PRODUCT MONOGRAPH

APO-CABERGOLINE

Cabergoline Tablets USP

0.5 mg

DOPAMINE RECEPTOR AGONIST

APOTEX INC.
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Toronto, Ontario
M9L 1T9

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APO-CABERGOLINE

Cabergoline Tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet / 0.5 mg	Lactose Anhydrous NF, Leucine USP and Magnesium Stearate NF.

INDICATIONS AND CLINICAL USE

APO-CABERGOLINE (cabergoline) is indicated for:

- **Treatment of hyperprolactinemic disorders:**
  APO-CABERGOLINE is indicated for the treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas.

- **Inhibition of physiological lactation:**
  APO-CABERGOLINE is indicated for the prevention of the onset of physiological lactation in the puerperium for clearly defined medical reasons.

These medical reasons may include birth of a still born baby, neonatal death, conditions interfering with suckling (cleft lip or palate of the baby), severe acute or chronic mental illness or medical conditions, maternal disease which may be transmitted to the baby that require medications which are excreted in the milk.

APO-CABERGOLINE is not indicated for the purpose of suppression of already established post-partum lactation.

Pediatrics (<16 years of age)

Safety and effectiveness of cabergoline in pediatric patients have not been established.

Geriatrics (>65 years of age)

Very limited data concerning experience of treatment of hyperprolactinemia in the elderly are available. However, available data do not indicate a special risk for this population.

CONTRAINDICATIONS

APO-CABERGOLINE (cabergoline) is contraindicated in patients with:

- uncontrolled hypertension,
- a history of pulmonary, pericardial and retroperitoneal fibrotic disorders. (See WARNINGS AND PRECAUTIONS),
- anatomical evidence of cardiac valvulopathy of any valve (e.g., echocardiogram showing valve leaflet thickening, valve restriction, valve mixed restriction-stenosis). Echocardiogram is required at pretreatment in patients being treated for hyperprolactinemic disorders (see WARNINGS AND PRECAUTIONS),
- a known hypersensitivity to this drug or any ergot derivatives and to any ingredient in the formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

General

Dopamine agonists in general should not be used in patients with pregnancy-induced hypertension, for example, preeclampsia and eclampsia, unless the potential benefit is judged to outweigh the possible risk.

Initial doses higher than 1.0 mg may produce orthostatic hypotension. Care should be exercised when administering APO-CABERGOLINE (cabergoline) with other medications known to lower blood pressure.

The effects of alcohol on overall tolerability of cabergoline are currently unknown.

Before APO-CABERGOLINE (cabergoline) administration, pregnancy should be excluded and after treatment pregnancy should be prevented for at least one month.

Carcinogenesis and Mutagenesis

Please see also TOXICOLOGY.

Cardiovascular

APO-CABERGOLINE (cabergoline) should be given with caution to subjects with cardiovascular disease and Raynaud's syndrome. Symptomatic hypotension can occur with cabergoline administration. Care should be exercised when administering APO-CABERGOLINE (cabergoline) concomitantly with other drugs known to lower blood pressure.

Fibrosis

As with other ergot derivatives, pleural effusion/pulmonary fibrosis has been reported following long-term administration of cabergoline. Therefore, APO-CABERGOLINE (cabergoline) should not be used in patients with a history of, or current signs and /or symptoms of respiratory or cardiac disorders linked to fibrotic tissue (see CONTRAINDICATIONS). Erythrocyte sedimentation rate (ESR) has been found to be abnormally increased in association with pleural effusion/fibrosis. Chest x-ray examination is recommended in cases of unexplained ESR increases to abnormal values. Serum creatinine measurements can also be used to help in the diagnosis of fibrotic disorder. Following diagnosis of pleural effusion/pulmonary fibrosis, the discontinuance of cabergoline has been reported to result in improvement of signs and symptoms.

Treatment for Hyperprolactinemia

Before initiating treatment:

All patients must undergo a cardiovascular evaluation, including echocardiogram to assess the potential presence of asymptomatic valvular disease. It is also appropriate to perform baseline investigations of erythrocyte sedimentation rate or other inflammatory markers, lung function/chest X-ray and renal function prior to initiation of therapy.

During treatment:

Fibrotic disorders can have an insidious onset and patients should be regularly monitored for possible manifestations of progressive fibrosis. Therefore, during treatment, attention should be paid to the signs and symptoms of:

- Pleuro-pulmonary disease such as dyspnoea, shortness of breath, persistent cough or chest pain
- Renal insufficiency or ureteral/abdominal vascular obstruction that may occur with pain in the loin/flank and lower limb oedema as well as any possible abdominal masses or tenderness that may indicate retroperitoneal fibrosis.
- Cardiac failure: cases of valvular and pericardial fibrosis have often manifested as cardiac failure. Therefore, valvular fibrosis (and constrictive pericarditis) should be excluded if such symptoms occur.

Clinical diagnostic monitoring for development of fibrotic disorders, as appropriate, is essential.

Additional appropriate investigations such as erythrocyte sedimentation rate, and serum creatinine measurements should be performed if necessary to support a diagnosis of a fibrotic disorder.

The need for other clinical monitoring (e.g., physical examination including cardiac auscultation, X-ray, CT scan) should be determined on an individual basis.

Cardiac Valvulopathy

There have been post-marketing reports of cardiac valvulopathy involving one or more valves in patients taking cabergoline. The incidence of treatment emergent cardiac valvulopathy has not yet been determined, although some studies have suggested that the risk is cumulative, and asymptomatic cases of valvulopathy have been identified using echocardiography.

Valvulopathy has been reported with substantially greater frequency during treatment with ergot derivatives with 5-HT2B agonist activity, including cabergoline, compared to non-ergot dopamine agonists.

APO-CABERGOLINE is contraindicated in patients with a history of cardiac valvulopathy (see CONTRAINDICATIONS). Physicians should inform patients/caregivers of the risk of cardiac valvulopathy.

Treatment of Hyperprolactinemia

Before initiating treatment:

All patients must undergo a cardiovascular evaluation, including echocardiogram to assess the potential presence of asymptomatic valvular disease. In patients with valvular regurgitation, it is not known whether cabergoline treatment might worsen the underlying disease. If fibrotic valvular disease is detected, the patient should not be treated with cabergoline (See CONTRAINDICATIONS).

During treatment:

Fibrotic disorders can have an insidious onset and patients should be regularly monitored for possible manifestations of progressive fibrosis. Therefore, during treatment, attention should be paid to the signs and symptoms of:

- Cardiac failure: cases of valvular and pericardial fibrosis have often manifested as cardiac failure. Therefore, valvular fibrosis (and constrictive pericarditis) should be excluded if such symptoms occur.

Following treatment initiation, the first echocardiogram must occur within 3-6 months; thereafter, the frequency of echocardiographic monitoring should be determined by appropriate individual clinical assessment with particular emphasis on the above-mentioned signs and symptoms, but must occur at least every 6 to 12 months.

Cabergoline should be discontinued if an echocardiogram reveals new or worsened valvular regurgitation, valvular restriction or valve leaflet thickening (see CONTRAINDICATIONS).

The need for other clinical monitoring (e.g., physical examination including cardiac auscultation, X-ray, CT scan) should be determined on an individual basis.

Gastrointestinal

APO-CABERGOLINE should be given with caution to subjects with peptic ulcer and gastrointestinal bleeding.

Hepatic

Since cabergoline is extensively metabolized by the liver, caution should be used, and careful monitoring exercised, when administering APO-CABERGOLINE to patients with hepatic impairment (see DETAILED PHARMACOLOGY, Pharmacokinetics, Special Populations).

Neurologic

Cabergoline has been associated with somnolence. Sudden sleep onset episodes that can be associated with dopamine agonists usually occur in patients with Parkinson's disease. A reduction of dosage or termination of therapy may be considered.

Patients being treated with cabergoline should be warned of the potential for experiencing somnolence. Patients should be cautioned about engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) in case somnolence does occur.

Psychiatric

APO-CABERGOLINE should be given with caution to subjects with a history of mental disease. Particular care should be taken when patients are taking concomitant psychoactive medication (see DRUG INTERACTIONS).

Aggression, psychotic behavior and impulse control disorders such as pathological gambling, increased libido, hypersexuality, compulsive spending or buying and compulsive eating have been reported in patients treated with dopamine agonists including cabergoline. This has been generally reversible upon reduction of the dose or treatment discontinuation.

Renal

APO-CABERGOLINE should be given with caution to subjects with renal insufficiency (see DETAILED PHARMACOLOGY, Pharmacokinetics, Special Populations).

Special Populations

Pregnant Women

Reproduction studies have been performed with cabergoline in mice, rats, and rabbits administered by gavage. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed (see TOXICOLOGY**)**. Before APO-CABERGOLINE administration, pregnancy should be excluded and after treatment

pregnancy should be prevented for at least one month.

Nursing Women
Based on information from animal studies, excretion in human milk is very likely (see DETAILED PHARMACOLOGY). Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cabergoline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Due to this interference with lactation, APO-CABERGOLINE should not be given to women postpartum who are breastfeeding or who are planning to breastfeed.

Pediatrics
Safety and effectiveness of cabergoline in pediatric patients have not been established.

Geriatrics
Very limited data concerning experience of treatment of hyperprolactinemia in the elderly are available. However, available data do not indicate a special risk for this population.

Monitoring and Laboratory Tests

Erythrocyte sedimentation rate (ESR) has been found to be abnormally increased in association with pleural effusion/fibrosis. Chest x-ray examination is recommended in cases of unexplained ESR increases to abnormal values. Serum creatinine measurements can also be used to help in the diagnosis of fibrotic disorder.

Treatment of Hyperprolactinemia

Before initiating treatment:

All patients must undergo a cardiovascular evaluation, including echocardiogram to assess the potential presence of asymptomatic valvular disease. It is also appropriate to perform baseline investigations of erythrocyte sedimentation rate or other inflammatory markers, lung function/chest X-ray and renal function prior to initiation of therapy. In patients with valvular regurgitation, it is not known whether cabergoline treatment might worsen the underlying disease. If fibrotic valvular disease is detected, the patient should not be treated with cabergoline (See CONTRAINDICATIONS).

During treatment:

Fibrotic disorders can have an insidious onset and patients should be regularly monitored for possible manifestations of progressive fibrosis. Therefore, during treatment, attention should be paid to the signs and symptoms of:

- Pleuro-pulmonary disease such as dyspnoea, shortness of breath, persistent cough or chest pain

- Renal insufficiency or ureteral/abdominal vascular obstruction that may occur with pain in the loin/flank and lower limb oedema as well as any possible abdominal masses or tenderness that may indicate retroperitoneal fibrosis.
- Cardiac failure: cases of valvular and pericardial fibrosis have often manifested as cardiac failure. Therefore, valvular fibrosis (and constrictive pericarditis) should be excluded if such symptoms occur.

Clinical diagnostic monitoring for development of fibrotic disorders, as appropriate, is essential. Following treatment initiation, the first echocardiogram must occur within 3-6 months; thereafter, the frequency of echocardiographic monitoring should be determined by appropriate individual clinical assessment with particular emphasis on the above-mentioned signs and symptoms, but must occur at least every 6 to 12 months.

Cabergoline should be discontinued if an echocardiogram reveals new or worsened valvular regurgitation, valvular restriction or valve leaflet thickening (see CONTRAINDICATIONS).

The need for other clinical monitoring (e.g., physical examination including cardiac auscultation, X-ray, CT scan) should be determined on an individual basis.

Additional appropriate investigations such as erythrocyte sedimentation rate, and serum creatinine measurements should be performed if necessary to support a diagnosis of a fibrotic disorder.

Information for Patients

A patient should be instructed to notify her physician if she suspects she is pregnant, becomes pregnant, or intends to become pregnant during therapy. A pregnancy test should be done if there is any suspicion of pregnancy and continuation of treatment should be discussed with her physician.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Hyperprolactinemic Disorders
The safety of cabergoline has been evaluated in more than 900 patients with hyperprolactinemic disorders. Most adverse events were mild or moderate in severity (see Tables 1 and 2 for the incidence of most common adverse events during the placebo-controlled studies). The most common adverse events were nausea, headache and dizziness and the most common reason for discontinuation was dizziness.

Inhibition of Physiological Lactation
Most side effects were transient and mild to moderate in severity. In women treated for inhibition of physiologic lactation the most frequently occurring adverse events were asymptomatic decreases in blood pressure, dizziness/vertigo, headache, nausea, and abdominal pain. In

addition, on rare occasions, palpitations, epigastric pain, somnolence, epistaxis, and transient hemianopia have been reported (see WARNINGS AND PRECAUTIONS).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Hyperprolactinemic Disorders

In a 4-week, double-blind, placebo-controlled study, treatment consisted of placebo or cabergoline at fixed doses of 0.125, 0.5, 0.75, or 1.0 mg twice weekly. Doses were halved during the first week. Since a possible dose-related effect was observed for nausea only, the four cabergoline treatment groups have been combined. The incidence of the most common adverse events during the placebo-controlled study is presented in Table 1.

Table 1
Incidence of Reported Adverse Events During the 4-Week, Double-Blind, Placebo-Controlled Trial

Adverse Event*	Cabergoline (n=168) 0.125 to 1 mg two times a week	Placebo (n=20)
	Number (percent)	
Gastrointestinal		
Nausea	45 (27)	4 (20)
Constipation	15 (10)	0
Abdominal pain	9 (5)	1 (5)
Dyspepsia	4 (2)	0
Vomiting	4 (2)	0
Central and Peripheral Nervous System		
Headache	43 (26)	5 (25)
Dizziness	25 (15)	1 (5)
Paresthesia	2 (1)	0
Vertigo	2 (1)	0
Body as A Whole		
Asthenia	15 (9)	2 (10)
Fatigue	12 (7)	0
Hot flashes	2 (1)	1 (5)
Psychiatric		
Somnolence	9 (5)	1 (5)
Depression	5 (3)	1 (5)
Nervousness	4 (2)	0
Autonomic Nervous System		
Postural hypotension	6 (4)	0
Reproductive - Female		
Breast pain	2 (1)	0
Dysmenorrhea	2 (1)	0
Vision		
Abnormal vision	2 (1)	0

* Reported at $\geq$ 1% for cabergoline

In the 8-week, double-blind period of the comparative trial with bromocriptine, cabergoline (at a

dose of 0.5 mg twice weekly) was discontinued due to an adverse event in 4 of 221 patients (2%) while bromocriptine (at a dose of 2.5 mg two times a day) was discontinued due to an adverse event in 14 of 231 patients (6%). The most common reasons for discontinuation from cabergoline were headache, nausea and vomiting (3, 2 and 2 patients respectively); the most common reasons for discontinuation from bromocriptine were nausea, vomiting, headache, and dizziness or vertigo (10, 3, 3, and 3 patients respectively). The incidence of the most common adverse events during the double-blind portion of the comparative trial with bromocriptine is presented in Table 2.

Table 2
Incidence of Reported Adverse Events During the 8-Week, Double-Blind Period of the Comparative Trial With Bromocriptine

Adverse Event*	Cabergoline (n=221)	Bromocriptine (n=231)
	Number (percent)	
Gastrointestinal		
Nausea	63 (29)	100 (43)
Constipation	15 (7)	21 (9)
Abdominal pain	12 (5)	19 (8)
Dyspepsia	11 (5)	16 (7)
Vomiting	9 (4)	16 (7)
Dry mouth	5 (2)	2 (1)
Diarrhea	4 (2)	7 (3)
Flatulence	4 (2)	3 (1)
Throat irritation	2 (1)	0
Toothache	2 (1)	0
Central and Peripheral Nervous System		
Headache	58 (26)	62 (27)
Dizziness	38 (17)	42 (18)
Vertigo	9 (4)	10 (4)
Paresthesia	5 (2)	6 (3)
Body as A Whole		
Asthenia	13 (6)	15 (6)
Fatigue	10 (5)	18 (8)
Syncope	3 (1)	3 (1)
Influenza-like symptoms	2 (1)	0
Malaise	2 (1)	0
Periorbital edema	2 (1)	2 (1)
Peripheral edema	2 (1)	1
Psychiatric		
Depression	7 (3)	5 (2)
Somnolence	5 (2)	5 (2)
Anorexia	3 (1)	3 (1)
Anxiety	3 (1)	3 (1)
Insomnia	3 (1)	2 (1)
Impaired concentration	2 (1)	1
Nervousness	2 (1)	5 (2)
Cardiovascular		
Hot flashes	6 (3)	3 (1)
Hypotension	3 (1)	4 (2)
Dependent edema	2 (1)	1
Palpitation	2 (1)	5 (2)
Reproductive - Female		
Breast pain	5 (2)	8 (3)
Dysmenorrhea	2 (1)	1
Skin and Appendages		
Acne	3 (1)	0
Pruritus	2 (1)	1

Table 2 Incidence of Reported Adverse Events During the 8-Week, Double-Blind Period of the Comparative Trial With Bromocriptine		
Adverse Event*	**Cabergoline (n=221)**	**Bromocriptine (n=231)**
	Number (percent)	
Musculoskeletal		
Pain	4 (2)	6 (3)
Arthralgia	2 (1)	0
Respiratory		
Rhinitis	2 (1)	9 (4)
Vision		
Abnormal vision	2 (1)	2 (1)

* Reported at ≥ 1% for cabergoline

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Hyperprolactinemic Disorders

Body As a Whole: facial edema, influenza-like symptoms, malaise

Cardiovascular System: hypotension, syncope, palpitations

Digestive System: dry mouth, flatulence, diarrhea, anorexia

Metabolic and Nutritional System: weight loss, weight gain

Nervous System: somnolence, nervousness, paresthesia, insomnia, anxiety

Respiratory System: nasal stuffiness, epistaxis

Skin and Appendages: acne, pruritus

Special Senses: abnormal vision

Urogenital System: dysmenorrhea, increased libido

Other Conditions

The safety of cabergoline has been evaluated in approximately 1,200 patients with Parkinson's disease in controlled and uncontrolled studies at dosages of up to 11.5 mg/day which greatly exceeds the maximum recommended dosage of cabergoline for hyperprolactinemic disorders. In addition to the adverse events that occurred in the patients with hyperprolactinemic disorders, the most common adverse events in patients with Parkinson's disease were dyskinesia, hallucinations, confusion, peripheral edema and sudden onset sleep. Heart failure, pleural effusion, pulmonary fibrosis, and gastric or duodenal ulcer occurred rarely. One case of constrictive pericarditis has been reported.

Post-Market Adverse Drug Reactions

The following events have been reported in patients who have received cabergoline: aggression,

psychotic disorder, delusions, impulse control disorders such as hypersexuality, increased libido, compulsive spending or buying, compulsive eating and pathological gambling, hepatic function abnormal, liver function tests abnormal, alopecia, blood creatinine phosphokinase increased, , dyspnea, edema, congenital abnormalities, fibrosis, hypersensitivity reaction, rash, respiratory disorder, respiratory failure, sudden sleep onset and valvulopathy. It should be noted that the uncontrolled nature of post-marketing surveillance makes it difficult to determine definitively if a reported event was actually caused by cabergoline, or to reliably assess causation in individual cases (see WARNINGS AND PRECAUTIONS).

The prevalence of asymptomatic valvular regurgitation is significantly greater than that of non-ergot dopamine agonists (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

DRUG INTERACTIONS

Overview

Ergot-Alkaloids
Although there is no conclusive evidence of an interaction between cabergoline and other ergot alkaloids, the concomitant use of these medications during long-term treatment with APO-CABERGOLINE is not recommended.

Dopamine Antagonists
Since cabergoline exerts its therapeutic effect by direct stimulation of dopamine receptors, it should not be concurrently administered with drugs that have dopamine-antagonist activity (such as phenothiazines, butyrophenones, thioxanthenes, metoclopramide) since these might reduce the prolactin-lowering effect of APO-CABERGOLINE.

Macrolide Antibiotics
By analogy with ergot derivatives, APO-CABERGOLINE should not be used in association with macrolide antibiotics (e.g., erythromycin) since systemic bioavailability and also adverse effects could increase.

Drug-Food Interactions

Food is not noted to affect the absorption of cabergoline tablets (see DOSAGE AND ADMINISTRATION, Dosing Considerations and ACTION AND CLINICAL PHARMA-COLOGY, Pharmacokinetics).

DOSAGE AND ADMINISTRATION

Dosing Considerations

Since the tolerability of this class of compounds is improved when administered with food, it is

recommended, that APO-CABERGOLINE (Cabergoline Tablets) be taken with meals, for all the therapeutic indications. Food is not noted to affect the absorption of cabergoline tablets (see DRUG INTERACTIONS, Drug-Food Interactions, ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Recommended Dose and Dosage Adjustment

Adults

Treatment of Hyperprolactinemia: The recommended initial dosage of APO-CABERGOLINE is 0.5 mg per week given in one or two (one-half of one 0.5 mg tablet) doses (e.g. on Monday and Thursday) per week. The weekly dose should be increased gradually, preferably by adding 0.5 mg per week at monthly intervals until an optimal therapeutic response is achieved. The therapeutic dosage is usually 1 mg per week and ranges from 0.25 mg to 2.0 mg per week.

The weekly dose may be given as a single administration or divided into two or more doses per week according to patient tolerability. Division of the weekly dose into multiple administrations is advised when doses higher than 1 mg per week are to be given, since the tolerability of doses greater than 1 mg taken as a single weekly dose has been evaluated only in a few patients.

Patients should be evaluated during dose escalation to determine the lowest dosage that produces the therapeutic response. Monitoring of serum prolactin levels at monthly intervals is advised since, once the effective therapeutic dosage regimen has been reached, serum prolactin normalization is usually observed within 2 to 4 weeks.

After a normal serum prolactin level has been maintained for 6 months, APO-CABERGOLINE may be discontinued, with periodic monitoring of the serum prolactin level to determine whether or when treatment with APO-CABERGOLINE should be reinstituted.

Missed Dose: If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time (e.g. 1 day) before the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double dose.

Inhibition of Physiological Lactation: For inhibition of physiological lactation the recommended therapeutic dosage is 1 mg (two 0.5 mg tablets) given as a single dose. APO-CABERGOLINE should be administered during the first day post-partum.

Administration

APO-CABERGOLINE is to be administered by the oral route.

OVERDOSAGE

There is no experience with cabergoline in humans of over dosage when used in the proposed indications. Doses of cabergoline up to 4.5 mg per week have been used in hyperprolactinemic patients. Symptoms of overdose would likely be those of over-stimulation of dopamine receptors. These might include nausea, vomiting, gastric complaints, hypotension, or

thought/perception disturbances (hallucinations), nasal congestion and syncope.

General supportive measures should be undertaken to remove any unabsorbed drug and maintain blood pressure if necessary. In addition, the administration of dopamine antagonist drug may be advisable. Measures to support blood pressure should be taken if necessary.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Cabergoline, the active ingredient in APO-CABERGOLINE, is a dopaminergic ergoline derivative endowed with a potent and long-lasting prolactin-lowering activity. It acts by direct stimulation of the D_2-dopamine receptors on pituitary lactotrophs, thus inhibiting prolactin secretion. In rats the compound decreases prolactin secretion at oral doses of 3 to 25 mcg/kg, and *in vitro* at a concentration of 45 pg/mL. In addition, cabergoline exerts a central dopaminergic effect via D_2-receptor stimulation at oral doses higher than those effective in lowering serum prolactin levels.

Pharmacodynamics

The long-lasting prolactin-lowering effect of cabergoline is probably due to its long persistence in the target organ as suggested by the slow elimination of total radioactivity from the pituitary after a single oral dose in rats ($t_{1/2}$ of approximately 60 hours).

The pharmacodynamic effects of cabergoline have been studied in healthy volunteers, puerperal women and hyperprolactinemic patients. After a single oral administration of cabergoline (0.3 to 1.5 mg), a significant decrease in serum prolactin levels was observed in each of the populations studied. The effect is prompt (within 3 hours from administration) and persistent (up to 7 to 28 days in healthy volunteers and hyperprolactinemic patients, and up to 14 to 21 days in puerperal women). The prolactin lowering effect is dose-related both in terms of degree of effect and duration of action.

With regard to the endocrine effects of cabergoline not related to the antiprolactinemic effect, available data from humans confirm the experimental findings in animals indicating that the test compound is endowed with a selective action with no effect on basal secretion of other pituitary hormones or cortisol. The pharmacodynamic actions of cabergoline not correlated with the therapeutic effect relate only to blood pressure decrease. The maximal hypotensive effect of a single dose usually occurs during the first 6 hours after drug intake and is dose-dependent both in terms of maximal decrease and frequency (see DETAILED PHARMACOLOGY, Pharmacodynamics).

Pharmacokinetics

The pharmacokinetic and metabolic profiles of cabergoline have been studied in healthy volunteers of both sexes and in female hyperprolactinemic patients.

Absorption

After oral administration of the labeled compound, radioactivity was rapidly absorbed from the gastrointestinal tract as the peak of radioactivity in plasma was between 0.5 and 4 hours. Ten days after administration, about 18% and 72% of the radioactive dose of ^{14}C-cabergoline was recovered in the urine and feces, respectively. Unchanged drug in urine accounted for 2% to 3% of the dose. Food does not appear to affect absorption and disposition of cabergoline (see DETAILED PHARMACOLOGY, Pharmacokinetics).

Distribution

In vitro experiments showed that the drug at concentrations of 0.1 to 10 ng/mL is 41% to 42% bound to plasma proteins (see DETAILED PHARMACOLOGY, Pharmacokinetics).

Metabolism

In urine, the main metabolite identified was 6-allyl-8b-carboxy-ergoline, which accounted for 4% to 6% of the dose. Three additional metabolites were identified in urine, which accounted overall for less than 3% of the dose. The metabolites have been found to be much less potent than cabergoline in inhibiting prolactin secretion *in vitro*.

The pharmacokinetics of cabergoline were found to be dose-independent in healthy volunteers at doses of 0.5 to 1.5 mg. On the basis of the elimination half-life, steady state conditions should be achieved after 4 weeks, as confirmed by the mean peak plasma levels of cabergoline obtained after a single dose (37 ± 8 pg/mL) and after a 4-week multiple-dose regimen (101 ± 43 pg/mL). While renal insufficiency has been shown not to modify cabergoline kinetics, hepatic insufficiency of severe degree (>10 Child-Pugh score, maximum score 12) has been shown to be associated with an increase of AUC (see DETAILED PHARMACOLOGY, Pharmacokinetics, Special Populations).

Excretion

The low urinary excretion of unchanged cabergoline has been confirmed also in studies with non-radioactive product. The elimination half-life of cabergoline, estimated from urinary excretion rates, is long (63 to 68 hours in healthy volunteers and 79 to 115 hours in hyperprolactinemic patients as assessed by radioimmunoassay) (see DETAILED PHARMACOLOGY, Pharmacokinetics).

Special Populations and Conditions

Renal Insufficiency

The pharmacokinetics of cabergoline were not altered in patients with moderate-to-severe renal insufficiency as assessed by creatinine clearance (see DETAILED PHARMACOLOGY, Pharmacokinetics, Special Populations).

Hepatic Insufficiency
Hepatic insufficiency of severe degree (>10 Child-Pugh score, maximum score 12) has been shown to be associated with an increase of AUC (about six-fold) (see DETAILED PHARMACOLOGY, Pharmacokinetics, Special Populations).

STORAGE AND STABILITY

Store at room temperature 15-25°C (59-77°F). Protect from light and moisture.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-CABERGOLINE (Cabergoline Tablets) is available as white, capsule-shaped, flat scored tablets containing 0.5 mg cabergoline. Each scored tablet has "APO" on one side of the scoreline and "CA" and "0.5" on either side of the bisect on the other side.

APO-CABERGOLINE is available in bottles of 8 tablets.

Composition

APO-CABERGOLINE Tablets for oral administration contain 0.5 mg cabergoline. The non-medicinal ingredients are lactose anhydrous, leucine and magnesium stearate.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

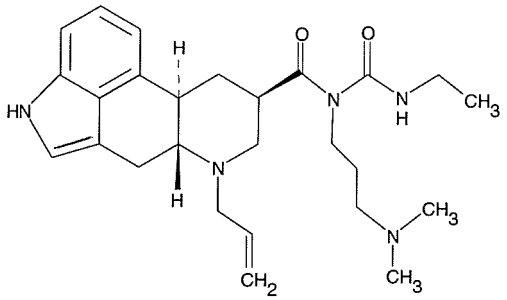
Proper Name: Cabergoline

Chemical Name: (8β)-*N*-[3-(dimethylamino)propyl]-*N*-[(ethylamino)carbonyl]-6-(2-propenyl)ergoline-8-carboxamide

Molecular Formula: $C_{26}H_{37}N_5O_2$

Molecular Weight: 451.60 g/mol

Structural Formula:



Physicochemical Properties:

Description: A cream to white powder

Solubility: Freely soluble in ethyl alcohol, chloroform, and *N,N*-dimethylformamide; slightly soluble in aqueous 0.1N HCl; very slightly soluble in *n*-hexane and insoluble in water

pH: 7.4 at 25°C in water.

pKa: $pKa_1 = 9.41 \pm 0.28$
$pKa_2 = 13.05 \pm 0.46$

CLINICAL TRIALS

Cabergoline was evaluated for the inhibition of lactation in two pivotal studies involving a total of 412 women: 256 received cabergoline (0.5-1.0 mg), 136 bromocriptine (2.5 mg twice daily for 14 days) and 20 placebo. In the placebo controlled, randomized dose ranging study, cabergoline was administered in 3 different single doses (0.5, 0.75, 1.0 mg) in puerperae requiring the inhibition of lactation. A total of 140 female patients (40 for each cabergoline dose and 20 for placebo) entered the study with a mean age of 27.6 years (range: 14-44 years). The

efficacy of cabergoline to inhibit the lactation was assessed by evaluating breast symptoms (spontaneous milk secretion, breast engorgement and breast pain). The existence of a linear component in the dose-response relationship was also investigated. Success rate (complete absence of breast symptomatology during entire 14 day observation period) was 20%, 42.5%, 62.5% and 90% in women receiving placebo or 0.5 mg, 0.75 mg and 1.0 mg cabergoline, respectively. A dose-response relationship between dose and clinical success was demonstrated ($p<0.0001$) for all the groups.

In the comparator randomized double-blind study with bromocriptine (cabergoline n=136, bromocriptine n=136), the mean age of patients was 28 years (range: 17-45 years). One of the objectives of the study was to determine if 1 mg cabergoline single dose is as effective as 2.5 mg bromocriptine bid for 14 days in inhibiting puerperal lactation as shown by absence of mammary symptoms up to day 15. The efficacy of the treatments was assessed by evaluating the breast symptomatology (spontaneous milk secretion, breast engorgement and breast pain) daily up to day 15. Women were also followed up to day 21 for possible rebound of breast symptomatology. Complete success was defined as complete absence of breast symptomatology from day 1 to day 15. Complete success was obtained in 85 women (62.5%) on bromocriptine and in 91 (66.9%) on cabergoline showing that cabergoline was at least as effective as bromocriptine in inhibition of lactation (less than 10% difference). Among women who achieved complete success, rebound symptomatology occurred in 23 (27.1%) on bromocriptine and 4 (4.4%) on cabergoline ($p<0.0001$).

The prolactin-lowering efficacy of cabergoline was demonstrated in hyperprolactinemic women in two randomized, double-blind, comparative studies, one with placebo and the other with bromocriptine. In the 4-week double-blind placebo-controlled study (placebo n = 20; cabergoline n=168), the majority of patients were Caucasian (99%), with a mean age of 31.8 years (range: 16-46 years). A total of 188 female patients with hyperprolactinemia (serum prolactin level $\geq$ 30 ng/mL or $\geq$ 700 nU/mL) were entered into the study. The main objective of the study was to investigate the possibility of a dose-response relationship for cabergoline at 0.25, 1.0, 1.5 and 2.0 mg/week. The treatment effectiveness was judged on the basis of serum prolactin levels obtained on Day 29. Complete success was defined as a normalization of serum prolactin (reduction <20 ng/mL). Complete success was achieved in 95% of patients receiving 2.0 mg/week and in 74%, 76% and 29% success was achieved in patients receiving 1.5, 1.0 or 0.25 mg/week; respectively. A significant dose-response relationship was observed across all groups ($p<0.001$). At 2-3 weeks after discontinuation of treatment, PRL levels remained within normal range in 12% to 81% of patients on cabergoline.

In the 8-week, double-blind period of the comparative trial with bromocriptine (cabergoline n=223; bromocriptine n=236 in the intent-to-treat analysis), the majority of patients were Caucasian except for 8; 6 Black, 1 Maghrebin, 1 mixed Black/Caucasian with a mean age of 31 years (range:16-46 years). A total of 459 female patients with amenorrhea (n=451) or other menstruation disorder due to hyperprolactinemia (serum prolactin >100% above the institution's upper limit of the normal range) of idiopathic origin or due to microprolactinemia, were entered into the study. The main objective of the study was to compare the efficacy in obtaining complete or partial normalization of prolactin levels (the decrease to <50% of pretreatment values). The prolactin was normalized in 77% of the patients treated with cabergoline at 0.5 mg

twice weekly compared with 59% of those treated with bromocriptine at 2.5 mg twice daily ($p<0.001$) at the end of the double-blind phase (8-week).

Comparative Bioavailability

A randomized, single-dose, two-way crossover comparative bioavailability study, conducted under fasting conditions was performed on healthy male volunteers. The rate and extent of absorption of cabergoline measured and compared following a single oral dose 1 mg (2 x 0.5 mg tablets) of Apo-Cabergoline (Cabergoline) 0.5 mg tablet (Apotex Inc.) and Dostinex® (Cabergoline) 0.5 mg tablet (Pfizer Canada Inc.) The results obtained from 29 volunteers who completed the study are summarized in the following table:

Cabergoline 1 mg (2 x 0.5 mg) From Measured Data Geometric Mean# Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_{72} (pg•h/mL)	1134.50 1175.90 (28)	1294.15 1343.62 (29)	87.7	80.8-95.1
C_{max} (pg/mL)	22.66 23.76 (32)	25.87 26.94 (31)	87.6	79.8 − 96.2
T_{max}§ (h)	16.99 (92)	16.70 (87)		

* Apo- Cabergoline (Cabergoline) 0.5 mg tablets (Apotex Inc.)

† Dostinex® (Cabergoline) 0.5 mg tablets (Pfizer Canada Inc.) was purchased in Canada.

§Expressed as arithmetic means (CV %) only.

AUC_{inf} and T_{half} are not reported; these parameters could not be accurately estimated due to the long half-life of cabergoline and the design of the study

DETAILED PHARMACOLOGY

Pharmacodynamics

Dose-response with inhibition of plasma prolactin, onset of maximal effect, and duration of effect has been documented following single cabergoline doses to healthy volunteers (0.05 to 1.5 mg) and hyperprolactinemic patients (0.3 to 1 mg). In volunteers, prolactin inhibition was evident at doses >0.2 mg, while doses $\geq$ 0.5 mg caused maximal suppression in most subjects. Higher doses produced prolactin suppression in a greater proportion of subjects and with an earlier onset and longer duration of action. In 12 healthy volunteers, 0.5, 1, and 1.5 mg doses

resulted in complete prolactin inhibition, with a maximum effect within 3 hours in 92% to 100% of subjects after the 1 and 1.5 mg doses compared with 50% of subjects after the 0.5 mg dose.

In hyperprolactinemic patients (N=51), the maximal prolactin decrease after a 0.6 mg single dose of cabergoline was comparable to 2.5 mg bromocriptine; however, the duration of effect was markedly longer (14 days vs 24 hours). The time to maximal effect was shorter for bromocriptine than cabergoline (6 hours vs 48 hours).

In 72 healthy volunteers, single or multiple doses (up to 2 mg) of cabergoline resulted in selective inhibition of prolactin with no apparent effect on other anterior pituitary hormones (GH, FSH, LH, ACTH, and TSH) or cortisol.

Pharmacokinetics

Absorption

Following single oral doses of 0.5 mg to 1.5 mg given to 12 healthy adult volunteers, mean peak plasma levels of 30 to 70 picograms (pg)/mL of cabergoline were observed within 2 to 3 hours. Over the 0.5 to 7 mg dose range, cabergoline plasma levels appeared to be dose-proportional in 12 healthy adult volunteers and nine adult parkinsonian patients.

A repeat-dose study in 12 healthy volunteers suggests that steady-state levels following a once-weekly dosing schedule are expected to be twofold to threefold higher than after a single dose. The absolute bioavailability of cabergoline is unknown. A significant fraction of the administered dose undergoes a first-pass effect. The elimination half-life of cabergoline estimated from urinary data of 12 healthy subjects ranged between 63 to 69 hours. The prolonged prolactin-lowering effect of cabergoline may be related to its slow elimination and long half-life.

Distribution

In animals, based on total radioactivity, cabergoline (and/or its metabolites) has shown extensive tissue distribution. Radioactivity in the pituitary exceeded that in plasma by >100-fold and was eliminated with a half-life of approximately 60 hours. This finding is consistent with the long-lasting prolactin-lowering effect of the drug. Whole body autoradiography studies in pregnant rats showed no fetal uptake but high levels in the uterine wall. Significant radioactivity (parent plus metabolites) detected in the milk of lactating rats suggests a potential for exposure to nursing infants. The drug is extensively distributed throughout the body. Cabergoline is moderately bound (40% to 42%) to human plasma proteins in a concentration-independent manner. Concomitant dosing of highly protein-bound drugs is unlikely to affect its disposition.

Metabolism

In both animals and humans, cabergoline is extensively metabolized, predominately via hydrolysis of the acylurea bond or the urea moiety. Cytochrome P-450 mediated metabolism appears to be minimal. Cabergoline does not cause enzyme induction and/or inhibition in the rat. Hydrolysis of the acylurea or urea moiety abolishes the prolactin-lowering effect of cabergoline, and major metabolites identified thus far do not contribute to the therapeutic effect.

Excretion
After oral dosing of radioactive cabergoline to five healthy volunteers, approximately 22% and 60% of the dose was excreted within 20 days in the urine and feces, respectively. Less than 4% of the dose was excreted unchanged in the urine. Non-renal and renal clearances for cabergoline are about 3.2 L/min and 0.08 L/min, respectively. Urinary excretion in hyperprolactinemic patients was similar.

Special Populations
Renal Insufficiency: The pharmacokinetics of cabergoline were not altered in 12 patients with moderate-to-severe renal insufficiency as assessed by creatinine clearance.

Hepatic Insufficiency: In 12 patients with mild-to-moderate hepatic dysfunction (Child-Pugh score <10), no effect on mean cabergoline C_{max} or area under the plasma concentration curve (AUC) was observed. However, patients with severe insufficiency (Child-Pugh score >10) show a substantial increase in the mean cabergoline C_{max} (less than two-fold) and AUC (about six-fold), and thus necessitate caution.

Elderly: Effect of age on the pharmacokinetics of cabergoline has not been studied.

Food-Drug Interaction
In 12 healthy adult volunteers, food did not alter cabergoline kinetics.

TOXICOLOGY

Acute Toxicity

Cabergoline has a very low acute toxicity in rats and mice, with median lethal doses which are several thousand times the clinical dose.

Long-Term Toxicity

Subchronic and chronic toxicity studies have been performed in mice/rats and monkeys. The maximum tolerated long-term dose for cabergoline appears to be between 250 and 1250 mcg/kg/day in monkeys, and between 400 and 3200 mcg/kg/day in rats. Most of the changes observed were in endocrine (rat) and central nervous (rat and monkeys) systems and are considered a consequence of the compound's stimulation of D2 receptors, resulting in an inhibition of prolactin secretion and central neurologic effects. The endocrine toxicity effect observed in the rat uterus (metritis), which has also been described for other anti-prolactin agents, is most likely due to the decrease of prolactin which has a luteotrophic effect in this species, but not in humans. This morphological uterine effect was not observed in monkeys treated daily for up to 52 weeks. In monkeys, the major findings were CNS effects which were not accompanied by histological changes in the brain.

Carcinogenicity

Carcinogenicity studies were conducted in mice and rats with cabergoline given by gavage at doses up to 0.98 mg/kg/day and 0.32 mg/kg/day, respectively. These doses are 7 times and 4 times the maximum recommended human dose calculated on a body surface area basis using total mg/m^2/week in rodents and mg/m^2/week for a 50 kg human.

There was a slight increase in the incidence of cervical and uterine leiomyomas and uterine leiomyosarcomas in mice. In rats, there was a slight increase in malignant tumors of the cervix and uterus and interstitial cell adenomas. The occurrence of tumors in female rodents may be related to the prolonged suppression of prolactin secretion because prolactin is needed in rodents for the maintenance of the corpus luteum. In the absence of prolactin, the estrogen/progesterone ratio is increased, thereby increasing the risk for uterine tumors. In male rodents, the decrease in serum prolactin levels was associated with an increase in serum luteinizing hormone, which is thought to be a compensatory effect to maintain testicular steroid synthesis. Since these hormonal mechanisms are thought to be species-specific, the relevance of these tumors to humans is not known.

Mutagenicity

The mutagenic potential of cabergoline was evaluated and found to be negative in a battery of *in vitro* tests. These tests included the bacterial mutation (Ames) test with *Salmonella typhimurium*, the gene mutation assay with *Schizosaccharomyces pombe* P1 and V79 Chinese hamster cells, DNA damage and repair in *Saccharomyces cerevisiae* D4, and chromosomal aberrations in human lymphocytes. Cabergoline was also negative in the bone marrow micronucleus test in the mouse.

No mutagenic effect was seen in the short-term tests *in vivo*. In female rats, a daily dose of 3.0 mcg/kg for 2 weeks prior to mating and throughout the mating period inhibited conception. This dose represents approximately 1/28 the maximum recommended human dose calculated on a body surface area basis using total mg/m^2/week in rats and mg/m^2/week for a 50 kg human. Because there are species differences in the role of prolactin, the effect may not be predictive of effects in humans.

Reproduction and Teratology

Reproduction studies have been performed with cabergoline in mice, rats, and rabbits administered by gavage. (Multiples of the maximum recommended human dose in this section are calculated on a body surface area basis using total mg/m^2/week for animals and mg/m^2/week for a 50 kg human.)

There were maternotoxic effects but no teratogenic effects in mice given cabergoline at doses up to 8 mg/kg/day (approximately 55 times the maximum recommended human dose) during the period of organogenesis.

A dose of 0.012 mg/kg/day (approximately 1/7 the maximum recommended human dose) during the period of organogenesis in rats caused an increase in post-implantation embryofetal losses. These losses could be due to the prolactin inhibitory properties of cabergoline in rats. At daily

doses of 0.5 mg/kg/day (approximately 19 times the maximum recommended human dose) during the period of organogenesis in the rabbit, cabergoline caused maternotoxicity characterized by a loss of body weight and decreased food consumption. Doses of 4 mg/kg/day (approximately 150 times the maximum recommended human dose) during the period of organogenesis in the rabbit caused an increased occurrence of various malformations. However, in another study in rabbits, no treatment-related malformations or embryofetotoxicity were observed at doses up to 8 mg/kg/day (approximately 300 times the maximum recommended human dose).

In rats, doses higher than 0.003 mg/kg/day (approximately 1/28 the maximum recommended human dose) from 6 days before parturition and throughout the lactation period inhibited growth and caused death of offspring due to decreased milk secretion.