

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cabergoline Hexal 2 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg cabergoline.

Excipient with known effect: lactose 150.6 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, capsule-shaped, biconvex tablets. Each tablet is scored on both sides and has 'CBG' on one side and '2' on the other side of the break line.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Parkinson's disease:

If treatment with a dopamine agonist is being considered, cabergoline is indicated as second line therapy in patients who are intolerant or fail treatment with a non-ergot compound, as monotherapy, or as adjunctive treatment to levodopa plus dopa-decarboxylase inhibitor, in the management of the signs and symptoms of Parkinson's disease.

Treatment should be initiated under specialist supervision. The benefit of continued treatment should be regularly reassessed, taking into account the risk of fibrotic reactions and valvulopathy (see sections 4.3, 4.4 and 4.8).

4.2 Posology and method of administration

Posology

The maximum dose is 3 mg cabergoline per day.

Adults and elderly patients:

As expected for dopamine agonists, dose response for both efficacy and undesirable effects appears to be linked to individual sensitivity. Optimization of dose should be obtained through slow initial dose titration, from starting doses of 0.5mg cabergoline (de novo patients) and 1 mg cabergoline (patients on L dopa) daily. The dosage of concurrent levodopa may be gradually decreased, while the dosage of cabergoline is increased, until the optimum balance is determined. In view of the long half-life of the

compound, increments of the daily dose of 0.5-1 mg cabergoline should be done at weekly (initial weeks) or bi-weekly intervals, up to optimal doses.

The recommended therapeutic dosage is 2 to 3 mg cabergoline /day as adjuvant therapy to levodopa/carbidopa. Cabergoline should be given as a single daily dose.

Use in children and adolescents:

The safety and efficacy of cabergoline has not been investigated in children or adolescents as Parkinson's disease does not affect this population.

Use in patients with hepatic or renal dysfunction

For patients with severe hepatic dysfunction or end stage renal failure see section 4.4.

Method of administration

Cabergoline is to be administered by the oral route. In order to reduce the risk of gastrointestinal undesirable effects it is recommended that cabergoline is taken with meals for all therapeutic indications.

4.3 Contraindications

Hypersensitivity to cabergoline, other ergot alkaloids or to any of the excipients listed in section 6.1. 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 – Fibrosis and cardiac valvulopathy and possibly related clinical phenomena).

4.4 Special warnings and precautions for use

General

As with other ergot alkaloids, cabergoline should be given with caution to subjects with severe cardiovascular disease, hypotension, Raynaud's syndrome, peptic ulcer or gastrointestinal bleeding. The effects of alcohol on overall tolerability of cabergoline are currently unknown.

Cabergoline should be given with caution to patients with a history of serious, particularly psychotic mental disease or where there is a risk of post-partum psychosis.

Hepatic Insufficiency:

Lower doses of cabergoline should be considered in patients with severe hepatic insufficiency. 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, particularly during the first days of administration of cabergoline. Care should be exercised when administering cabergoline concomitantly with other drugs known to lower blood pressure.

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 of 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. 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)

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:

- Pleuropulmonary disease, such as dyspnoea, shortness of breath, persistent cough or chest pain.
- Renal insufficiency or ureteral/abdominal vascular obstruction that may occur with pain in the loin/flank, and lower limb oedema, as well as any possible abdominal masses or tenderness that may indicate retroperitoneal fibrosis.
- Cardiac failure; cases of valvular and pericardial fibrosis have often manifested as cardiac failure. Therefore, valvular fibrosis (and constrictive pericarditis) should be excluded if such symptoms occur.

Clinical diagnostic monitoring for development of fibrotic disorders, as appropriate, is essential. Following treatment initiation, the first echocardiogram must occur within 3-6 months, thereafter, the frequency of echocardiographic monitoring should be determined by appropriate individual clinical assessment with particular emphasis on the above-mentioned signs and symptoms, but must occur at least every 6 to 12 months.

Cabergoline should be discontinued if an echocardiogram reveals new or worsened valvular regurgitation, valvular restriction or valve leaflet thickening or fibrotic valvular disease (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.

Hypotension

Symptomatic hypotension can occur within 6 hours following administration of cabergoline; particular attention should be paid when administering cabergoline concomitantly with other medical product known to lower blood pressure. Because of its elimination half-life hypotensive effects may persist for

a few days after cessation of therapy. Monitoring of treatment with regular checks of blood pressure is recommended in the first 3-4 days after initiation of treatment.

Somnolence/sudden sleep onset

Cabergoline has been associated with somnolence and episodes of sudden sleep onset, in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported. 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. during treatment with cabergoline (see section 4.7). Furthermore a reduction of dosage or termination of therapy may be considered.

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 cabergoline. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Renal insufficiency

No overall differences in the pharmacokinetics of cabergoline were observed in moderate to severe renal disease. The pharmacokinetics of cabergoline has not been studied in patients having end-stage renal failure, or in patients on haemodialysis; these patients should be treated with caution.

Other

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions with other medicinal products and other forms of interactions

The concomitant use of antiparkinson non-dopamine agonists (e.g. selegiline, amantadine, biperiden, trihexyphenidyl) was allowed in clinical studies for patients receiving cabergoline.

In studies where the pharmacokinetic interactions of cabergoline with L-dopa or selegiline were evaluated, no interactions were observed.

No information is available about possible interactions between cabergoline and other ergot alkaloids. Therefore, long-term treatment with cabergoline is not advised in combination with these medicinal products.

Precautions

Interactions with other medicinal products that reduce blood pressure should be taken into consideration.

Pharmacokinetic interactions with other medicinal products cannot be predicted based on available information about the metabolism of cabergoline. 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 therapeutic effect of cabergoline.

As with other ergot derivatives, cabergoline should not be used in association with macrolide antibiotics (such as erythromycin) due to increased systemic availability.

4.6 Fertility, pregnancy and lactation

Pregnancy

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.

It is recommended that contraception is used whilst on treatment with cabergoline.

Cabergoline should only be used during pregnancy if clearly indicated and after an accurate benefit/risk evaluation.

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 medicinal product.

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.

Fertility

Cabergoline restores ovulation and fertility in women with hyperprolactinaemic hypogonadism: since pregnancy might occur prior to reinitiation of menses, pregnancy testing is recommended as appropriate during the amenorrhoeic 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 effective non-hormonal contraception during treatment and after cabergoline withdrawal for at least 4 weeks.

Lactation

In rats, cabergoline and/or its metabolites are excreted in milk. No information is available on the excretion in breast milk in humans; however, lactation is expected to be inhibited/suppressed by cabergoline, in view of its dopamine agonist properties.

Mothers should be advised not to breast-feed while being treated with cabergoline.

4.7 Effects on ability to drive and use machines

Cabergoline reduces blood pressure, which may impair the reactions of certain patients. This should be taken into account in situations requiring intense awareness, such as when driving a car or operating machinery.

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

Patients 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 episodes and somnolence have resolved (see section 4.4 –Somnolence/sudden Sleep Onset).

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with cabergoline with the following frequencies:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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
Immune system disorders	Uncommon	Hypersensitivity reaction
Psychiatric disorders	Common	Hallucinations, sleep disturbances, increased libido, confusion
	Uncommon	Delusions, psychotic disorder
	Not Known	Aggression, hypersexuality, pathological gambling
Nervous system disorders	Common	Headache, somnolence, dizziness/vertigo, dyskinesia
	Uncommon	Hyperkinesia
	Not Known	Sudden sleep onset, syncope, tremor
Eye disorders	Not known	Visual impairment
Cardiac disorders	Very common	Valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion)
	Common*	Angina pectoris
Vascular disorders	Common	Cabergoline generally exerts a hypotensive effect in patients on long-term treatment; postural hypotension
	Uncommon	Erythromelalgia
	Not Known	Digital vasospasm
Respiratory, thoracic and mediastinal disorders	Common	Dyspnea
	Uncommon	Pleural effusion, pulmonary fibrosis
	Very rare	Fibrosis (including pleural fibrosis)
	Not Known	Respiratory disorder, respiratory failure, pleuritis, chest pain
Gastrointestinal disorders	Very common	Nausea
	Common	Constipation, dyspepsia, gastritis, vomiting
Hepatobiliary disorders	Uncommon	Hepatic function abnormal

Skin and subcutaneous tissue disorders	Uncommon	Rash
	Not Known	Alopecia
Musculoskeletal and connective tissue disorders	Not Known	Leg cramps
General disorders and administration site conditions	Very common	Peripheral edema
	Common	Asthenia
	Uncommon	Edema, fatigue
Investigations	Common	Liver function tests abnormal, decreased hemoglobin, hematocrit, and/or red blood cell (>15% vs baseline)
	Not Known	Blood creatinine phosphokinase increased

* When concomitant use with levodopa therapy

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 cabergoline (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 reaction via [TO BE COMPLETED NATIONALLY]

4.9 Overdose

Symptoms of overdose would likely be those of over-stimulation of dopamine receptors, e.g. nausea, vomiting, gastric complaints, postural hypotension, reduced blood pressure, 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: Dopamine agonist

ATC code: N04BC06

Cabergoline is a synthetic ergot alkaloid and an ergoline derivate with long-acting dopamine agonist and prolactin-inhibiting properties. A central dopaminergic effect via D2-receptor stimulation is achieved through higher doses than doses that reduce the levels of serum prolactin.

Controlled clinical studies have demonstrated that cabergoline is effective at an average dose of 4 mg/day following titration (up to 5-6 mg cabergoline/day in the different studies). Cabergoline reduces daily fluctuations in the motor function in patients with Parkinson's disease that are being treated with levodopa/carbidopa. In newly diagnosed patients, cabergoline administered as monotherapy has been shown to produce somewhat less frequent clinical improvement compared with levodopa/carbidopa.

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 active substance intake and is dose-dependent both in terms of maximal decrease and frequency.

5.2 Pharmacokinetic properties

Absorption

After oral administration cabergoline is rapidly absorbed from the gastrointestinal tract as the peak plasma concentration is received within 0.5 to 4 hours.

Food does not appear to affect absorption and disposition of cabergoline.

Distribution

"In-vitro" experiments showed that cabergoline at concentrations of 0.1 – 10 ng/ml is 41-42% bound to plasma proteins.

Biotransformation

In urine, the main metabolite identified is 6-allyl-8 β -carboxy-ergoline, which accounts for 4-6% of the dose. Three additional metabolites are identified in urine, which account 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".

Elimination

The elimination half-life of cabergoline, is long; (63-68 hours in healthy volunteers and 79-115 hours in hyperprolactinaemic patients).

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) for 0.5 cabergoline dose.

Ten days after administration about 18% and 72% of the dose is recovered in urine and faeces, respectively. Unchanged cabergoline in urine accounts for 2-3% of the dose.

Linearity/Non-linearity

The pharmacokinetic profile is linear up to 7 mg per day.

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

Anhydrous lactose

L-Leucin

Magnesium stearate (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture. The drying capsule or bag with silica gel must not be removed from the bottle.

6.5 Nature and contents of container

Brown glass bottles (type III) that contain a desiccation capsule or bag with silica gel. The brown glass bottle has an induction-sealed childproof aluminium membrane and a childproof HDPE top. External box.

Packaging sizes: 2, 8, 14, 15, 16, 20, 28, 30, 32, 40, 48, 50, 60, 90, 96, 100, 200 (2x100).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirement.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8 MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 2006-06-16

Date of last renewal: 2009-05-07

10 DATE OF REVISION OF TEXT

2016-11-14