromocriptine 2.5mg (as mesylate) tablet blister pack (AUST R 13367), PARLODEL bromocriptine 5mg (as mesylate) capsule bottle* (AUST R 13365), PARLODEL bromocriptine 10mg (as mesylate) capsule bottle* (AUST R 13366), PARLODEL bromocriptine 2.5mg (as mesylate) tablet bottle* (AUST R 13340)

* Not all presentations are available

APPROVED BY THE THERAPEUTIC GOODS ADMINISTRATION:

27 March 1995

DATE OF MOST RECENT AMENDMENT:

10 May 2013