SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cabergoline Teva 1 mg tablets
Cabergoline Teva 2 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg cabergoline.

Excipient(s) with known effect: lactose 75.3 mg

Each tablet contains 2 mg cabergoline.

Excipient(s) with known effect: lactose 150.6 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

The tablet can be divided into equal doses.

White, oval-shaped, biconvex tablets with scores on both sides. One side is debossed with 'CBG' and '1' on either side of the score.
White, capsule-shaped, biconvex tablets with scores on both sides. One side is debossed with 'CBG' and '2' on either side of the score.

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 with Parkinson's disease:

- as monotherapy or
- as adjunctive treatment to levodopa plus a dopa-decarboxylase-inhibitor,

when treatment with non-ergot dopamine-agonists have failed, were not sufficient enough or were not tolerated.

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 of 3 mg/day of cabergoline must not be exceeded.

Adults and elderly
As expected for dopamine agonists, dose response for both efficacy and undesirable effects appears to be linked to individual sensitivity. Optimisation of dose should be obtained through slow initial dose titration, from starting doses of 0.5 mg cabergoline (de novo patients) and 1 mg cabergoline (patients on levodopa) 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.

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

Special Populations
Patients with hepatic impairment
Cabergoline is not indicated in patients with severe hepatic impairment, see section 4.3, 4.4 and 5.2.

Patients with renal impairment
No change in dose is needed in patients with light to moderate renal insufficiency.
Patients having end-stage renal failure or patients on haemodialysis should be treated with caution, as pharmacokinetics have not been studied, see section 4.4 and 5.2.

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 the active substance, any ergot alkaloid or to any of the excipients listed in section 6.1
- Pre-eclampsia, eclampsia
- Uncontrolled hypertension or hypertension post-partum
- Severe hepatic impairment, see section 4.2, 4.4 and 5.2
- 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).

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, hepatic diseases (see section 4.2, 4.3 and 5.2), renal impairment (see section 4.2 and 5.2), hypotension, Raynaud's syndrome, peptic ulcer or gastrointestinal bleeding.

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

Cabergoline should be used with caution in patients with severe mental illness, especially in patients with a history of psychotic disorders, or in patients at risk of postpartum psychosis.

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. Special caution is advised in patients with a history of known pleural effusions.

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 discontinuation 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 ESR 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 a 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.

During treatment, attention should be paid to the signs and symptoms of:
- Pleuro-pulmonary disorders, such as dyspnoea, shortness of breath, persistent cough, or chest pain.
- Renal insufficiency or ureteral/abdominal vascular obstructions 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 insufficiency; cases of valvular and pericardial fibrosis have often manifested as cardiac insufficiency. Therefore, valvular fibrosis (and constrictive pericarditis) should be excluded if such symptoms occur.

Clinical diagnostic monitoring for development of fibrotic disease is essential. Following treatment initiation, the first echocardiogram must be performed 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 be performed at least every 6 to 12 months.

Cabergoline should be discontinued if an echocardiogram reveals new or worsened valvular regurgitation, valvular restriction, valve leaflet thickening or fibrotic valvular disease (see section 4.3).

The need for further clinical monitoring (e.g. physical examination including cardiac auscultation, X-ray, CT-scan) should be determined on an individual basis.

Additional investigations such as erythrocyte sedimentation rate, and serum creatinine measurements should be performed if necessary to support a diagnosis of 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 medicinal products 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 to 4 days after initiation of treatment.

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.

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 activities, in some cases without awareness or warning signs, has been reported. Patients must be informed and advised to exercise caution when driving or operating machinery during treatment with cabergoline.

Patients with a history of somnolence and/or episodes of sudden onset of sleep should not drive or operate machinery during treatment with cabergoline. 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 cabergoline. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

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

4.5 Interactions with other medicinal products and other forms of interactions

Concomitant administration not recommended:

- when combined with **macrolide antibiotics** (e.g. erythromycin), as it may lead to increased bioavailability of cabergoline.
- when combined with **dopamine antagonists**. Cabergoline acts via direct stimulation of dopamine receptors. Therefore, it should not be combined with medicinal products with a dopamine antagonist effect (e.g. phenothiazines, butyrophenones, thioxanthenes, metoclopramide) as these may reduce the therapeutic effect of cabergoline.

- when combined with **other ergot alkaloids**. No information is available on possible interactions between cabergoline and other ergot alkaloids. Therefore, long-term treatment with cabergoline in combination with these medicinal products is not recommended.

Percautionary measures
- **Antihypertensives**: Interactions with other medicinal products that reduce blood pressure should be taken into consideration.
- **Other anti-Parkinson-medications**: The concomitant use of antiparkinson non-dopamine agonists (eg, selegiline, amantadine, biperiden, trihexyphenidyl) was allowed in clinical studies for patients receiving cabergoline. In studies where the pharmacokinetic interactions of cabergoline with levodopa or selegiline were evaluated, no interactions were observed.

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

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 embryo-toxicity and reduced fertility 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.

In rats, cabergoline has been shown to cross the placenta. It is not known if this also applies for humans.

For women of childbearing potential pregnancy should be excluded before cabergoline administration and effective contraception is recommended during treatment with cabergoline and for at least 4 weeks after treatment.

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 drug.

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.

Breast-feeding

Cabergoline inhibits lactation. Therefore, it should not be used in mothers who want to breast-feed their infants. No information is available if cabergoline is excreted in human breast milk. However, in rats, cabergoline and/or its metabolites have been shown to be excreted in milk.

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

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 of childbearing potential should be advised to use effective non-hormonal contraception during treatment with cabergoline and for at least 4 weeks after cabergoline withdrawal. Because of limited experience on the safety of foetal exposure to cabergoline, it is advisable that women seeking pregnancy conceive at least one month after cabergoline discontinuation given that ovulatory cycles persist in some patients for 6 months after withdrawal.

4.7 Effects on ability to drive and use machines

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

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 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 (eg, operating machines) until such episodes and somnolence have resolved (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile
The adverse reactions are generally dose-dependent and can be reduced by gradually tapering the dose.

About 1,070 parkinsonian patients have received cabergoline as adjuvant therapy to levodopa in clinical studies. 74% of these patients had at least one adverse event, mainly of mild to moderate severity and transient in nature, and requiring discontinuation in a small proportion of cases.

Tabulated list of adverse reactions
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).

System organ class	**Very common** (≥ 1/10)	**Common** (≥ 1/100, < 1/10)	**Uncommon** (≥ 1/1.000, < 1/100)	**Very rare** (< 1/10.000)	**Not known** (cannot be estimated from the available data)
Immune system disorders			Hypersensitivity reaction		

System organ class	**Very common** (≥ 1/10)	**Common** (≥ 1/100, < 1/10)	**Uncommon** (≥ 1/1.000, < 1/100)	**Very rare** (< 1/10.000)	**Not known** (cannot be estimated from the available data)
Psychiatric disorders		Hallucinations, sleep disturbances, increased libido, confusion	Delusions, psychotic disorder		Aggression, hypersexuality, pathological gambling
Nervous system disorders		Headache, somnolence, dizziness/vertigo, dyskinesia	Hyperkinesia		Sudden sleep onset, syncope, tremor
Eye disorders					Visual impairment
Cardiac disorders	Valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion)	Angina pectoris*			
Vascular disorders		Cabergoline generally exerts a hypotensive effect in patients on long-term treatment; postural hypotension, hot flushes/facial redness	Erythromelalgia		Digital vasospasm
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Pleural effusion, pulmonary fibrosis	Fibrosis (including pleural fibrosis)	Respiratory disorder, respiratory failure, pleuritis, chest pain
Gastrointestinal disorders	Nausea	Constipation, dyspepsia, gastritis, vomiting			
Hepatobiliary disorders			Hepatic function abnormal		
Skin and subcutaneous tissue disorders			Rash		Alopecia
Musculoskeletal and connective					Leg cramps

System organ class	Very common (≥ 1/10)	Common (≥ 1/100, < 1/10)	Uncommon (≥ 1/1.000, < 1/100)	Very rare (< 1/10.000)	Not known (cannot be estimated from the available data)
tissue disorders					
General disorders and administration site conditions	Peripheral oedema	Asthenia	Oedema, fatigue		
Investigations		Liver function tests abnormal, decreased hemoglobin, hematocrit, and/or red blood cell (>15% vs baseline)			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 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 the national reporting system listed in Appendix V.

4.9 Overdose

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

Supportive measures should be initiated. In particular, unabsorbed drug should be removed and the blood pressure should be stabilised, 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. The prolactin-reducing effect has a fast onset (within 3 hours from administration), lasts for long (7-28 days) and is dose-dependent for both effect and duration.

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-8ß-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.

Hepatic impairment

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. See section 4.2, 4.3 and 4.4.

Renal impairment
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; see section 4.2 and 4.4.

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
L-Leucine
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 or PP top. External box.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8 MARKETING AUTHORISATION NUMBERS

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 2004-05-07
Date of last renewal: 2009-05-07

[To be completed nationally]

10 DATE OF REVISION OF THE TEXT

[To be completed nationally]17 November 2022