PRODUCT MONOGRAPH

PrPARLODEL*

(bromocriptine mesylate)

Tablets 2.5 mg

Prolactin Inhibitor

Growth Hormone Suppressant in Acromegaly

Adjunctive Medication in Parkinson's Disease

Novartis Pharmaceuticals Canada Inc.
Dorval, Quebec
H9S 1A9

Control#: 106906

DATE OF PREPARATION:
Sept. 14, 1976

DATE OF REVISION:
June 6, 2007

PRODUCT MONOGRAPH

NAME OF DRUG

[Pr]PARLODEL*

(bromocriptine mesylate)

Tablets 2.5 mg

THERAPEUTIC CLASSIFICATION

Prolactin Inhibitor

Growth Hormone Suppressant in Acromegaly

Adjunctive Medication in Parkinson's Disease

CLINICAL PHARMACOLOGY

PARLODEL* (bromocriptine mesylate) is a dopaminomimetic ergot derivative with D_2-type dopamine receptor agonist activity, which also has D_1 dopamine receptor antagonist properties.

PARLODEL* inhibits the release and synthesis of prolactin by acting directly on the prolactin secreting cells of the anterior pituitary. In patients with acromegaly, in addition to lowering prolactin and elevated levels of growth hormone, PARLODEL* has a beneficial effect on clinical symptoms and on glucose tolerance.

The dopaminomimetic activity of PARLODEL* in the nigro-striatal pathway is considered responsible for the clinical benefits seen in patients with Parkinson's disease.

The metabolism of dopamine, from exogenous and endogenous origin, is known to involve the formation of peroxides and free radicals. It has been postulated that these agents may in fact contribute to the progression of Parkinson's disease by accelerating the rate at which neuronal cells are lost. Bromocriptine's metabolic pathway does not involve the formation of such peroxides and free radicals. It has been suggested that because bromocriptine attenuates the timing and rate of levodopa dosage increase, early use of the drug may reduce risk of formation of potentially toxic peroxides and free radicals.

In man, bromocriptine is rapidly absorbed after oral administration with an absorption half-life of approximately 0.3 hours. An oral dose of 5 mg of bromocriptine results in a C_{max} of 0.465 ng/mL.

The amount absorbed is about 65 - 95% of the oral dose. About 7% of the dose reaches the systemic circulation unchanged due to a high hepatic extraction rate and first pass metabolism. The plasma protein binding amounts to 96%.

Bromocriptine undergoes extensive first-pass metabolism in the liver, reflected by complex metabolic profiles and almost complete absence of parent drug in urine and faeces. Unchanged drug represents about 10 - 15% of peak levels of radioactivity in plasma measured after single dose of labelled drug.

Bromocriptine is both a substrate and a potent inhibitor of CYP3A4 (calculated IC_{50} value of 1.69 μM). Therefore, inhibitors and/or potent substrates of CYP3A4, would be expected to inhibit the clearance of bromocriptine and lead to increased levels. However, given the low therapeutic concentrations of free bromocriptine in patients, a significant alteration of the metabolism of a concomitant drug whose clearance is mediated by CYP3A4 would not be expected**.**

The active parent drug and the metabolites are primarily excreted via the liver, only 6% being eliminated via the kidney. In plasma, the elimination half-life was between 2 to 8 hours for the parent drug and 50 to 70 hours for the metabolites after single oral doses.

The extreme variability in GI tract absorption and the extensive and individually variable first-pass metabolism are responsible for the broad variability in plasma concentrations of bromocriptine and, in part, for the variability in dose response.

INDICATIONS AND CLINICAL USE

Hyperprolactinemia-Associated Dysfunctions

PARLODEL* (bromocriptine mesylate) is indicated for the treatment of dysfunctions associated with hyperprolactinemia including amenorrhea with or without galactorrhea, prolactin-dependent menstrual disorder and infertility (e.g., secondary amenorrhea, ovulatory insufficiency and short luteal phase). PARLODEL* is also indicated for the treatment of prolactin-dependent male hypogonadism.

PARLODEL* treatment is indicated in patients with prolactin-secreting adenomas, as a treatment for inoperable macroadenomas or prior to surgery in order to facilitate removal, and as an alternative to surgery in patients with microadenomas. Prolactin-secreting adenomas may be the basic underlying endocrinopathy contributing to the above clinical presentations

Acromegaly

The first-line treatment of this condition is by surgery or radiotherapy. PARLODEL* (bromocriptine mesylate) may be a useful adjunct to such treatment, and can be used as monotherapy in special cases.

Since the effects of external pituitary radiation may not become maximal for several years, adjunctive therapy with PARLODEL* offers potential benefit before the effects of irradiation are manifested.

Parkinson's disease

PARLODEL* is effective when used as adjunct therapy to levodopa in the symptomatic management of Parkinson's Disease. Used concomitantly with levodopa, PARLODEL* facilitates the use of lower doses of levodopa in early disease and attenuates the rate of increase in the levodopa dosages on long-term usage. In this way the risk of long-term complications such as prominent dyskinesias and/or end-of-dose failure can be reduced.

Continued efficacy of PARLODEL* therapy during treatment of more than 2 years has not been established.

Data are insufficient to evaluate potential benefit from treating newly diagnosed Parkinson's disease with PARLODEL*. Studies have shown, however, significantly more adverse reactions (notably nausea, hallucinations, confusion and hypotension) in PARLODEL*-treated patients than in levodopa/carbidopa-treated patients.

Patients unresponsive to levodopa are poor candidates for PARLODEL* therapy.

CONTRAINDICATIONS

Hypersensitivity to bromocriptine or to any of the components of PARLODEL*, or 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 patients being treated for hyperprolactinemia, PARLODEL* should be withdrawn when pregnancy is diagnosed.(see also WARNINGS, "Diagnosis of Pregnancy while being treated with PARLODEL*")

Coronary artery disease and other severe cardiovascular conditions, symptoms and/or a history of serious psychic disorders

WARNINGS

Diagnosis of Pregnancy while being treated with PARLODEL*

In patients receiving PARLODEL*, immunological confirmation of suspected conception should be performed as soon as possible and PARLODEL* treatment stopped unless, in the opinion of the treating physician, the possible benefit to the patient outweighs the potential risk to the fetus. In any event, the patient must be monitored closely throughout pregnancy for signs and symptoms which may develop if a previously undetected prolactin-secreting tumor enlarges.

When PARLODEL* is being used to treat acromegaly, prolactinoma, or Parkinson's disease in patients who subsequently become pregnant, a decision should be made as to whether the therapy continues to be medically necessary or can be withdrawn. The drug should be withdrawn in patients who may experience hypertensive disorders of pregnancy unless withdrawal of

PARLODEL* is considered to be medically contraindicated. (see also PRECAUTIONS, Use in Pregnancy and Lactation).

In the event that PARLODEL* is reinstituted to control a rapidly expanding macroadenoma and a patient experiences a hypertensive disorder of pregnancy, the benefit of continuing PARLODEL* must be weighed against the possible risk of its use during a hypertensive disorder of pregnancy.

Treatment of Post-Partum Women

In rare cases, serious adverse events including hypertension, myocardial infarction, seizures and strokes, or psychic disorders have been reported in postpartum women treated with PARLODEL* for the inhibition of lactation. In some patient the development of seizures or strokes was preceded by severe headache and/or visual disturbances. Causal relationship of these events to the drug is uncertain.

The use of PARLODEL* in the routine inhibition of physiological lactation is not recommended. When the drug is used for the treatment of other conditions, periodic monitoring of blood pressure is advisable. 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.

Concomitant Use with other Ergot-Containing Products

Because there is a theoretical basis for additive effects of the vasospastic effects of ergot-containing products, the concomitant use of ergot-containing products (including triptans, dihydroergotamine or methysergide) with bromocriptine is not recommended (see also,

WARNINGS, Concomitant use with Drugs that Alter Blood Pressure; and also DRUG INTERACTIONS).

Galactorrhea and Discontinuation of PARLODEL*

In women with non-puerperal galactorrhea, reduction of prolactin levels may lead to resumption of normal menses. Following discontinuation of medication, galactorrhea returns in some patients and leads to suspicion of pituitary adenomas; a complete investigation at specialized units to identify these patients is advisable.

Patients with Pituitary Tumors

Treatment with PARLODEL* (bromocriptine mesylate) may effectively lower prolactin levels in patients with pituitary tumors but does not obviate the necessity for radiotherapy or surgical intervention where appropriate.

Fibrotic Complications

Long-term treatment (6-36 months) with PARLODEL* in doses ranging from 20-100 mg/day has been associated with pulmonary infiltrates, pleural and pulmonary fibrosis, pleural and pericardial effusion, constrictive pericarditis and thickening of the pleura in a few patients. Patients with unexplained pleuropulmonary disorders should be examined thoroughly and discontinuation of PARLODEL* should be contemplated. In those instances in which PARLODEL* treatment was terminated, the changes generally slowly reverted toward normal, although complete resolution does not always occur.

In a few patients treated over years with PARLODEL*, particularly on long-term and high dose treatment, at daily doses higher than 30 mg, 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, edema of the lower limbs, impaired kidney function) should be watched in this category of patients. PARLODEL* medication should be withdrawn immediately if fibrotic changes in the retroperitoneum are diagnosed or suspected.

In a few patients treated over years with PARLODEL*, particularly on long-term and high dose treatment, at daily doses higher than 30 mg, 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, edema of the lower limbs, impaired kidney function) should be watched in this category of patients. PARLODEL* medication should be withdrawn immediately if fibrotic changes in the retroperitoneum are diagnosed or suspected.

Concomitant use with Drugs that Increase Blood Pressure

Particular attention should be paid to patients who have recently been treated or are on concomitant therapy with drugs that can increase blood pressure- e.g. vasoconstrictors such as sympathomimetics or ergot alkaloids including ergometrine or methylergometrine. The concomitant use of such drugs with PARLODEL* in the puerperium is not recommended.

Sudden onset of sleep

Patients receiving treatment with PARLODEL* (bromocriptine) and other dopaminergic agents have reported suddenly falling asleep while engaged in activities of daily living, including the driving of a car, which has sometimes resulted in accidents. Although some of the patients reported somnolence while on PARLODEL*, others perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event.

Physicians should alert patients of the reported cases of sudden onset of sleep, bearing in mind that these events are NOT limited to initiation of therapy. Patients should also be advised that sudden onset of sleep has occurred without warning signs and should be specifically asked about factors that may increase the risk with PARLODEL* such as concomitant medications or the presence of sleep disorders. Given the reported cases of somnolence and sudden onset of sleep (not necessarily preceded by somnolence), physicians should caution patients about the risk of operating hazardous machinery, including driving motor vehicles, while taking PARLODEL*. If drowsiness or sudden onset of sleep should occur, patients should be informed to immediately contact their physician.

(see also PRECAUTIONS, Operating Machinery)

Episodes of falling asleep while engaged in activities of daily living have also been reported in patients taking other dopaminergic agents, therefore, symptoms may not be alleviated by substituting these products.

Currently, the precise cause of this event is unknown. It is known that many Parkinson's disease patients experience alterations in sleep architecture, which results in excessive daytime sleepiness or spontaneous dozing, and that dopaminergic agents can also induce sleepiness. There is insufficient information to determine whether this event is associated specifically with PARLODEL* all dopaminergic agents, or Parkinson's disease itself.

Galactose Intolerance or Malabsorption

Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take this medication, as it contains lactose.

PRECAUTIONS

Operating Machinery

PARLODEL* (bromocriptine mesylate) may cause hypotension, primarily postural; periodic monitoring of the blood pressure, particularly during the first days of therapy, is advisable. In some patients dizziness (vertigo) may occur with PARLODEL*; patients should therefore be cautioned against activities requiring rapid and precise responses such as driving an automobile or operating dangerous machinery until their response has been determined. (see also **WARNINGS**, Sudden Onset of Sleep)

Care should be exercised when administering PARLODEL* concomitantly with phenothiazines or with other medications known to lower blood pressure. Dosage should be adjusted accordingly.

Concomitant Use of Alcohol

In some patients the concomitant use of PARLODEL* and alcohol has given rise to alcohol intolerance and the tolerability to PARLODEL* may be reduced by alcohol.

Potential for Reversal of Infertility

In patients being treated with PARLODEL* for galactorrhea, prolactin induced amenorrhea, menstrual disorders or acromegaly, infertility might be reversed by restoration of normal menses and ovulation. Women who do not wish to conceive should, therefore, use a reliable method of contraception. Since pregnancy may occur prior to initiation of menses it is recommended that a pregnancy test be conducted at least every four weeks during the amenorrheic period, and, once menses are reinitiated, every time a patient misses a menstrual period.

Digital Vasospasm

Cold-sensitive digital vasospasm has been observed in some acromegalic patients treated with PARLODEL*. The response, should it occur, can be reversed by reducing the dose of PARLODEL* and may be prevented by keeping the fingers warm.

Because there is a theoretical basis for additive effects of the vasospastic effects of ergot-containing products, caution should be used in co-administering any ergot-based drug with bromocriptine (including triptans, dihydroergotamine or methysergide) (See also, WARNINGS, Concomitant Use with other Ergot-Containing Products)

Gastrointestinal Bleeding

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.

Lack of Data Regarding Use in Patients with Severe Renal or Hepatic Impairment

Safety and efficacy of PARLODEL* has not been established in patients with severe renal or hepatic disease.

Lack of Data Regarding Long term Use in Management of Amenorrhea/Galactorrhea

PARLODEL* therapy has been demonstrated to be effective in the short term management of amenorrhea/galactorrhea. Data are not available on the safety or effectiveness of its use in long-term continuous dosage in this indication or in patients given repeated courses of treatment following recurrence of amenorrhea/galactorrhea after initial treatment. Recurrence rates are reportedly very high, ranging from 70 to 80%.

Nausea, Vomiting, or Vertigo with PARLODEL*

PARLODEL* should always be taken with food. In cases where adverse effects, such as nausea, vomiting and vertigo are severe or persistent, the therapeutic dosage of PARLODEL* should be reduced to half of one tablet daily (1.25 mg) and increased gradually to that recommended. The dopamine antagonist domperidone may be useful in the control of severe gastrointestinal side effects in Parkinsonian patients receiving PARLODEL* (see DRUG INTERACTIONS).

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.

Possible tumor expansion while receiving PARLODEL* therapy has been reported in a few patients. Since the natural history of growth hormone-secreting tumors is unknown, all patients should be carefully monitored and, if evidence of tumor expansion develops, discontinuation of

treatment and alternative procedures considered.

In some patients with prolactin secreting adenomas treated with PARLODEL, cerebrospinal fluid rhinorrhea has been observed. The data suggest that this may result from shrinkage of invasive tumors.

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.

Neurologic

Neuroleptic Malignant Syndrome

A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious aetiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy. This has been reported very rarely for PARLODEL* (including one death); in all reports, the onset of NMS started between one and six days after withdrawal of PARLODEL*, and in some cases, other antiparkinsonian therapy,

Psychiatric

Compulsive Behaviours

Patients treated with dopamine agonists for Parkinson's disease, especially at high doses, have been reported as exhibiting impulse control symptoms including compulsive behaviours such as pathological gambling and hypersexuality, generally reversible upon reduction of the dose or

treatment discontinuation. In some cases, other factors were present such as a history of compulsive behaviours or concurrent dopaminergic treatment. Very rarely, such reports have also been received for PARLODEL*.

Formatted: English (U.K.), Not Highlight

Skin

Some epidemiological studies have shown that patients with Parkinson's disease have a higher risk (perhaps 2- to 4-fold higher) of developing melanoma than the general population. Whether the observed increased risk was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, was unclear. PARLODEL* is one of the drugs used to treat Parkinson's disease. Although PARLODEL* has not been associated with an increased risk of melanoma specifically, its potential role as a risk factor has not been systematically studied. Patients treated with PARLODEL* should be made aware of these results and should undergo periodic dermatologic screening.

Use in Pregnancy and Lactation

In patients receiving PARLODEL*, immunological confirmation of suspected conception should be performed as soon as possible and PARLODEL* treatment stopped unless, in the opinion of the treating physician, the possible benefit to the patient outweighs the potential risk to the fetus. In any event, the patient must be monitored closely throughout pregnancy for signs and symptoms which may develop if a previously undetected prolactin-secreting tumor enlarges.

(See also WARNINGS, Diagnosis of Pregnancy while being treated with PARLODEL*; and WARNINGS, Treatment of Post-partum Women)

In human studies with PARLODEL* (reviewed by Turkalj, I. et al), there were 1410 reported pregnancies, which yielded 1236 live and 5 stillborn infants from women who took PARLODEL* during early pregnancy. Among the 1241 infants, 43 cases (31 minor and 12 major) of congenital anomalies were reported. The incidence (3.46%) and type of congenital malformations and the incidence of spontaneous abortions (11.13%) in this group of pregnancies does not exceed that generally reported for such occurrences in the population at large.

Patients with pronounced enlargement of the sella turcica or with a visual field defect should, in the first instance, be treated by surgery and/or radiotherapy. If pregnancy occurs in the presence of a pituitary microadenoma, close supervision throughout pregnancy is essential. This includes regular checking of the visual fields.

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

Use in Parkinson's Disease

Use of PARLODEL*, particularly in high doses, may be associated with mental confusion and mental disturbances. Since patients with Parkinson's Disease may manifest varying degrees of dementia, caution should be exercised when treating such patients with PARLODEL*.

PARLODEL* administered alone or concomitantly with levodopa may cause visual or auditory hallucinations. These usually resolve with dosage reduction but discontinuation of PARLODEL* may be required in some cases. Rarely, after high doses, hallucinations have persisted for several weeks following discontinuation of PARLODEL*. Caution should be exercised when administering PARLODEL* to patients with a history of myocardial infarction, particularly if they have a residual atrial, nodal or ventricular arrhythmia.

Symptomatic hypotension can occur and, therefore, caution should be exercised when administering PARLODEL*, particularly in patients receiving antihypertensive medication. Periodic evaluation of hepatic, hematopoietic, cardiovascular and renal function is recommended.

Drug Interactions

Bromocriptine is both a substrate and a potent inhibitor of CYP3A4. Caution should, therefore, be used when co-administered with drugs which are strong inhibitors and/or substrates of this enzyme (eg azole antimycotics, HIV protease inhibitors). The concomitant use of macrolide antibiotics such as erythromycin or josamycin has been shown to increase bromocriptine plasma levels.

The concomitant treatment of acromegalic patients with bromocriptine and octreotide (a somatostatin analogue) led to increased plasma levels of bromocriptine due to an approximately 40% increase in the bioavailability; the mechanism is not established.

There are spontaneous reports of hypertension-related adverse events with concomitant use of methylergometrine, another ergot-containing drug. Because there is a theoretical basis for additive effects of the vasospastic effects of ergot-containing products, caution should be used in co-administering any ergot-based drug with bromocriptine (including triptans, dihydroergotamine or methysergide).

Since PARLODEL* exerts its therapeutic activity by stimulating central dopamine receptors, dopamine antagonists such as some antipsychotics (eg phenothiazines, butyrophenones and thioxanthenes) may reduce its activity, as may metoclopramide and domperidone as well.

Domperidone, a peripheral dopamine antagonist, may cause increases in serum prolactin. In so doing, domperidone may antagonise the therapeutically relevant prolactin lowering effect of PARLODEL*. It is possible that the anti-tumorigenic effect of PARLODEL* in patients with prolactinomas may be partially blocked by domperidone administration.

ADVERSE REACTIONS

The most frequently observed adverse reactions are nausea, vomiting, headache and gastrointestinal side effects such as abdominal pain, diarrhea and constipation. All these effects may be minimized or even prevented by giving small initial doses of bromocriptine and by taking it with food.

Postural hypotension can, on rare occasions, lead to fainting and "shock-like" syndromes have been reported in sensitive patients. This is most likely to occur during the first few days of PARLODEL* treatment.

Pleural and pericardial effusions, pleural and pulmonary fibrosis or retroperitoneal fibrosis and constrictive pericarditis have been reported rarely in patients treated with PARLODEL* (see **WARNINGS,** Fibrotic Complications).

PARLODEL* is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes (see **WARNINGS,** Sudden Onset of Sleep)

In clinical studies to date, the following adverse events were noted:

In postpartum women treated with bromocriptine mesylate, some rare serious adverse events (about 1 in 100,000) have been reported. These include hypertension, visual disturbances, myocardial infarction, seizures and strokes, or psychic disorders. In some patient the occurrence of seizures or strokes was preceded by severe headache and/or visual disturbances. Causal relationship of these events to the drug is uncertain.

Amenorrhea/Galactorrhea/Female Infertility/Acromegaly

The incidence of side effects in these indications is 68% and are generally mild to moderate in degree. Therapy was discontinued in approximately 6% of patients because of adverse effects. In decreasing order of frequency these are: nausea 51%, headache 18%, dizziness 16%, fatigue 8%, abdominal cramps 7%, lightheadedness 6%, vomiting 5%, nasal congestion 5%, constipation 3% and diarrhea 3%.

Parkinson's Disease

When PARLODEL* is added to levodopa therapy, the incidence of adverse reactions may increase. The most common newly appearing adverse reactions in combination therapy with levodopa are: nausea, abnormal involuntary movements, hallucinations, confusion, "on-off" phenomenon, dizziness, drowsiness, faintness, fainting, vomiting, asthenia, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, hypotension, shortness of breath, constipation and vertigo.

General

Less common adverse reactions include, anorexia, anxiety, blepharospasm, dry mouth, dysphagia, edema of the feet and ankles, erythromelalgia, epileptiform seizures, fatigue, headache, lethargy, mottling of skin, nasal congestion, nervousness, nightmares, paresthesia, skin rash, hair loss, changes in urinary frequency, urinary incontinence and urinary retention. Usually, these side effects are dose dependent and can be controlled by a reduction in dosage. Rarely signs of symptoms of ergotism such as tingling of fingers, cold feet, numbness, muscle cramps of feet and legs or exacerbation of Raynaud's syndrome may occur.

Abnormalities in laboratory tests may include elevation of blood urea nitrogen, AST (SGOT), ALT (SGPT), GGT, CPK, alkaline phosphatase and uric acid, which are usually transient and not of clinical significance.

The occurrence of adverse reactions may be lessened by temporarily reducing the dosage to 1.25 mg two or three times daily.

Spontaneous Reports of Adverse Reactions not listed above:

Spontaneous reports of adverse reactions occurring with the use of PARLODEL* include rare reports of**:** psychotic disorders, visual disturbances and blurred vision, tinnitus, tachycardia, bradycardia and arrhythmia, pleurisy and dyspnea, gastrointestinal hemorrhage, increased libido and hypersexuality (generally reversible upon reduction of the dose or treatment discontinuation) and very rare reports of a syndrome resembling neuroleptic malignant syndrome on abrupt withdrawal of PARLODEL* (see also PRECAUTIONS, Neurological, Neuroleptic Malignant Syndrome)

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been several reports of acute overdosage with PARLODEL* (bromocriptine mesylate) in children and adults. All patients who have taken an overdosage of PARLODEL* alone have survived; the maximum single dose so far ingested is 325 mg. Symptoms reported could have resulted from over-stimulation of dopaminergic receptors; they included nausea, vomiting, dizziness, drowsiness, hypotension, tachycardia, somnolence, lethargy and hallucinations.

In the case of overdose, administration of activated charcoal is recommended. In the case of very recent oral intake, gastric lavage may be considered

The management of acute intoxication is largely symptomatic. The cardiovascular system should be monitored. Metoclopramide can be used to antagonize the emesis and hallucinations in patients who have taken high doses.

DOSAGE AND ADMINISTRATION

PARLODEL* (bromocriptine mesylate) should always be taken with food. In order to establish tolerance, the first dose of 1.25 - 2.5 mg (½ - 1 tablet), depending on the indication should be

given at bedtime with food. Please consult the detailed dosage recommendations for each indication.

Galactorrhea with or without amenorrhea due to hyperprolactinemia

1.25 - 2.5 mg (½ to 1 tablet) at bedtime with food to establish tolerance; gradually increase after 2-3 days to 2.5 mg twice daily with meals. If required the dose may be increased to 2.5 mg t.i.d. Continue treatment until milk secretion has ceased completely or, in the case of menstrual dysfunction, until the menstrual cycle has returned to normal.

Prolactin-dependent menstrual disorders and infertility

1.25 - 2.5 mg (½ to 1 tablet) at bedtime with food to establish tolerance. Gradually increase after 2-3 days to one tablet twice daily with meals. If required, the dose may be increased to 2.5 mg t.i.d.

Prolactin secreting adenomas

1.25 mg (½ a tablet) 2 or 3 times daily, increasing gradually (average maintenance dose: 5 - 7.5 mg daily). If necessary to keep plasma prolactin adequately suppressed, dosage may be increased gradually over a period of several weeks to 10 - 20 mg daily (4 to 8 tablets) with meals.

Hyperprolactinaemia in men

1.25 - 2.5 mg (½ to 1 tablet) at bedtime to establish tolerance. Gradually increase after 2-3 days to 2.5 mg twice daily with meals or more, as required, to 2.5 mg three times per day with meals.

Acromegaly

1.25 - 2.5 mg (½ to 1 tablet) at bedtime with food to establish tolerance, increasing gradually over a period of 2-4 weeks, to 10 - 20 mg (4 to 8 tablets) daily with meals, depending on clinical response. Daily requirements of 20 mg should be taken in four equally divided doses.

The maximum recommended daily dose is 20 mg [8 (2.5 mg) tablets]. In the event of serious or persistent adverse effects, the dosage should be reduced to 1.25 mg (½ tablet) and increased again gradually to the recommended dose. If reactions such as nausea, vomiting, vertigo or headaches continue to be severe, PARLODEL* should be discontinued.

Parkinson's Disease

PARLODEL* should be added to levodopa therapy. It is desirable to combine a slow increase of bromocriptine with a concomitant, limited and gradual reduction of levodopa.

PARLODEL* dosage should be individualized. The initial dose is 1.25 mg (½ tablet) at bedtime to establish tolerance. Thereafter, the recommended dosage is 2.5 mg daily in two divided doses, with meals. The dosage may be increased, if necessary, by adding an additional 2.5 mg per day, once every 2 to 4 weeks, taken in 2 or 3 divided doses with meals.

The maximum recommended daily dosage is 40 mg. Clinical assessments are recommended during dosage titration to ensure that the lowest effective dose is employed.

PHARMACEUTICAL INFORMATION

Proper name: Bromocriptine mesylate

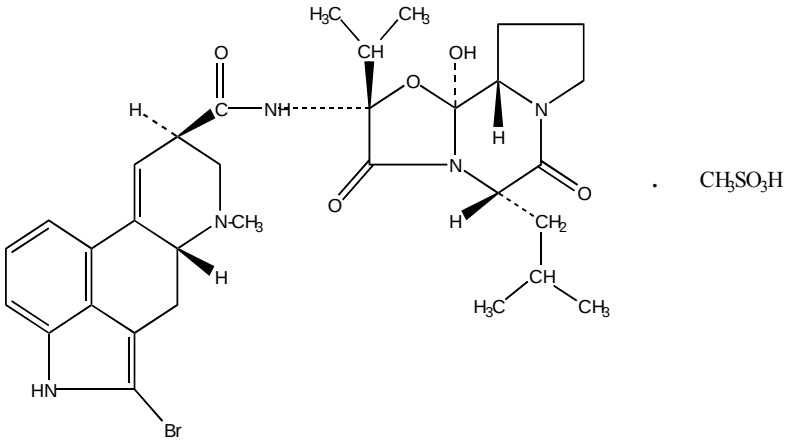
Molecular Formula: $C_{32}H_{40}BrN_5O_5.CH_4O_3S$

Molecular Weight: 750.70

Chemical Name: 2-bromo-α-ergocryptine mesylate

Description: Bromocriptine mesylate is a grey-tinged white, or light yellow fine crystalline powder, odourless or with a weak characteristic odour.

Structural Formula:



AVAILABILITY OF DOSAGE FORMS

~~1.~~Easy-to-break TABLETS each containing 2.87 mg bromocriptine mesylate, corresponding to 2.5 mg bromocriptine base, available in bottles of 100.

White, oval shaped tablets, with parting facilitated score line. Upper is sloped face and embossed with double heads, bisect, double heads, with lower flat and embossed "PARLODEL".

Storage Requirements

Protect from light and store between 15° and 25°C.

As with all medication, PARLODEL* should be kept safely out of the reach of children.

PHARMACOLOGY

Introduction

Bromocriptine is a semi-synthetic brominated ergot alkaloid. It is largely devoid of the pharmacological properties usually associated with ergot, such as uterotonic, vasoconstrictive or pressor effects. It is a dopamine agonist of D_2-type receptors and an antagonist of D_1-type receptors.

Effects on the Endocrine System

Bromocriptine is a potent inhibitor of prolactin secretion and synthesis. This activity has been demonstrated in a variety of animal tests. Using lactation, a prolactin dependent process, as an index, bromocriptine has been shown to inhibit milk production in a variety of animal species such as the rat, rabbit, pig and dog. This effect has been confirmed also in humans.

Bromocriptine inhibits the increase in prolactin induced by suckling stimuli in the lactating rat, and by tactile stimulation of the teat in goats and cows, but it exerts no effect on the concurrently induced release of growth hormone.

In the pro-estrus rat, bromocriptine blocks the natural increase in prolactin secretion (the prolactin surge), in a dose-dependent manner. In the rat, it also shows antiprogestational and antifertility effects, demonstrated by the interruption of pseudopregnancy and a dose-related prevention of pregnancy in the rat, which are reversed by the administration of exogenous prolactin.

Evidence suggests that the mechanism responsible for the bromocriptine-induced antifertility effect in the rat depends upon the inhibition of prolactin-induced activation of the corpus luteum, thus interfering with the progestative state, and thereby preventing implantation of the blastocyst. The antifertility effect is not due to anovulation as bromocriptine only weakly inhibits ovulation in rats. In contrast to the rat, bromocriptine exerts no antifertility effect in the rabbit, a species where luteotrophic activity is not dependent on prolactin.

Experimental evidence suggests that the mode and site of action of bromocriptine in inhibiting prolactin is by a direct action on the prolactin cells of the anterior pituitary. In cultures of rat and human pituitary cells, bromocriptine inhibits prolactin synthesis and secretion: this effect is due to its dopamine agonist property. In intact mice treated with bromocriptine, pituitary prolactin

synthesis and secretion are inhibited and anterior pituitary weight decreased, without any changes in growth hormone content.

There is also evidence that bromocriptine exerts an effect on the hypothalamus. In the rat, it decreases turnover of dopamine in the median eminence and the dopaminergic tubero-infundibular region, a system which is thought to control prolactin synthesis and secretion.

Effects on the Cardiovascular System

Bromocriptine lowers blood pressure as a result of its dopaminergic effect on vascular smooth muscle, peripheral sympathetic nerve terminals and the central nervous system.

Effects on the Central Nervous System

The central nervous system effects of bromocriptine are consistent with a dopamine agonist effect in the basal ganglia, the mesolimbic system and the hypothalamus.

In small animals a biphasic effect on motor activity, similar to that of levodopa, is seen, with initial depression being followed by strong locomotor activity. A reduced turnover of dopamine is observed.

Direct administration into both nuclei accumbens of the rat does not produce motor stimulation, but inhibits dopamine-induced hyperactivity suggesting a dopamine antagonistic effect at this site.

Stereotyped behaviour such as repetitive sniffing, gnawing and (rarely) biting is seen after bromocriptine and can be inhibited by pimozide, a selective blocker of dopaminergic receptors. Intact synthesis and storage of dopamine appear necessary for these effects.

Bromocriptine, like other central dopamine agonists, is a potent inhibitor of behavioural depression induced by depletion of catecholamine stores.

Neurochemical investigations in the rat brain indicate that bromocriptine is a direct dopamine agonist. In addition there is evidence that it also increases noradrenaline turnover, but that it has minimal effects on serotonin turnover. In terms of ability to bind to receptor sites, bromocriptine is a mixed agonist/antagonist at both presynaptic and postsynaptic sites. Antagonistic activity at D_1-type receptors is demonstrated in the dispersed bovine parathyroid cell system where bromocriptine blocks the ability of dopamine to increase the accumulation of cyclic AMP.

Other Actions

Bromocriptine significantly inhibits the development of carcinogen-induced (DMBA) mammary tumors in female rats, and in mice it inhibits the growth of preneoplastic mammary nodules. Spontaneous mammary tumors in rats regressed during treatment with bromocriptine.

In experimental animals, dopamine agonists, including bromocriptine, have been shown to reduce the mitotic activity of pituitary cells stimulated by estrogen. There are a number of reports in the literature of regression of pituitary tumors in patients receiving bromocriptine.

TOXICOLOGY

ACUTE TOXICITY STUDIES

Species	LD_{50} (mg/kg ± S.D.)	
	I.V.	**P.O.**
Mouse	190 ± 9.3	2620 ± 604
Rat	72 ± 3.5	≥2000
Rabbit	12.5 ± 3.6	≥1000

It was possible to calculate an oral LD_{50}, only for mice, and even here the limits of confidence had to be extrapolated since at the highest dose that it was possible to administer, mortality was only 80%. In rats and rabbits no deaths occurred at the highest dose possible (2000 and 1000 mg/kg respectively).

CHRONIC TOXICITY STUDIES

Rats

Bromocriptine, mixed in food, was given to rats at dose levels of 5, 20 and 82 mg/kg/day for 53 weeks. At the 5 mg level no in-life drug effects were noted, but postmortem revealed increased adrenal weights and decreased pituitary weights in females. An increase in the number of cystic follicles with decreased luteal tissue in the ovaries was associated with some squamous metaplasia of the endometrium and indicated a drug effect on the pituitary gonadotrophic axis resulting in a picture of estrogen dominance. Similar endometrial changes were observed at the two higher dose levels but were more pronounced.

A subsequent two-ear toxicity study in rats showed that bromocriptine treatment at doses of 1.7 to 44 mg/kg/day again caused endometrial squamous metaplasia and that malignant neoplasms of the endometrium and myometrium occurred in a few animals. In ageing female rats, the cyclicity of reproductive function is lost due to hypothalamic changes in the presence of responsive ovaries and one of two stable conditions result: pseudopregnancy (progesterone dominance), which is a prolactin-dependent state, or continuous estrus (estrogen dominance), which occurs because of ovulation failure. The former is obviously prevented from occurring by the prolactin inhibitory action of bromocriptine, so that nearly all bromocriptine-treated rats are brought to continuous estrus. Both the metaplastic and the neoplastic endometrial changes are directly related to a situation of unopposed estrogen dominance peculiar to this species and did not occur in similar studies carried out in the mouse and dog.

Dogs

Bromocriptine in gelatin capsules was given once daily to dogs 7 days a week for 62 weeks. Initial doses were small (0.1 mg/kg/day) because of emesis but were escalated for the first ten weeks until dose levels of 1, 3, and 10 mg/kg/day were obtained and subsequently maintained for 52 weeks. During full dosage the following effects were observed: slight mydriasis, slight sedation, superficial epithelial necrosis of dependent ear margins characteristic of overdosage with ergot derivatives in dogs with low-hanging external ears, small cystic follicles and poorly formed or cystic corpora lutea in the ovaries, morphological evidence of thyroid hyperactivity, as well as non-specific pathologic changes in various organs. The above changes are all considered to be an expression of exaggerated pharmacodynamic effects. The macroscopic and microscopic appearance of the uteri of treated dogs was completely normal.

Monkeys

Bromocriptine as a suspension was also given by gavage to Rhesus monkeys, 7 days a week, for 13 weeks at doses of 2, 8, 32 mg/kg/day. At the low and mid-dose levels, neither in-life examinations nor postmortem studies revealed drug related effects. At the high dose level of 32 mg/kg/day some swollen basophils in the anterior pituitaries of 2/4 monkeys were found. No specific toxic effects of bromocriptine emerged in this study. Eight mg/kg/day can be regarded as an oral non-toxic effect level for the Rhesus monkey.

TERATOLOGY

Bromocriptine was given to pregnant rats at 3, 10 and 30 mg/kg/day from day 6 to 15 and 8 to 15 postcoitum, administered in 2% gelatin by gavage. Bromocriptine demonstrated no embryolethal or teratogenic effect at any of the dose levels used. When the drug was given during the period of implantation, inhibition of implantation was observed with 10 and 30 mg/kg/day. Because this effect was not observed when the drug was administered later, it is most probably attributable to the prolactin-inhibiting action of bromocriptine in this species.

Bromocriptine was given to pregnant rabbits at 3, 10, 30 and 100 mg/kg/day for days 16 to 18 postcoitum, administered in 2% gelatin by gavage. Two additional doses of 300 and 1000 mg/kg/day were given to characterize the toxic effects of bromocriptine on pregnant females, so that findings in the fetuses could be set in relation to maternal toxicity. Doses of 3 and 10 mg/kg/day were well tolerated by the dams whereas higher doses were toxic. Only at doses which produced maternal toxicity did questionable increases in prenatal mortality and the incidence of fetal abnormalities occur.

It is concluded that bromocriptine does not exert any embryolethal or teratogenic activity in the rabbit when given in non-toxic doses.

Female rats were given bromocriptine orally at doses of 1 and 3 mg/kg/day during the entire test period. After 14 days they were mated. Half of the animals were killed 13 days post-coitum; the other half were allowed to deliver and rear their offspring until 21 days postpartum. Bromocriptine was found to have no effects on the fertility of the dams, embryonic development or postnatal viability of the offspring.

MUTAGENICITY STUDIES

Bromocriptine has been tested in the following systems: the Ames test (using Salmonella typhimurum bacteria), micronucleus test in mice, the dominant lethal test in male mice and a cytogenetic analysis of Chinese hamster bone marrow cells (all tests for chromosome damaging potential). In none of these test systems did bromocriptine prove to be mutagenic.

CARCINOGENICITY

Bromocriptine has been subjected to prolonged toxicity studies (life time in rats and mice, 62 weeks in dogs, 13 weeks in primates) - See (CHRONIC TOXICITY).

SELECTED BIBLIOGRAPHY

1. Archer, DF et al: Reduction of serum prolactin with 2-Brom-α-Ergocryptine (CB 154) in women with galactorrhea. Fertil. and Steril. 26:191, 1975.
2. Archer, DF et al: Response to serum prolactin to thyrotropin-releasing hormone in women with 2-brom-α-ergocryptine. Gynec. Invest. 6: 54, 1975.
3. Ayres, J et al.: Alcohol increases bromocriptine's side effects. N. Engl. J. Med. 302: 806, 1980.
4. Bateman DE, Tunbridge WMG: Bromocriptine in the treatment of acromegaly. Drugs 17: 359-364, 1979.
5. Belforte L, Camanni F, et al: Long-term treatment with 2-Br-α-ergocryptine in acromegaly. Acta Endocrinol. 85: 235-248, 1977.
6. Berde B: Pharmacology of ergot alkaloids in clinical use. Med. J. Australia. 2: (Suppl.) 3-13 (Nov.4) 1978.
7. Besser, GM et al: Galactorrhea: Successful treatment with reduction of plasma prolactin levels by brom-ergocryptine. Br. Med. J. 3: 669-672, (Sept. 16), 1972.
8. Besser, GM et al: Absence of uterine neoplasia in patients on bromocriptine. Br. Med. J. 2: 868, 1977.
9. Besser, GM, Wass JAH, Thorner MO: Bromocriptine in the medical management of acromegaly. Ergot compounds & brain function: neuroendocrine & neuropsychiatric aspects. Edited by M. Goldstein et al, Raven Press, New York, 1980.
10. Bowler, JV, Ormerod, IE, Legg, NJ: Retroperitoneal fibrosis and bromocriptine. Lancet 2: 466, 1986.
11. Boyd, AE et al: Galactorrhea-amenorrhea, brom-ergocryptine, and the dopamine receptor. New Eng. J. Med. 293: 451-452 (Aug. 28), 1975.
12. Brook, NM et al: Bromocriptine-induced mania? Br. Med. J. 1:790, 1978.
13. Brooks AP, Stephen PJ et al: Bromocriptine and acromegaly: Therapeutic implications. J.R. Soc. Med. 72: 562-564, 1979.

14. Brun del Re, R et al: Prolactin inhibition and suppression of puerperal lactation by a br-ergocryptine (CB 154). Obstet. & Gynec. 41: 884-890 (June), 1973.

15. Calne DB et al: An ergot derivative in the treatment of Parkinson's Disease. Postgrad. Med. J. 52: 81-82, 1976.

16. Cassar J, Mashiter K, Joplin GF: Bromocriptine treatment of acromegaly. Metabolism 26(5): 539-546, 1977.

17. Chong, PN: Drug treatment of Parkinson's disease: Current concepts. Annals Academy of Medicine. 20(1), 1991.

18. Cohen, G: Monoamine oxydase and oxydative stress at dopaminergic synapses. Neural. Trasm. 32:229-238, 1990.

19. Copinschi, G et al: 2-bromo-α-ergocryptine (CB 154) inhibition of prolactin secretion and galactorrhoea in a case of pituitary tumour. Hormones & Antagonists Gynec. Invest. 2:128-129, 1971/72.

20. del Pozo, E et al: Clinical and hormonal response to bromocriptin (CB 154) in the galactorrhea syndromes. J. Clin. Endocrinol. Metab. 39: 18-26 (July), 1974.

21. del Pozo, E et al: Prolactin inhibition: experimental and clinical studies. International Congress Series No. 308 (ISBN 90 219 0231 1) Human Prolactin. Proceedings of the International Symposium on Human Prolactin, Brussels, June 12-14, 1973. Excerpta Medica, Amsterdam. 291-301.

22. del Pozo, E et al: Endocrine profile of a specific prolactin inhibitor: Br-ergocryptine (CB 154) a preliminary report. Schweiz. Med. Wschr. 103: 847-848, 1973.

23. del Pozo, E et al: The Inhibition of prolactin secretion in man by CB 154 (2-Br-α-Ergocryptine). J. Clin. Endocrinol. 35:768-771, 1972.

24. del Pozo E, Maclay WP: Gastrointestinal bleeding in patients on bromocriptine. Lancet 2: 906-907, 1976.

25. Demonet, JF et al: Retroperitoneal fibrosis and treatment of parkinson's disease with high doses of bromocriptine. Clin. Neuropharmacol. 9:200-201, 1986.

26. Descotes, J et al: Acute poisoning by the suicidal ingestion of bromocriptine. Bull. Méd. Lég. Toxicol. 22: 487-490, 1979.

27. Editorial: Prolactin Updated. Br. Med. J. 2: 846-848, 1977.

28. Eisler, T et al: Erythromelalgia-like eruption in parkinsonian patients treated with bromocriptine. Neurol. 29: 571, 1979.

29. Fournier, PJR et al: Current understanding of human prolactin physiology and its diagnostic and therapeutic applications: A review. Am. J. Obstet. & Gynecol. 118: 337-343 (Feb. 1), 1974.

30. Friesen, HG et al: The use of bromocriptine in the galactorrhoea-amenorrhoea syndromes: The Canadian Cooperative Study. Clin. Endocrinol. 6: Suppl., 915-99s, 1977.

31. Gaspar L, Laszlo FA: Long-term bromocriptine treatment and somatostatin in acromegaly. Endokrinologie 76 (2): 152-162, 1980.

32. Glantz, R et al.: The effect of bromocriptine (BCT) on the on-off phenomenon. J. Neural Transm. 52: 41-47, 1981.

33. Graille, R et al.: A propos d'une enquête de pharmacovigilance sur la bromocriptine utilisée dans l'inhibition de la lactation. Lettre de pharmacologue 9:16-17, 1995.

34. Grauwiler, J et al: Acute toxicity studies with 2-bromo-α-ergocryptine mesylate (CB 154). In: IRCS, Res. Endocrine Syst. Neurobiol. Neurophysiol. Pharmacol. Reproduct. Obstet. & Gynecol. 2: 1516, 1974.

35. Griffith, RW: Toxicity studies with 2-bromo-α-ergocryptine mesylate (CB 154): Effect of prolonged oral administration in rats. In: IRCS, Res. Endocrine Syst. Neurobiol. Neurophysiol. Pharmacol. Reproduct. Obstet. & Gynecol. 2:1661, 1974.

36. Grimes, JD and Hassan, MN: Bromocriptine in the long-term management of advanced Parkinson's Disease. Can. J. Neurol. Sci. 10: 86-90, 1983.

37. Grimes, JD and Hassan, MN: Method of addition of bromocriptine to the drug regime of patients with advanced Parkinson's Disease. Can. J. of Neurol. Sci. 8: 31-34, 1981.

38. Halse J, Naugen HN, Bohmer, T: Bromocriptine treatment in acromegaly: Clinical and biochemical effects. Acta Endocronol. 86: 464-472, 1977.

39. Ho Yuen, B et al: Efficacy of bromocriptine and chlorotrianisene in preventing postpartum lactation. Can. Med. Assoc. J. 117: 919-921, 1977.

40. Kissner, DG et al: Side effects of bromocriptine. N. Engl. J. Med. 302: 749, 1980.

41. Kobberling, J et al: More on bromocriptine in acromegaly. N. Engl. J. Med. 306: 748, 1982.

42. Kulig, K. et al: Bromocriptine-associated headache: possible life-threatening sympathomimetic interaction. Obstet & Gynec 78:941-943, 1991.

43. Kunzig, HJ et al: Treatment of galactorrhea-amenorrhea syndrome with 2-br-alpha-ergocryptine (CB 154). Clinical response and pattern of pituitary and steroid hormones before and during therapy. Arch. Gynak. 218: 85-94, 1975.

44. Kvistborg Flogstad, A. et al: A comparison of octreotide, bromocriptine or a combination of both drugs in acromegaly. J Clin Endocrinol Metab 79:461-465, 1994.

45. Larkin, JA: Bromocriptine: adverse reactions and interactions, ADIS Reactions No. 43, 27 November, 1981.

46. Le Blaye, I. et al: Bromocriptine overdose. Experience obtained from spontaneous reports to the manufacturer. Drug Invest 6/5:271-275, 1993.

47. Lightner ES, Winter JSD: Treatment of juvenile acromegaly with bromocriptine. J. Pediatr. 98(3): 494-496, 1981.

48. Linch DC, Shaw KM, et al: Bromocriptine-induced postural hypotension in acromegaly. Lancet 2: 320-321, 1978.

49. Lindholm J, Riishede J et al: No effect of bromocriptine in acromegaly. A controlled trial. N. Engl. J. Med. 304: 1450-1454, 1981.

50. Lindholm, J et al: Bromocriptine in acromegaly. N. Engl. J. Med. 305: 1092, 1982.

51. Lindholm J, et al: More on bromocriptine in acromegaly. N. Engl. J. Med. 306: 749, 1982.

52. Lloyd, SJ et al: Amenorrhea and galactorrhea: results of therapy with 2-brom-α-ergocryptine (CB 154). Am. J. Obstet. & Gynecol. 122: 85-89, (May 1), 1975.

53. Lutterbeck, PM et al: Treatment of non-peurperal galactorrhoea with an ergot alkaloid. Br. Med. J. 3: 228-229, (July 24), 1971.

54. Maneschi, F: Reappraisal of bromocriptine treatment for acromegaly. Horm. Res. 12: 191-205, 1980.

55. Maneschi, F et al: Shock syndrome after bromocriptine, Lancet 2: 462-463, 1977.

56. March CM et al: The efficacy of 2-br-α-ergocryptine in the management of amenorrhea and galactorrhea. Programme Abstracts of the Endocrine Society, 57th Annual Meeting, New York, N.Y. June 18-20, 1975, p. 285.

57. McGregor AM, Ginsberg J: Dilemmas in the management of functioning pituitary tumours. Brit. J. of Hosp. Medecine 25: 344-352, 1981.

58. Mehta AE et al: Pharmacology of bromocriptine in health and disease. Drugs 17: 313-325, 1979.

59. Meites, J: Neuroendocrinology of lactation. J. Invest. Dermat. 63: 119-124, 1974.

60. Molina-Negro, P et al: Bromocriptine (PARLODEL*) in the treatment of Parkinson's Disease. Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 6: 503-508, 1982.

61. Morrish DW, Crockford PM: Acrocyanosis treated with bromocriptine. Lancet 2: 85, 1976.

62. Mroueh, AM et al: Restoration of ovulation with 2-br-α-ergocryptine in patients with amenorrhea-galactorrhea and refractoriness to exogenous gonadotropins. Programme abstracts of the Endocrine Society, 57th Annual Meeting, New York, N.Y. June 18-20, 1975, p. 295.

63. Nakanishi, T et al: Third interim report of the nationwide collaborative study on the long-term effects of bromocriptine in the treatment of Parkinsonian patients. Eur. Neurol. 30 (suppl. 1):3-8, 1990.

64. Olanow, CW: Oxydation reactions in Parkinson's disease. Neurology. 40 (suppl. 3):32-37, 1990.

65. Olsson, JE et al: Early treatment with a combination of bromocriptine and levodopa compared with levodopa monotherapy in the treatment of Parkinson's disease. Current Therapeutic Research. 46(5), 1989.

66. Olsson, J.E. and the European Multicentric Trial Group: Bromocriptine and levodopa in early combination in Parkinson's disease: First results of the collaborative European multicentric trial. Advances in Therapy. 53:421-423, 1990.

67. Pearson, KC: Mental disorders from low-dose bromocriptine. N. Engl. J. Med. 305: 173, 1981.

68. Pearson, KC: Bromocriptine-PARLODEL*, hypertension-seizure cerebrovascular accidents in postpartum women. ADR Highlights 83-12, FDA, 5600 Fishers Lane, Rockville, ND. 20857.

69. Pelkonen, R, Ylikahri R, Karonen SL: Bromocriptine treatment of patients with acromegaly resistant to conventional therapy. Clin. Endocr. 12: 219-224, 1980.

70. Pepperell, RJ et al: Serum prolactin levels and the value of bromocriptine in the treatment of anovulatory infertility. Br. J. Obstet. Gynaecol. 84: 58-66, 1977.

71. Quabbe, H-J: Treatment of acromegaly by trans-sphenoidal operation, 90 - Yttrium implantation and bromocriptine: results in 230 patients. Clin. Endocr. 16: 107-119, 1982.

72. Reaville, C et al: Pharmacological and biochemical aspects of the mechanisms of action of bromocriptine. Res. Clin. Forums 3: 7-17, 1981.

73. Rinne, UK: Early combination of bromocriptine and levodopa in the treatment of Parkinson's disease: A 5-year follow-up. Neurology. 37:826-828, 1987.

74. Rinne, UK: Early dopamine agonist therapy in Parkinson's disease. Movement Disorders. 4(suppl.1):586-594, 1989.

75. Rjosk, HK et al: Suppression of prolactin in menstrual disorders. Acta. Endocr. (Kbh.) Suppl. 193: 8, 1975.

76. Rolland, R et al: The role of prolactin in the restoration of ovarian function during the early post-partum period in the human female II. A study during inhibition of lactation by bromergocryptine. Clin. Endocrin. 4: 27-38, 1975.

77. Rolland, R et al: Successful treatment of galactorrhoea and amenorrhoea and subsequent restoration of ovarian function by a new ergot alkaloid 2-brom-α-ergocryptine. Clin. Endocr. 3: 155-165, 1974.

78. Rozencweig, M et al: Effects of 2-br-α-ergocryptine, L-Dopa and cyclic imides on serum prolactin in postmenopausal women. Europ. J. Cancer, 9: 657-664, 1973.

79. Sachdev Y, Gomez-Pan A et al: Bromocriptine therapy in acromegaly. Lancet 2: 1164-1168, 1975.

80. Schindler, AE et al: Diagnostic evaluation and follow up of patients with amenorrhea-galactorrhea under treatment with bromoergocryptine (CB 154). Acta. Endocr. (Kbh.) Suppl. 194: 25, 1975.

81. Schran, HF et al: The pharmacokinetics of bromocriptine in man, In: M.0. Thorner, D. Calne, A. Liebermann and M. Goldstein (eds.), Ergot compounds and brain function neuroendocrine and neuropsychiatric aspects, pp. 125-139, Raven Press, New York, 1980, p. 125-139.

82. Schulz, KD et al: Some endocrine effects of 2-bromo-α-ergocryptine (CB 154) in women. Acta. Endocr. (Kbh.) (Suppl.) 193: 27, 1975.

83. Schwinn G, Dirks H et al: Metabolic and clinical studies on patients with acromegaly treated with bromocriptine over 22 months. Eur. J. Clin. Invest. 7: 101-107, 1977.

84. Seki, K et al: Effect of CB 154 (2-Br-α-ergocryptine) on serum follicle stimulatine hormone, luteinizing hormone and prolactin in women with the amenorrhoea-galactorrhoea syndrome. Acta. Endocr. (Kbh.) 79: 25-33, 1975.

85. Seppala, M et al: Raised serum prolactin levels in amenorrhea. Br. Med. J. 2: 305-306, (May 10), 1975.

86. Sibley, WA, Laguna, JF: Enhancement of bromocriptine clinical effect and plasma levels with erythromycin. In: l2th World Congress Neurol., Kyoto (Japan), 1981. Publ. Excerpta Medica, Amsterdam, 1981. p. 329-330.

87. Smithline, F et al: Prolactin and breast carcinoma. New Eng. J. Med. 292: 784-792, (April 10), 1975.

88. Spark RF et al: Bromocriptine reduces pituitary tumor size and hypersecretion. JAMA, 247: 311-316, 1982.

89. Steinbeck K, Turtle JR: Treatment of Acromegaly with Bromocriptine. Aust. NZ J. Med. 9: 217-224, 1979.

90. Thorner, M0 et al: Bromocriptine, a Clinical and Pharmacological Review. Raven Press. New York, 1980, p. 14-23.

91. Thorner, M0 et al: Bromocriptine in Acromegaly. N. Engl. J. Med., 305: 1092, 1982.

92. Thorner, M0 et al: Long-term Treatment of Galactorrhoea and Hypogonadism with Bromocriptine. Br. Med. J. 2: 419-422, (May 25), 1974.

93. Thorner, M0: Prolactin. Clin. Endocrinol. Metab. 6: 201-222, 1977.

94. Thorner, M0 et al: Rapid Regression of Pituitary Prolactinomas during Bromocriptine Treatment. J.Clin. Endocr. 51: 438-445, 1980.

95. Tolis, G et al: Prolactin and Human Reproduction. Can. Med. Assoc. J. 115: 709-711, 1976.

96. Tolis, G et al: Prolactin Secretion in Sixty-five Patients with Galactorrhea. Am. J. Obstet. & Gynecol. 118: 91-100, (Jan. 1), 1974.

97. Turkalj, I et al: Surveillance of Bromocriptine in Pregnancy. JAMA 247: 1589-1591, 1982.

98. Tyson, JE et al: Neuroendocrine Dysfunction in Galactorrhea-Amenorrhea After Oral Contraceptive Use. Obstet. & Gynec. 46: 1-II, 1975.

99. Van Loon, GR: Bromocriptine-induced Orthostatic Hypotension. Clin. Invest. Med. 2: 131-134, 1980.

100. Varga, L et al: Treatment of Galactorrhea-Amenorrhea Syndrome with Br-Ergocryptine (CB 154): Restoration of Ovulatory Function and Fertility. Am. J. Obstet. & Gynecol. 117: 75-79, (Sept. 1), 1973.

101. Vlissides, DN et al: Bromocriptine-induced mania? Br. Med. J. 1:510, 1978.

102. Voller, GW and Ulm G: Bromocriptine in Parkinson's syndrome. Med. Welt (Stuttg.) 30:1930-1933, 1979.

103. Wang, C, Chan V, Yeung, RTT: Treatment of Acromegaly with Bromocriptine. Aust. NZ J. Med. 9:225-232, 1979.

104. Warren, DE, Nakfoor, E: Acute Overdosage of Bromocriptine. Drug Intell. Clin. Pharm. 17:374, 1983.