

GOLINE

Tablet

Composition

Each tablet contains Cabergoline 0.5 mg tablet

Action

Mechanism of Action

Goline is a dopaminergic ergoline derivative with potent and long-lasting Prolactin-lowering activity. It acts by direct stimulation of the D2-dopamine receptors on pituitary lactotrophs, thus inhibiting Prolactin secretion. In addition Goline exerts a central dopaminergic effect via D2 receptor stimulation at oral doses higher than those effective in lowering serum Prolactin levels. The long-lasting Prolactin-lowering effect of Cabergoline is probably due to its long persistence in the target organ ($t_{1/2}$ of approximately 60 hours).

The pharmacodynamic effects of Cabergoline have been studied in healthy women, puerperal women and hyperprolactinaemic patients. After a single oral administration of Cabergoline (0.3-1.5 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 7-28 days in healthy volunteers and hyperprolactinaemic patients and up to 14-21 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 antiprolactinaemic effect, data available 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. The pharmacodynamic actions of Goline not correlated with the therapeutic effect only relate to blood pressure decrease. The maximal hypotensive effect of Cabergoline as a single dose usually occurs during the first 6 hours after medicine intake and is dose-dependent both in terms of maximal decrease and frequency.

Inhibition/suppression of physiological lactation

Cabergoline given as a single 1 mg administration during the first day post-partum was effective in inhibiting milk secretion, as well as breast engorgement and pain in 70-90% of the women. Less than 5% of women experienced rebound breast symptomatology during the third post-partum week (which was usually mild in severity).

Hyperprolactinaemic disorders

On chronic therapy, Cabergoline at doses ranging between 1 and 2 mg per week was effective in normalizing serum prolactin levels in approximately 84% of hyperprolactinaemic patients. Regular cycles were resumed in 83% of previously amenorrhic women. Restoration of ovulation was documented in 89% of women with progesterone levels monitored during the luteal phase. Galactorrhoea disappeared in 90% of cases showing this symptom before therapy. Reduction in tumor size was obtained in 50-90% of female and male patients with micro- or macroprolactinoma.

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 hyperprolactinaemic patients was similar.

Special Populations

Renal Insufficiency

The pharmacokinetics of cabergoline was 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} and AUC, and thus necessitate caution.

Elderly

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

Indications

Prevention of the onset of lactation in the puerperium only for clearly defined medical reasons

Goline is indicated for the inhibition of physiological lactation soon after delivery.

- After parturition, when breast feeding is contraindicated due to medical reasons related to the mother or the new-born.
- After stillbirth or abortion.

Treatment of hyperprolactinaemic disorders

Goline is indicated for the treatment of dysfunctions associated with hyperprolactinaemia, including amenorrhoea, oligomenorrhoea, anovulation and galactorrhoea. Goline is indicated in patients with prolactin-secreting pituitary adenomas (micro- and macroprolactinomas), idiopathic hyperprolactinaemia, or empty sella syndrome with associated hyperprolactinaemia, which represent the basic underlying pathologies contributing to the above clinical manifestations.

Contraindications

- Hypersensitivity to cabergoline, any other component of the product, or any ergot alkaloid.
- History of pulmonary, pericardial and retroperitoneal fibrotic disorders.

- Anatomical evidence of cardiac valvulopathy of any valve (e.g. echocardiogram showing valve leaflet thickening, valve restriction, valve mixed restriction-stenosis).

Adverse Reactions

In women treated for inhibition/suppression 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, rarely palpitations, epigastric pain, epistaxis, transient hemianopsia, vomiting, syncope, asthenia and hot flushes have been reported.

In patients treated for hyperprolactinaemia

The side-effects in decreasing rank of frequency were nausea, headache, dizziness/vertigo, abdominal pain, dyspepsia/gastritis, asthenia/fatigue, constipation, vomiting, breast pain, hot flushes, depression and paresthesia. Symptomatic hypotension or fainting was occasionally reported.

Cabergoline generally exerts a hypotensive effect in patients. Symptoms mainly appear during the first two weeks of therapy and disappear 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.

Warnings and Precautions

General

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.

Lower doses should be considered in patients with severe hepatic insufficiency who receives prolonged treatment with Cabergoline. Compared to normal volunteers and those with lesser degrees of hepatic insufficiency, an increase in AUC has been seen in patients with severe hepatic insufficiency (Child-Pugh score >10) who received a single 1 mg dose.

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.

Postural hypotension can occur following administration of cabergoline. Care should be exercised when administering Goline concomitantly with other drugs known to lower blood pressure.

Fibrosis and Cardiac Valvulopathy

As with other ergot derivatives, fibrotic and serosal inflammatory disorders such as pleuritis, pleural effusion, 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.

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.

Fibrotic disorders can have an insidious onset. Therefore during treatment, attention should be paid to the signs and symptoms of: pleuropulmonary disease, renal insufficiency, and cardiac failure. 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 creatine measurements can also be used to help in the diagnosis of 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. 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.

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.

Inhibition/Suppression of Physiologic Lactation

As with other ergot derivatives, Cabergoline should not be used in women with preeclampsia or postpartum hypertension.

A single dose of 0.25 mg of Cabergoline should not be exceeded in nursing women treated for suppression of established lactation to avoid potential postural hypotension.

Treatment of Hyperprolactinaemic Disorders

A complete evaluation of the pituitary is indicated before treatment with Cabergoline is initiated.

Cabergoline restores ovulation and fertility in women with hyperprolactinaemic hypogonadism. Because pregnancy might occur prior to reinitiation of menses, a pregnancy test is recommended at least every 4 weeks during the amenorrheic period and, once menses are reinitiated, every time a menstrual period is delayed by more than 3 days. Women who wish to avoid pregnancy should be advised to use mechanical contraception during treatment with Cabergoline and after discontinuation of Cabergoline until recurrence of anovulation. As a precautionary measure, women who become pregnant should be monitored to detect signs of pituitary enlargement since expansion of pre-existing pituitary tumors may occur during gestation.

Psychiatric

Pathological gambling, increased libido, and hypersexuality have been reported in patients treated with dopamine agonists including cabergoline. This has been generally reversible upon reduction of the dose or treatment discontinuation.

Pregnancy

Category B

Before Cabergoline administration, pregnancy should be excluded.

Animal studies with cabergoline have not demonstrated teratogenic effects or effects on overall reproductive performance. However, there are no adequate and well-controlled studies in pregnant women. Cabergoline should be used during pregnancy only if clearly needed. If conception occurs during therapy with Cabergoline, discontinuation of treatment should be considered, after careful evaluation of the risks and benefits to mother and fetus. Pregnancy should be avoided for at least one month following discontinuation of treatment with Cabergoline due to the long half-life of the drug and the limited data on in utero exposure, although the use of Cabergoline at 0.5 to 2 mg/week for hyperprolactinaemic disorders does not appear to be associated with an increased risk of abortion, premature delivery, multiple pregnancy or congenital abnormalities.

Nursing Mothers

It is not known whether this drug is excreted in human milk. 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. Use of Cabergoline for the inhibition or suppression of physiologic lactation is not recommended.

The prolactin-lowering action of Cabergoline suggests that it will interfere with lactation. Due to this interference with lactation, Cabergoline should not be given to women postpartum who are breastfeeding or who are planning to breastfeed.

Pediatric Use

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

Geriatric Use

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy

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.

Drug Interactions

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.

No information is available about interaction between cabergoline and other ergot alkaloids; therefore, the concomitant use of these medications during long-term treatment 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 that have dopamine-antagonist activity (such as phenothiazines, butyrophenones, thioxanthenes, metoclopramide) since these might reduce the prolactin-lowering effect of cabergoline.

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

As with other ergot derivatives, cabergoline should not be used with macrolide antibiotics (eg, erythromycin) due to increased systemic bioavailability of cabergoline.

Dosage and Administration

Goline is to be administered by the oral route; it is recommended that Goline be preferably taken with meals.

Inhibition of physiological lactation

Goline should be administered during the first day post-partum. The recommended therapeutic dose is 1 mg (two 0.5 mg tablets) as a single dose.

Treatment of hyperprolactinaemic disorders

The recommended initial dosage of Goline is 0.5 mg per week given in one or two ($\frac{1}{2}$ of a 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 the optimal therapeutic response is achieved. The therapeutic dosage is usually 1 mg per week and ranges from 0.25 to 2 mg per week. Doses of Goline up to 4.5 mg 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 1 mg per week are to be given. Patients should be evaluated during dose escalation to determine the lowest dosage that produces the required therapeutic response. Monitoring of serum prolactin levels at monthly intervals is advised since; once the effective dosage regimen has been reached serum prolactin normalization is usually observed within two to four weeks.

After Goline withdrawal, recurrence of hyperprolactinaemia is usually observed. However persistent suppression of prolactin levels has been observed for several months in some patients. In most women, ovulatory cycles persist for at least 6 months after Goline discontinuation.

Severe hepatic insufficiency

Lower doses should be considered in patients with severe hepatic insufficiency who receives prolonged treatment with GOLINE.

Overdosage

There is no experience in humans of overdosage with cabergoline in the proposed indications: it is likely to lead to symptoms due to over-stimulation of dopamine receptors. These might include nausea, vomiting, gastric complaints, hypotension, nasal congestion, confusion hallucinations, and psychosis or thought/perception disturbances. 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.

Storage

Store at room temperature (i.e. below 25° C)

Presentation

Goline 0.5

Jar of 2 tablets