Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dostinex 500 microgram tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 micrograms cabergoline.

Excipients with known effect:
Each tablet also contains 75.9 mg anhydrous lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
4 x 8 mm capsule-shaped, flat, white tablets. Scored, with a letter P on one side of the score and U on the other on one face; and "700" with a short score in the middle of the upper and lower extremity of the tablet surface on the opposite face of the tablet. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

It may be used to suppress lactation where it is considered essential, but should not be used for the routine suppression of lactation, or for the relief of symptoms of post-partum pain and engorgement, which can be adequately treated with simple analgesics and breast support.

4.2 Posology and method of administration

Cabergoline is to be administered by the oral route. 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 that cabergoline is preferably taken with meals for all the therapeutic indications.

Treatment of Hyperprolactinaemic disorders:
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 and ranges from 0.25 mg to 2 mg per week. Doses of up to 4.5 mg per week have been used in hyperprolactinaemic patients. The maximum dose on any one day should not exceed 3 mg.

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

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

After cabergoline withdrawal, recurrence of hyperprolactinaemia is usually observed. However, persistent suppression of prolactin levels has been observed for several months in some patients. Of the group of women followed up, most had ovulatory cycles which continued for greater than 6 months after cabergoline discontinuation.

For inhibition of puerperal lactation:
Cabergoline 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 of one 0.5 mg tablet) every 12 hours for two days (1 mg total dose). This dosage regimen has been demonstrated to be better tolerated than the single dose regimen in women electing to suppress lactation having a lower incidence of adverse events, in particular of hypotensive symptoms.

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

Use in the elderly:
As a consequence of the indications for which cabergoline is presently proposed, the experience in elderly is very limited. Available data do not indicate a special risk.

4.3 Contraindications

Hypersensitivity to cabergoline or to any of the excipients listed in section 6.1 or any ergot alkaloid.

Cabergoline is contraindicated in patients with hepatic insufficiency and with toxaemia of pregnancy.

History of pulmonary, pericardial and retroperitoneal fibrotic disorders.

For long-term treatment: Evidence of cardiac valvulopathy as determined by pre-treatment echocardiography. (See section 4.4)

Cabergoline should not be co-administered with anti-psychotic medications or administered to women with a history of puerperal psychosis.

4.4 Special warnings and precautions for use

General:
The safety and efficacy of cabergoline have not yet been established in patients with renal and hepatic disease. As with other ergot derivatives, cabergoline should be given with caution to patients with severe cardiovascular disease, Raynaud's syndrome, renal insufficiency, peptic ulcer or gastrointestinal bleeding, or with a history of serious, particularly psychotic, mental disorders.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

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.

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.

Serious adverse events including hypertension, myocardial infarction, seizures, stroke or psychiatric disorders have been reported in postpartum women treated with cabergoline for inhibition of lactation. In some patients the development of seizures or stroke was preceded by severe headache and/or transient visual disturbances. Blood pressure should be carefully monitored after the treatment. If hypertension, suggestive chest pain, severe, progressive, or unremitting headache (with or without visual disturbances), or evidence of central nervous system toxicity develop, cabergoline should be discontinued and the patient should be evaluated promptly.

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).

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

Treatment of Hyperprolactinaemic Disorders:
Because hyperprolactinaemia accompanied 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.

Cabergoline restores ovulation and fertility in women with hyperprolactinaemic hypogonadism.

Before administration of cabergoline, pregnancy should be excluded. Because clinical experience is still limited and the product has a long half-life, as a precautionary measure it is recommended that once regular ovulatory cycles have been achieved women seeking pregnancy discontinue cabergoline one month before intended conception.

Because pregnancy might occur prior to reinitiation of menses, a pregnancy test is recommended at least every 4 weeks during the amenorrhoeic 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. Should pregnancy occur during treatment, cabergoline 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 tumours may occur during gestation.

Regular gynaecological assessment, including cervical and endometrial cytology, is recommended for patients taking cabergoline for extensive periods.

Fibrosis and cardiac valvulopathy and possibly related clinical phenomena:
Fibrotic and serosal inflammatory disorders such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy involving one or more valves (aortic, mitral and tricuspid) or retroperitoneal fibrosis have occurred after prolonged usage or ergot derivatives with agonist activity at the serotonin $5HT_{2B}$ receptor, such as cabergoline. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of cabergoline.

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.

Valvulopathy has been associated with cumulative doses, therefore patients should be treated with the lowest effective dose. At each visit, the risk benefit profile of cabergoline treatment for the patient should be reassessed to determine the suitability of continued treatment with cabergoline.

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).

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).

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. 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 4.7)

Impulse control disorders:
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Dostinex. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of other drugs during early puerperium, particularly of ergot alkaloids, was not 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 which 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 Fertility, pregnancy and lactation

There are no adequate and well-controlled studies from the use of cabergoline in pregnant women. Animal studies have not demonstrated teratogenic effects, but reduced fertility and embryo-toxicity were observed in association with pharmacodynamic activity (see section 5.3).

In a twelve year observational study on pregnancy outcomes following cabergoline therapy, information is available on 256 pregnancies.Seventeen of these 256 pregnancies (6.6%) eventuated in major congenital malformations or abortion.Information is available on 23/258 infants who had a total of 27 neonatal abnormalities, both major and minor.Musculoskeletal malformations were the most common neonatal abnormality (10), followed by cardio-pulmonary abnormalities (5).There is no information on perinatal disorders or long-term development of infants exposed to intra-uterine cabergoline.Based on recent published literature, the prevalence of major congenital malformations in the general population has been reported to be 6.9% or greater.Rates of congenital abnormality vary between different populations. It is not possible to accurately determine if there is an increased risk as no control group was included.

Cabergoline should only be used during pregnancy if clearly indicated and after an accuratebenefit/risk evaluation. (see section 4.4).

Due to the long half-life of the drug and limited data on in utero exposure, women planning to become pregnant should discontinue cabergoline one month before intended conception. If conception occurs during therapy, treatment should be discontinued as soon as pregnancy is confirmed to limit foetal exposure to the drug.

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 machines

Patients should be careful when performing actions which require fast and accurate reaction during treatment initiation.

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) until such episodes and somnolence have resolved. (see section 4.4).

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with cabergoline with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Cardiac disorders	Very Common	Valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion)
	Uncommon	Palpitations
	Not Known	Angina pectoris
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea, pleural effusion, fibrosis, (including pulmonary fibrosis), epistaxis
	Very rare	Pleural fibrosis
	Not Known	Respiratory disorder, respiratory failure, pleuritis chest pain
Immune system disorders	Uncommon	Hypersensitivity reaction
Nervous system disorders	Very common	Headache*, dizziness/vertigo*
	Common	Somnolence
	Uncommon	Transient hemianopsia, syncope, paraesthesia

	Not Known	Sudden sleep onset, tremor
Eye disorders	Not Known	Visual impairment
Psychiatric disorders	Common	Depression
	Uncommon	Increased libido
	Not Known	Aggression, delusions, hypersexuality, pathological gambling, psychotic disorder, hallucinations
Vascular disorders	Common	Cabergoline generally exerts a hypotensive effect in patients on long-term treatment; Postural hypotension, hot flushes**
	Uncommon	Digital vasospasm, fainting
Gastrointestinal disorders	Very common	Nausea*, dyspepsia, gastritis, abdominal pain*
	Common	Constipation, vomiting**
	Rare	Epigastric pain
General disorders and administration site conditions	Very Common	Asthenia***, fatigue
	Uncommon	Oedema, peripheral oedema
Hepato-biliary disorders	Not Known	Hepatic function abnormal
Skin and subcutaneous tissue disorders	Uncommon	Rash, alopecia
Musculoskeletal and connective tissue disorders	Uncommon	Leg cramps
Reproductive system and breast disorders	Common	Breast pain
Investigations	Common	Asymptomatic decreases in blood pressure (≥ 20 mmHg systolic and ≥ 10 mmHg diastolic)
	Uncommon	A decrease in haemoglobin values have been observed in amenhorrheic women during the first few months after menses.
	Not Known	Blood creatinine phosphokinase increased, liver function tests abnormal

*Very common in patients treated for hyperprolactinaemin disorders; Common in patients treated for inhibition/suppression of lactation
** Common in patients treated for hyperprolactinaemin disorders; Uncommon in patients treated for inhibition/suppression of lactation
*** Very common in patients treated for hyperprolactinaemin disorders; Uncommon in patients treated for inhibition/suppression of lactation

Impulse control disorders
Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Dostinex (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

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

Pharmacotherapeutic group: Prolactine inhibitors, ATC code: G02CB03

Cabergoline is a dopaminergic ergoline derivative endowed 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 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 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 (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 antiprolactinaemis 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.

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-8beta-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

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

A dose of 0.012 mg/kg/day (approximately 1/7 the maximum recommended human dose) during the period of organogenesis in rats caused an increase in post-implantation embryo foetal losses. These losses could be due to the prolactin inhibitory properties of cabergoline in rats. At daily doses of 0.5 mg/kg/day (approximately 19 times the maximum recommended human dose) during the period of organogenesis in the rabbit, cabergoline caused maternotoxicity characterized by a loss of body weight and decreased food consumption. Doses of 4 mg/kg/day (approximately 150 times the maximum recommended human dose) during the period of organogenesis in the rabbit caused an increased occurrence of various malformations. However, in another study in rabbits, no treatment-related malformations or embryofoetotoxicity were observed at doses up to 8 mg/kg/day (approximately 300 times the maximum recommended human dose).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous
Leucine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25˚C.
Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Class I amber glass bottles, stoppered with an aluminium tamper-evident screw cap with silica gel insert or high-density polyethylene (HDPE) bottles with child-resistant polypropylene (PP) cap with inner low-density polyethylene (LDPE) desiccant canister containing silica gel.

Each bottle contains 2, 4 or 8 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland Unlimited Company
The Watermarque Building
Ringsend Road
Dublin 4
D04 K7N3
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8 MARKETING AUTHORISATION NUMBER

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