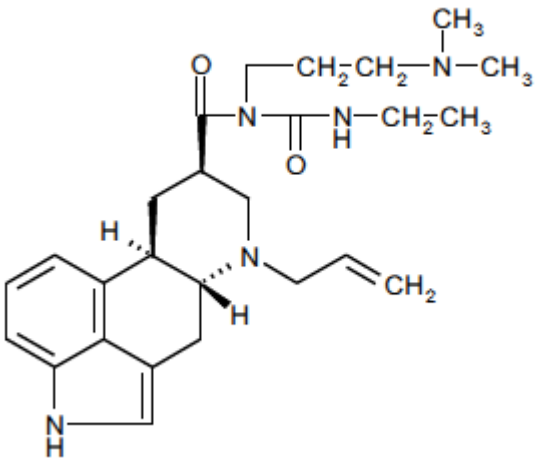
APO-CABERGOLINE TABLET

NAME OF THE MEDICINE

Cabergoline

Chemical Name: 1-[(6a*R*,9*R*,10a*R*)-7-allyl-4,6,6a,7,8,9,10,10a-octahydroindole[4,3-*fg*]-quinoline-9-carbonyl]-1-(3-dimethyl-aminopropyl)-3-ethylurea

Structural Formula:



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

Molecular Weight: 451.62

CAS Registry Number: 81409-90-7

DESCRIPTION

Cabergoline is a dopaminergic ergoline derivative, which has a potent and long lasting prolactin (PRL)-lowering activity.

Each tablet contains cabergoline as the active ingredient. In addition, each tablet contains the following inactive ingredients: lactose anhydrous and magnesium stearate.

PHARMACOLOGY

Pharmacological Actions

Cabergoline is a dopaminergic ergoline derivative with a potent and long lasting PRL-lowering activity. It acts by direct stimulation of the D_2-dopamine receptors on pituitary lactotrophs, thus inhibiting PRL secretion.

In addition, cabergoline exerts a central dopaminergic effect via D_2 receptor stimulation at oral doses higher than those effective in lowering serum PRL levels.

The long lasting PRL-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 hyperprolactinaemic patients. After a single oral administration of cabergoline (300microgram - 1.5mg) a significant decrease in serum PRL levels was observed in each of the populations studied. The effect is prompt (within 3 hours from administration) and persistent (up to 7-

28 days in healthy volunteers and hyperprolactinaemic patients and up to 14-21 days in puerperal women). The PRL-lowering effect is dose-related both in terms of degree of effect and duration of action.

There are limited clinical data on the efficacy of cabergoline in treatment of pathological hyperprolactinaemia in adult males.

With regard to the endocrine effects of cabergoline not related to the antiprolactinaemic effect, available data from humans confirm the experimental findings in animals indicating that the test compound is endowed with a very selective action with no effect on basal secretion of other pituitary hormones or cortisol. Other pharmacodynamic actions of cabergoline, not correlated with the therapeutic effect, relate to lowering blood pressure. The maximal hypotensive effect of cabergoline as 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.

Pharmacokinetics

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

Absorption

After oral administration of the labelled compound, radioactivity was rapidly absorbed from the gastrointestinal tract, and the peak of radioactivity in plasma was between 0.5 and 4 hours.

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 1mg dose (37 ± 8pg/mL) and after a 4 week regimen of 1 mg/week (101 ± 43pg/mL).

In vitro experiments showed that the drug at concentrations of 100microgram/mL to 10mg/mL is 41-42% bound to plasma proteins.

In limited studies, food did not appear to have an effect on the absorption of cabergoline.

Distribution

Ten days after administration about 18% and 72% of the radioactive dose was recovered in urine and faeces, respectively. Unchanged drug in urine accounted for 2-3% of the dose.

Metabolism

In urine, the main metabolite identified was 6-allyl-8ß-carboxy-ergoline, which accounted for 4-6% 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 PRL secretion *in vitro.*

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 (63-68 hours in healthy volunteers, 79-115 hours in hyperprolactinaemic patients).

In rats, cabergoline and/or its metabolites are excreted in milk; no information on its excretion in maternal milk in humans is available.

INDICATIONS

- **Inhibition of physiological lactation**

  Cabergoline is indicated for the prevention of the onset of physiological lactation in the puerperium for clearly defined medical reasons.

- **Treatment of hyperprolactinaemic disorders**

  Cabergoline is indicated for the treatment of pathological hyperprolactinaemia.

CONTRAINDICATIONS

- Hypersensitivity to cabergoline, other ergot alkaloids, or to any of the excipients.
- History of pulmonary, pericardial and retroperitoneal fibrotic disorders.
- Anatomical evidence of cardiac valvulopathy of any valve as determined by pre-treatment (e.g. echocardiogram showing valve leaflet thickening, valve restriction, valve mixed restriction-stenosis).

PRECAUTIONS

General

As with other ergot derivatives, cabergoline should be given with caution to patients with severe cardiovascular disease, Raynaud's syndrome, liver disease, renal insufficiency, peptic ulcer or gastrointestinal bleeding, or with a history of serious, particularly psychotic, mental disorders.

Renal and Hepatic Disease

The safety and efficacy of cabergoline have not yet been established in patients with renal and hepatic disease. Since available data indicate that biliary excretion represents the main route of elimination of the drug, it is advisable not to administer the drug to subjects with severe liver insufficiency.

Fibrosis and Cardiac Valvulopathy

As with other ergot derivatives, fibrotic and serosal inflammatory disorders such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy or retroperitoneal fibrosis have occurred after prolonged usage of cabergoline. The valvular effects were predominantly seen at doses exceeding the maximum recommended dose for treatment of hyperprolactinaemic disorders and maybe associated with cumulative dose. Some reports were in patients previously treated with ergotinic dopamine agonists. In some cases, following diagnosis of pleural effusion/pulmonary fibrosis or valvulopathy, the discontinuance of cabergoline has been reported to result in improvement of signs and symptoms. Progression of signs and symptoms may continue for a time before improvement occurs. 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.

Before initiating long-term treatment:

It is recommended that before initiating treatment with cabergoline all patients undergo a cardiovascular evaluation, including an echocardiogram, to assess potential presence of an occult 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.

During long-term 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:

- Pleuropulmonary 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.

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.

Cabergoline should be discontinued if fibrotic or serosal inflammatory disorders are diagnosed or an echocardiogram reveals valvular regurgitation, valvular restriction or valve leaflet thickening (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**).

The need for other subsequent clinical monitoring (e.g. physical examination, careful cardiac auscultation, x-ray, additional echocardiogram, CT scan) should be determined on an individual basis.

Inhibition/Suppression of Physiologic Lactation

By analogy with other ergot derivatives, cabergoline should not be used in women with preeclampsia or post-partum hypertension.

Postural Hypotension

Symptomatic hypotension can occur with cabergoline administration for any indication: periodic monitoring of blood pressure is advised and care should be exercised when administering cabergoline concomitantly with other drugs known to lower blood pressure.

Treatment of Hyperprolactinaemic Disorders

Since hyperprolactinaemia with amenorrhoea/galactorrhoea and infertility may be associated with pituitary tumours, a complete evaluation of the pituitary is indicated before treatment with cabergoline is initiated.

Somnolence/Sudden Sleep Onset

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

Patients being treated with cabergoline and presenting with somnolence must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) unless patients have overcome such experiences of somnolence (Also see **Effects on Ability to Drive and Use Machines**).

Psychiatric

Impulse control disorders such as pathological gambling, increased libido, hypersexuality, compulsive shopping, eating or medication use, and punding (repetitive purposeless activity) have been reported in patients treated with dopamine agonists including cabergoline. This has been generally reversible upon reduction of the dose or treatment discontinuation. Prescribers, patients and caregivers should be alert to the possibility of such behaviour.

Effects on Fertility

Fertility of female rats was completely inhibited by cabergoline at oral doses of 3mg/kg/day and above, while male fertility was not affected at doses up to 320mg/kg/day. The complete inhibition of fertility in female rats is related to inhibition of prolactin secretion and its effects on nidation.

Use in Pregnancy (Category B1)

Before cabergoline administration, pregnancy should be excluded and after treatment pregnancy should be prevented for at least one month.

In women treated for hyperprolactinaemic hypogonadism, pregnancy may occur prior to reinitiation of menses: a pregnancy test is recommended at least every four weeks during the amenorrhoeic period and, once menses are reinitiated, every time a menstrual period is delayed by more than three days. In women conceiving during treatment with cabergoline, the risk of abortion, premature delivery, multiple pregnancy, or congenital abnormalities does not appear to be increased. However, because

clinical experience is still limited, as a precautionary measure, it is recommended that women seeking pregnancy conceive at least one month after cabergoline discontinuation. Women not seeking pregnancy should be advised to use mechanical contraception during treatment and after cabergoline withdrawal, until recurrence of an ovulation. Should pregnancy occur during treatment, cabergoline is to be discontinued.

Data from animal studies indicated that cabergoline crosses the placental barrier in rats and skeletal malformations, possibly associated with maternal toxicity, were observed in rabbits at oral doses >2mg/kg.

As a precautionary measure, women who become pregnant should be monitored to detect signs of pituitary enlargement since expansion of pre-existing tumours may occur during gestation.

Use in Lactation

Cabergoline should not be administered to mothers who elect to breast feed their infants, since it prevents lactation and no information on the excretion of the compound in maternal milk in humans is available. For the same reason, puerperal women should not breast-feed in case of failed lactation inhibition/ suppression by cabergoline.

Cabergoline has been shown to cross into and accumulate in milk from nursing rats.

Paediatric Use

The safety and efficacy of cabergoline has not been established in subjects less than 16 years of age.

Use in the Elderly

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

Genotoxicity

Gene mutation and cytogenetic assays *in vitro* and *in vivo* suggest that cabergoline does not possess genotoxic activity.

Carcinogenicity

Two year carcinogenicity studies were conducted in rats and mice at maximum doses of 0.32 and 0.98mg/kg/day corresponding to exposure (based on AUC) levels 0.86 and 0.72 times that expected in humans. In rats, the oral administration of cabergoline at doses of 0.02 to 0.32mg/kg/day resulted in an increased incidence of benign Leydig cell tumours in males, and an increased incidence of reproductive tract tumours, such as squamous carcinoma, stromal sarcoma and adenocarcinoma in females. In mice, oral doses of 0.02 to 0.98mg/kg/day resulted in a low incidence of uterine and cervical leiomyomas and leiomyosarcomas at dose levels of 0.14mg/kg/day and above. The carcinogenic effects in rodents may involve endocrine mechanisms resulting from disturbances of the hypothalamo-pituitary-gonadal axis secondary to inhibition of prolactin secretion. However, even though there is no known correlation between uterine malignancies occurring in cabergoline treated rodents and human risk, there are no human data to substantiate this conclusion.

Effect on Laboratory Tests

Alterations in standard laboratory tests are uncommon during long term therapy with cabergoline: a decrease in haemoglobin values have been observed in amenorrhoeic women during the first few months after menses resumption.

Effects on Ability to Drive and Use Machines

Patients being treated with cabergoline and presenting with somnolence must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) unless patients have overcome such experiences of somnolence.

INTERACTIONS WITH OTHER MEDICINES

The concomitant use of other drugs during early puerperium, particularly of methylergometrine maleate, has not been associated with detectable interactions modifying the efficacy and safety of cabergoline.

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

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

Mono-oxygenase activity was increased 1.5 to 3 fold in female rats treated with cabergoline 100microgram/kg/day to 1.5mg/kg/day orally. Concomitant administration of cabergoline with drugs metabolised by mono-oxygenases may result in altered exposure and activity.

Cabergoline should not be used with macrolide antibiotics (e.g. erythromycin) due to increased systemic bioavailability of cabergoline.

ADVERSE EFFECTS

Side effects are generally dose related. In patients known to be intolerant of dopaminergic drugs, side effects may be lessened by starting cabergoline therapy with reduced doses (e.g. 250microgram once a week) with subsequent gradual increase until the therapeutic range is reached. In case of persistent or severe adverse events, temporary reduction of dosage followed by a more gradual increase (e.g. in steps of 250microgram per week fortnightly) may result in reversal of side effects once they have occurred.

In women treated for inhibition of physiological lactation the most frequently occurring adverse events are asymptomatic decreases in blood pressure, dizziness/vertigo, headache, nausea, somnolence and abdominal pain. In addition, on rare occasions, palpitations, epigastric pain, epistaxis, transient hemianopia, vomiting, syncope, asthenia, and hot flushes have been reported.

Most side effects are transient and mild to moderate in severity.

In patients treated for hyperprolactinaemia, the most common symptoms in decreasing rank of frequency are nausea, headache, dizziness/vertigo, abdominal pain/dyspepsia/gastritis, asthenia/fatigue, constipation, vomiting, breast pain, hot flushes, depression and paraesthesia.

Cabergoline generally exerts a hypotensive effect in patients treated chronically: however, symptomatic hypotension or fainting has been rarely reported. The symptoms are generally mild to moderate in degree, mainly appearing during the first two weeks of therapy, and mostly disappearing despite continued therapy.

Being an ergot derivative, cabergoline may also act in some patients as a vasoconstrictor: digital vasospasm and leg cramps have been occasionally reported.

Discontinuation of cabergoline because of adverse events was required in only approximately 3% of patients. Cabergoline withdrawal results in reversal of side effects, usually within a few days after discontinuation.

Alterations in standard laboratory tests are uncommon during long term therapy with cabergoline: a decrease in haemoglobin values have been observed in amenorrhoeic women during the first few months after menses resumption.

Pleuropulmonary changes (pleural effusions, pneumonitis, pleural and pulmonary fibrosis) have been reported (see **PRECAUTIONS**).

Post-marketing Surveillance

There have been reports of fibrotic and serosal inflammatory conditions, such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy and retroperitoneal fibrosis in patients taking cabergoline (see **PRECAUTIONS**).

The following events have also been reported in association with cabergoline: aggression, alopecia, blood creatinine phosphokinase increased, delusions, dyspnoea, oedema, hepatic function abnormal, hypersensitivity reaction, impulse control disorders such as hypersexuality, increased libido and pathological gambling, liver function tests abnormal, psychotic disorder, rash, respiratory disorder and respiratory failure.

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

DOSAGE AND ADMINISTRATION

Cabergoline is to be administered by the oral route. Since in clinical studies cabergoline has been mainly administered with food and since the tolerability of this class of compounds is improved with food, it is recommended, to promote compliance, that cabergoline be taken with meals, for all the therapeutic indications. Food is not noted to affect the absorption of cabergoline (see **PHARMACOLOGY, Pharmacokinetics**).

Adults

For the prevention of onset of physiological lactation in the puerperium: cabergoline should be administered during the first day post-partum. The recommended therapeutic dosage is 1mg (two 500microgram tablets) given as a single dose.

For treatment of pathological hyperprolactinaemia: the recommended initial dosage of cabergoline is 500microgram per week given in one or two (one-half of one 500microgram tablet) doses (e.g. on Monday and Thursday) per week. The weekly dose should be increased gradually, preferably by adding 500microgram per week at monthly intervals until an optimal therapeutic response is achieved. The therapeutic dosage is usually 1mg per week and ranges from 250microgram to 2mg per week. Doses of cabergoline up to 4.5mg per week have been used in hyperprolactinaemic patients.

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 1mg per week are to be given, since the tolerability of doses greater than 1mg 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 PRL levels at monthly intervals is advised since, once the effective therapeutic dosage regimen has been reached, serum PRL normalisation is usually observed within two to four weeks.

Children

The safety and efficacy of cabergoline has not been established in subjects less than 16 years of age.

Elderly

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

OVERDOSAGE

There is limited experience of overdosage in humans.

Symptoms

Symptoms of overdosage would likely be those of over-stimulation of dopamine receptors. These might include nausea, vomiting, gastric complaints, hypotension, nasal congestion, syncope, hallucinations or thought/perceptual disturbances.

Treatment

Treatment of overdose is symptomatic and supportive. Supportive measures should be directed to maintain blood pressure, if necessary.

Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

In addition, in case of pronounced central nervous system effects the administration of dopamine antagonist drugs may be advisable.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

APO-CABERGOLINE tablets are intended for oral administration.

Each tablet contains 500 micrograms of cabergoline as the active ingredient.

0.5mg Tablets:

White coloured, capsule shaped, flat, scored tablets with debossed “APO” on one side and “CA” bisect “0.5” on the other side.
Bottle (Amber coloured, glass round III 28mm bottles with 28mm polypropylene white CR caps with desiccant) of 2 or8 tablets (AUST R 218126)

Not all pack sizes may be available.

Storage

Store below 25°C. Protect from heat, light and moisture.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

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POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

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