LPD Title : Cabergoline
LPD Date : 02 August 2018
Country : Malaysia
Reference : CDS 05 February 2013
Reason for Change : To update Sections 4.4, 4.7 and 4.8 based on BOH recommendation.
Update to storage condition & Nature and Contents of Container

PFIZER
DOSTINEX*
Cabergoline

1. NAME OF THE MEDICINAL PRODUCT

DOSTINEX

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Available as tablets each containing 0.5 mg Cabergoline.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Inhibition/Suppression of Physiological Lactation:

Cabergoline is indicated for 1) the inhibition of physiological lactation soon after parturition and 2) suppression of established lactation.

Treatment of Hyperprolactinaemic Disorders:

Cabergoline is indicated for the treatment of hyperprolactinemic disorders.

4.2. Posology and method of administration

General:

Cabergoline tablets are for oral administration. Since the tolerability of dopaminergic agents is improved when administered with food, it is recommended that cabergoline be taken with meals.

In patients known to be intolerant to dopaminergic drugs, the likelihood of adverse events may be lessened by starting therapy with cabergoline 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: The recommended dose is 1 mg (two 0.5 mg tablets) given as a single dose during the first post-partum day.

For suppression of established lactation: The recommended dosage is 0.25 mg (one-half 0.5 mg tablet) every 12 hours for 2 days (1 mg total dose) (See section **4.4 Special warnings and precautions for use** – Inhibition/Suppression of Physiologic Lactation).

Treatment of Hyperprolactinemic Disorders (See sections **4.3 Contraindications** and **4.4 Special warnings and precautions for use** - Long-term treatment):

The recommended initial dosage of 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 but may range from 0.25 mg to 2 mg per week (See section **4.4 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.

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

After discontinuation of cabergoline, 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 discontinuation of cabergoline.

Patients with Severe Hepatic Insufficiency:

Lower doses of cabergoline should be considered in patients with severe hepatic insufficiency (See section **4.4 Special warnings and precautions for use** – Hepatic Insufficiency).

Children:

Safety and efficacy have not been established in patients younger than 16 years.

Elderly:

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

4.3. Contraindications

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

History of pulmonary, pericardial and retroperitoneal fibrotic disorders (See section **4.4 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 **4.4 Special warnings and precautions for use** – Fibrosis/Valvulopathy).

4.4. Special warnings and precautions for use

General:

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

Hepatic Insufficiency:

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

Postural Hypotension:

Postural hypotension can occur following administration of cabergoline. Care should be exercised when administering cabergoline 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, cabergoline should not be used 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 **4.3 Contraindications**).

Long-term treatment:

Before initiating long-term 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 section **4.3 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 **4.3 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:

Cabergoline has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with cabergoline. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered (See section **4.7 Effects on ability to drive and use machines**).

Inhibition/Suppression of Physiologic Lactation:

As with other ergot derivatives, cabergoline 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.

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 (See section **4.2 Posology and method of administration** – Inhibition/Suppression of Physiologic Lactation and subsection above – Postural Hypotension).

Treatment of Hyperprolactinemic Disorders:

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

Cabergoline restores ovulation and fertility in women with hyperprolactinemic 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:

Impulse control disorders such as 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.

4.5. Interaction with other medicinal products and other forms of interaction

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.

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

4.6. Pregnancy & lactation

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 hyperprolactinemic disorders does not appear to be associated with an increased risk of abortion, premature delivery, multiple pregnancy or congenital abnormalities (See section **4.4 Special warnings 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 cabergoline. Since it prevents lactation, cabergoline should not be administered to mothers with hyperprolactinemic disorders who wish to breast-feed their infants.

4.7. Effects on ability to drive and use of machines

Patients being treated with cabergoline and presenting with somnolence and/or sudden sleep episodes 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) until such recurrent episodes and somnolence have resolved (See section **4.4 Special warnings and precautions for use** – Somnolence/Sudden Sleep Onset).

4.8. Undesirable effects

Inhibition/Suppression of Lactation:

Approximately 14% of women treated in clinical trials with a single 1 mg dose of cabergoline for inhibition of physiologic lactation reported at least one adverse event. Reported adverse events were transient and mild to moderate in severity. The most frequent adverse events were dizziness/vertigo, headache, nausea, and abdominal pain. Palpitations, epigastric pain, epistaxis, and transient hemianopsia were also reported. Cabergoline is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes. (See section **4.4 Special warnings and precautions for use** – Somnolence/Sudden Sleep Onset and section **4.7 Effects on ability to drive and use machines**)

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

Adverse events have been observed in approximately 14% of nursing women treated with 0.25 mg of cabergoline every 12 hours for 2 days for suppression of lactation. Most adverse events were transient and mild to moderate in severity. The most frequent adverse events were dizziness/vertigo, headache, nausea, somnolence (See section **4.4 Special warnings and precautions for use** – Somnolence/Sudden Sleep Onset and section **4.7 Effects on ability to drive and use machines**) and abdominal pain. Vomiting, syncope, asthenia, and hot flushes were also reported.

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 therapy with cabergoline. The adverse events were generally mild to moderate in severity, mainly appearing during the first 2 weeks of therapy. Most disappeared with continued therapy. Severe adverse events were reported at least once during therapy by 14% of patients. Therapy was discontinued because of adverse events in approximately 3% of patients. Adverse events subsided upon discontinuation of cabergoline, usually within a few days.

The most common adverse events reported, in decreasing order of frequency, were: nausea, headache, dizziness/vertigo, abdominal pain/dyspepsia/gastritis, asthenia/fatigue, constipation, vomiting, breast pain, hot flushes, depression and paresthesia.

General:

Adverse events are generally dose-related (See section **4.2 Posology and method of administration** – General).

Cabergoline generally exerts a hypotensive effect in patients on long-term therapy; however, postural hypotension (See section **4.4 Special warnings and precautions for use** – Postural

Hypotension and Inhibition/Suppression of Physiologic Lactation) or fainting has been rarely reported.

Being an ergot derivative, cabergoline 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 cabergoline; a decrease in hemoglobin values have been observed in amenorrheic 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, impulse control disorders such as hypersexuality, increased libido and pathological gambling, liver function tests abnormal, psychotic disorder, rash, respiratory disorder, respiratory failure, and valvulopathy (See section **4.3 Contraindications** and section **4.4 Special warning 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 **4.3 Contraindications** and section **4.4 Special warnings and precautions for use** – Fibrosis/Valvulopathy).

4.9. Overdose

Symptoms of overdose would likely be those of over-stimulation of dopamine receptors, e.g., nausea, vomiting, gastric complaints, postural hypotension, confusion/psychosis or hallucinations.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Cabergoline is a dopaminergic ergoline derivative endowed with a potent and long-lasting prolactin (PRL)-lowering activity. It acts by direct stimulation of the D_2-dopamine receptors on pituitary lactotrophs, thus inhibiting PRL secretion. In rats the compound decreases PRL secretion at oral doses of 3-25 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 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 single oral dose in rats ($t_{½}$ 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 (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 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.

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. The pharmacodynamic actions of cabergoline not correlated with the therapeutic effect only relate to blood pressure decrease. The maximal hypotensive effect of cabergoline 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 **4.4 Special warnings and precautions for use** –Fibrosis/Valvulopathy and section **4.8 Undesirable effects**).

5.2. Pharmacokinetic Properties

The pharmacokinetic and metabolic profiles of cabergoline have been studied in healthy volunteers of both sexes and in female hyperprolactinaemic 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-8β-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 prolactin secretion *in vitro*. Cabergoline biotransformation was also studied in plasma of healthy male volunteers treated with [^{14}C]-cabergoline: a rapid and extensive biotransformation of cabergoline was shown.

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 – using a radio-immuno assay, 79-115 hours in hyperprolactinaemic 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 cabergoline 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 cabergoline.

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Lactose
Leucine

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

Please refer to EXP date on outer carton.

6.4. Special Precautions for Storage

Store below 30°C.

6.5. Nature and Contents of Container

The tablets are contained in a high-density polyethylene (HDPE) bottle and a child-resistant polypropylene (PP) cap with an inner low-density polyethylene (LDPE) desiccant canister containing silica gel.
Each bottle contains 2 or 8 tablets and is enclosed in an outer cardboard carton. Not all pack sizes may be marketed.

6.6. Instruction for Use/Handling

CabergolineTablets are supplied with desiccant in the caps. This desiccant must not be removed.

7. MANUFACTURER

Pfizer Italia S.r.l.
Localita Marino del Tronto
Ascoli Piceno
Italy

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