

Prescribing Information

DOSTINEX

Composition

Cabergoline 0.5 mg

Pharmaceutical forms

Tablets

Therapeutic indications

Treatment of hyperprolactinemic disorders (See sections Contraindications and Special warnings and precautions for use – Long term treatment)

Dostinex is indicated for the treatment of dysfunctions associated with hyperprolactinemia, including amenorrhea, oligomenorrhea, anovulation and galactorrhea. Dostinex is indicated in patients with prolactin-secreting pituitary adenomas (micro and macroprolactinomas), idiopathic hyperprolactinemia, or empty sella syndrome with associated hyperprolactinemia.

Inhibition/suppression of physiological lactation

Posology and method of administration

General:

Dostinex is to be administered by the oral route. Since the tolerability of this class of compounds is improved with food, it is recommended that Dostinex be preferably taken with meals for all the therapeutic indications.

In patients known to be intolerant to dopaminergic drugs, the likelihood of adverse events may be lessened by starting therapy with DOSTINEX at reduced doses (e.g., 0.25 mg once a week) with subsequent gradual increase until the therapeutic dosage is reached. If persistent or severe adverse events occur, temporary reduction of dosage followed by a more gradual increase (e.g., increments of 0.25 mg per week every two weeks) may increase tolerability.

Inhibition/suppression of physiological lactation

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

For suppression of established lactation: The recommended therapeutic dosage regimen is 0.25 mg (one half 0.5 mg tablet) every 12 hours for two days (1 mg total dose). (See section Special warnings and precautions for use – Inhibition/Suppression of Physiologic Lactation)

Treatment of hyperprolactinemic disorders (See sections Contraindications and Special warnings and precautions for use – Long term treatment)

The recommended initial dosage of Dostinex 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 mg per week. Doses of Dostinex up to 4.5 mg per week have been used in hyperprolactinemic patients (See section **Special warnings and precautions for use** – Treatment of Hyperprolactinemic Disorders).

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 dose 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 two to four weeks.

After Dostinex withdrawal, recurrence of hyperprolactinemia 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 Dostinex discontinuation.

Patients with Severe Hepatic Insufficiency:

Lower doses of DOSTINEX should be considered in patients with severe hepatic insufficiency. (See section Special warnings and precautions for use – Hepatic Insufficiency)

Children

Safety and efficacy of Dostinex has not been established in patients younger than 16 years.

Elderly

Dostinex has not been formally studied in elderly patients with hyperprolactinemic disorders.

Contra-indications

Hypersensitivity to cabergoline, any other component of the product, or any ergot alkaloid.

History of pulmonary, pericardial and retroperitoneal fibrotic disorders. (See section **Special warnings and precautions for use** – Fibrosis/Valvulopathy)

Long-term treatment:

Anatomical evidence of cardiac valvulopathy of any valve (as determined by pre-treatment echocardiogram showing valve leaflet thickening, valve restriction, valve mixed restriction-stenosis). (See section **Special warnings and precautions for use** – Fibrosis/Valvulopathy).

Special warnings and special precautions for use

General

As with other ergot derivatives, Dostinex should be given with caution to subjects with severe cardiovascular disease, Raynaud's syndrome, peptic ulcer or gastrointestinal bleeding, or with a history of serious, particularly psychotic, mental disorders. Particular care should be taken when patients are taking concomitant psychoactive medication.

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

Hepatic Insufficiency:

Lower doses should be considered in patients with severe hepatic insufficiency who receive prolonged treatment with DOSTINEX. 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 Class C) who received a single 1 mg dose.

Postural Hypotension:

Symptomatic hypotension can occur with Dostinex administration. Care should be exercised when administering Dostinex concomitantly with other drugs known to lower blood pressure.

Fibrosis/Valvulopathy:

As with other ergot derivatives, pleural effusion/pulmonary fibrosis and valvulopathy have been reported following long-term administration of cabergoline. Some reports were in patients previously treated with ergotinic dopamine agonists. Therefore, Dostinex should be used with caution in patients with a history of, or current signs and/or clinical symptoms of, respiratory or cardiac disorders linked to fibrotic tissue. 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 or valvulopathy, the discontinuance of cabergoline has been reported to result in improvement of signs and symptoms. (See section **Contraindications**).

Long-term treatment:

Before initiating long-term treatment:

All patients must undergo a cardiovascular evaluation, including an 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 section **Contraindications**).

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:

- 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 Section **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.

Somnolence/Sudden Sleep Onset:

Dostinex 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. (See section Effects on ability to drive and use machines)

Inhibition/suppression of physiological lactation:

As with other ergot derivatives, Dostinex should not be used in women with pregnancy-induced hypertension, for example, preeclampsia or post-partum hypertension, unless the potential benefit is judged to outweigh the possible risk.

In post-partum studies with Dostinex, blood pressure decreases were mostly asymptomatic and were frequently observed on a single occasion 2 to 4 days after treatment. Since decreases in blood pressure are frequently noted during the puerperium, independently of drug therapy, it is likely that many of the observed decreases in blood pressure after Dostinex administration were not drug-induced. However, periodic monitoring of blood pressure, particularly during the first days after Dostinex administration, is advised.

Dostinex should not be administered as a single dose greater than 0.25 mg in nursing women treated for suppression of established lactation to avoid potential postural hypotension since a clinical study exploring the efficacy and tolerability of 0.5 mg of Dostinex given as a single dose for suppression of lactation has shown that the risk of side effects is approximately doubled in this indication if the drug is administered as a single dose of 0.5 mg. (See section **Posology and method of administration – Inhibition/Suppression of Physiologic Lactation**).

Treatment of hyperprolactinemic disorders:

Since hyperprolactinemia with amenorrhea/galactorrhea and infertility may be associated with pituitary tumors, a complete evaluation of the pituitary is indicated before treatment with Dostinex is initiated.

Dostinex restores ovulation and fertility in women with hyperprolactinemic hypogonadism: since pregnancy might occur prior to reinitiation of menses, a pregnancy test is recommended at least every four weeks during the amenorrheic period and, once menses are reinitiated, every time a menstrual period is delayed by more than three days. Women not seeking pregnancy should be advised to use mechanical contraception during treatment and after Dostinex withdrawal until recurrence of anovulation. Because of the still limited experience on the safety of fetal exposure to Dostinex, until further data become available it is advisable that women seeking pregnancy conceive at least one month after Dostinex discontinuation given that ovulatory cycles persist in most patients for at least 6 months after drug withdrawal. Should pregnancy occur during treatment, Dostinex is to be discontinued. 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

Interactions with other medicaments and other forms of interaction

The concomitant use of other drugs during early puerperium, particularly of methylergonovine maleate, was not associated with detectable interactions modifying the efficacy and safety of Dostinex.

No information is available about interaction between cabergoline and other ergot alkaloids; therefore, the concomitant use of these medications during long term treatments with Dostinex is not recommended.

Since Dostinex 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 prolactin-lowering effect of Dostinex.

By analogy with other ergot derivatives, Dostinex should not be used in association with macrolide antibiotics (e.g. erythromycin) since the systemic bioavailability and also adverse effects could increase.

Pregnancy and lactation

Studies in animal models have not demonstrated any teratogenic effect or effects on overall reproductive performance. However, there are no adequate and well-controlled studies in pregnant women. Dostinex should be used during pregnancy only if clearly needed. If conception occurs during therapy with Dostinex, 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 Dostinex due to the long half-life of the drug and the limited data on in utero exposure, although the use of Dostinex at 0.5 to 2 mg/week for hyperprolactinemic disorders does not appear to be associated with an increased risk of abortion, premature delivery, multiple pregnancy or congenital abnormalities. (See section **Special warning and precautions for use – Treatment of Hyperprolactinemic Disorders**)

In rats, cabergoline and/or its metabolites are excreted in milk. No information is available on the excretion in breast milk in humans; however, mothers should be advised not to breast-feed in case of failed lactation inhibition/suppression by Dostinex. Since it prevents lactation, Dostinex should not be administered to mothers with hyperprolactinemic disorders who wish to breast-feed their infants.

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. (See section Special warnings and precautions for use – Somnolence/Sudden Sleep Onset).

Undesirable effects

Inhibition/suppression of lactation

Approximately 14% of women treated with a single 1 mg Dostinex for inhibition of physiological lactation complained of at least one side effect. All side effects were mild to moderate in severity and of a transient nature. The most frequently occurring adverse events were dizziness/vertigo, headache, nausea and abdominal pain. In addition, rarely palpitations, epigastric pain, somnolence (See section **Special warnings and precautions for use – Somnolence/Sudden Sleep Onset** and section **Effects on ability to drive and use machines**), epistaxis and transient hemianopsia were reported.

Asymptomatic decreases in blood pressure (≥ 20 mmHg systolic and ≥ 10 mmHg diastolic) may occur usually once during the first 3-4 days post-partum.

Adverse effects have been observed in approximately 14% of nursing women treated with 0.25 mg of Dostinex every 12 hours for two days for suppression of lactation. The most frequent symptoms were dizziness/vertigo, headache, nausea, somnolence (See section **Special warnings and precautions for use – Somnolence/Sudden Sleep Onset** and section **Effects on ability to drive and use machines**) and abdominal pain. In addition, vomiting, syncope, asthenia and hot flashes were reported. Most side effects were transient and mild to moderate in severity.

Hyperprolactinemic disorders

Data obtained in a controlled clinical trial of 6 months therapy with doses ranging between 1 and 2 mg per week given in two weekly administrations, indicate a 68% incidence of adverse events during Dostinex therapy; this was significantly lower than the incidence observed for the reference standard compound. Moreover, the symptoms were generally mild to moderate in degree, mainly appearing during the first two weeks of therapy, and mostly disappearing despite continued therapy. Severe adverse events were reported at least once during therapy by 14% of patients but therapy was discontinued because of adverse events in only approximately 3% of patients. Dostinex withdrawal results in reversal of side effects, usually within a few days after discontinuation. The most common symptoms in decreasing rank of frequency were nausea, headache, dizziness/vertigo, abdominal pain/ dyspepsia/ gastritis, asthenia/fatigue, constipation, vomiting, breast pain, hot flashes, depression and paresthesia.

General:

Side effects are generally dose-related. (See section **Posology and method of administration – General**)

Dostinex generally exerts a hypotensive effect in patients on long-term therapy; however, postural hypotension (See section **Special warnings and precautions for use – Postural Hypotension** and **Inhibition/Suppression of Physiologic Lactation**) or fainting have been rarely reported.

Being an ergot derivative, Dostinex may act as a vasoconstrictor. Digital vasospasm and leg cramps have been reported.

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

Post-marketing Surveillance:

The following events have been reported in association with cabergoline: aggression, alopecia, blood creatinine phosphokinase increased, delusions, dyspnea, edema, fibrosis, hepatic function abnormal, hypersensitivity reaction, hypersexuality, increased libido, liver function tests abnormal, pathological gambling, psychotic disorder, rash, respiratory disorder, respiratory failure, and valvulopathy. (See section **Contraindications** and section **Special warnings and precautions for use** – Fibrosis/Valvulopathy and Psychiatric).

The prevalence of asymptomatic valvular regurgitation is significantly greater than that of non-ergot dopamine agonists. (See section **Contraindications** and section **Special warnings and precautions for use** – Fibrosis/Valvulopathy)

Overdose

There is no experience in humans of overdosage with Dostinex in the proposed indication: it is likely to lead to symptoms due to over-stimulation of dopamine receptors. These might include nausea, vomiting, gastric complaints, postural hypotension, confusion/psychosis or hallucinations.

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

Pharmacological properties

Action

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

Pharmacodynamic properties

Dostinex is a dopaminergic ergoline derivative endowed with a potent and long-lasting prolactin (PRL)-lowering activity. It acts by direct stimulation of the D₂-dopamine receptors on pituitary lactotrophs, thus inhibiting PRL secretion. In rats the compound decreases PRL secretion at oral doses of 3-25 mg/kg, and *in vitro* at a concentration of 45 pg/ml. In addition, Dostinex exerts a central dopaminergic effect via D₂ receptor stimulation at oral doses higher than those effective in lowering serum PRL levels.

The long-lasting PRL-lowering effect of Dostinex 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 Dostinex have been studied in healthy volunteers, puerperal women and hyperprolactinemic patients. After a single oral administration of Dostinex (0.3-1.5 mg), 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 hyperprolactinemic 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.

With regard to the endocrine effects of Dostinex 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 very selective action with no effect on basal secretion of other pituitary hormones or cortisol. The pharmacodynamic actions of Dostinex not correlated with the therapeutic effect only relate to blood pressure decrease. The maximal hypotensive effect of Dostinex as single dose usually occurs during the first 6 hours after drug intake and is dose-dependent both in terms of maximal decrease and frequency.

Fibrosis and valvulopathy

A multi-country, retrospective cohort study using general practice records and record linkage systems in the UK, Italy and the Netherlands was conducted to assess the association between new use of dopamine agonists including cabergoline (n = 27,812) for Parkinson's disease and hyperprolactinemia and cardiac valvular regurgitation (CVR), other fibroses and other cardiopulmonary events over a maximum of 12 years of follow up. In the analysis confined to persons with dopamine agonist-treated hyperprolactinemia (n=8,386), when compared to non-use (n=15,147), persons exposed to cabergoline did not have an elevated risk of CVR. (See section **Special warnings and precautions for use –Fibrosis/Valvulopathy** and section **Undesirable effects.**)

Pharmacokinetic properties

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

After oral administration of the labelled 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 was recovered in urine and faeces, respectively. Unchanged drug in urine accounted for 2-3% of the dose.

In urine, the main metabolite identified was 6-allyl-8b-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 Dostinex in inhibiting prolactin secretion "in vitro". Dostinex biotransformation was also studied in plasma of healthy male volunteers treated with [¹⁴C] cabergoline: a rapid and extensive biotransformation of cabergoline was shown.

The low urinary excretion of unchanged Dostinex has been confirmed also in studies with non-radioactive product. The elimination half-life of Dostinex, estimated from urinary excretion rates, is long (63-68 hours in healthy volunteers, 79-115 hours in hyperprolactinemic patients- using a HPLC method).

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 Dostinex obtained after a single dose (37 ± 8 pg/ml) and after a 4 week multiple-regimen (101 ± 43 pg/ml).

In vitro experiments showed that the drug at concentrations of 0.1-10 ng/ml is 41-42% bound to plasma proteins. Food does not appear to affect absorption and disposition of Dostinex.

Preclinical safety data

Almost all the findings noted throughout the series of preclinical safety studies are a consequence of the central dopaminergic effects or the long-lasting inhibition of PRL in species (rodents) with a specific hormonal physiology different to man.

Preclinical safety studies of Dostinex indicate a large safety margin for this compound in rodents and in monkeys, as well as a lack of teratogenic, mutagenic or carcinogenic potential.

List of excipients

Lactose anhydrous

Leucine

Incompatibilities

Not applicable.

Shelf life

24 months.

The medicine can be used within 30 days after first opening the bottle.

Special precautions for storage

Store below 25⁰C.

Nature and contents of container

The tablets are contained in type I amber glass bottles with tamper resistant screw caps and containing silica gel desiccant.

Each bottle contains 2 or 8 tablets and is enclosed in an outer cardboard carton.

Instructions for use/handling

Bottles of Dostinex are supplied with desiccant in caps. This desiccant must not be removed.

Manufacturer: Pfizer Italia S.r.l, Italy.

License holder: Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Hertzliya Pituach 46725.