SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cabergoline Teva 0.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5 mg cabergoline.

Excipient(s) with known effect: lactose 75.8 mg
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, oval-shaped, flat bevelled tablets. One side is smooth and the other side has a dividing score line and is debossed with 'CBG' and '0.5' on either side of the score.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Inhibition or suppression of post-partum lactation for medical reasons
- Hyperprolactinaemic conditions
- Prolactin-secreting pituitary adenoma
- Idiopathic hyperprolactinaemia

4.2 Posology and method of administration

It is recommended that the medicinal product is initially prescribed by an appropriate specialist or after consulting a specialist.

Posology
Monitoring of treatment with regular check of blood pressure is recommended in the first 3 to 4 days after initiation of treatment, as hypotensive symptoms might occur.
The maximum dose of 3 mg/day of cabergoline must not be exceeded in any condition.

Inhibition of post-partum lactation
A single dose of 1 mg (2 tablets of 0.5 mg) cabergoline should be administered within the first 24 hours post-partum, but only after stabilisation of heart rate, breathing and other vital signs.

Inhibition/Suppression of already initiated lactation
A single dose of 0.25 mg (half tablet of 0.5 mg) cabergoline should not be exceeded in nursing women treated for suppression of established lactation to avoid potential postural hypotension.

Treatment of hyperprolactinaemic conditions
The recommended initial dosage is 0.5 mg cabergoline per week given in one or two doses (e.g. on Monday and Thursday) per week.
If necessary the weekly dose should be increased gradually, preferably by adding 0.5 mg cabergoline per week at monthly intervals until an optimal therapeutic response is achieved.

The therapeutic dosage is usually 1 mg cabergoline per week and ranges from 0.25 mg to 2 mg cabergoline per week. Doses of up to 4.5 mg cabergoline per week have been used in hyperprolactinaemic patients.

Depending to the patient's tolerability the weekly dose may be given as a single administration or divided into two or more doses per week. Division of the weekly dose into multiple administrations is advised when doses higher than 1 mg cabergoline per week are to be given.

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.

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.

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.

Paediatric population
The safety and efficacy of cabergoline in children and adolescents less than 16 years of age have not been established.

Method of administration
Cabergoline should be administered orally.
To reduce the risk of gastrointestinal side effects cabergoline should be taken with a meal.

4.3 Contraindications

- Hypersensitivity to the active substance, any ergot alkaloid or to any of the excipients listed in section 6.1
- History of psychosis or risk of post-partum psychosis
- Pre-eclampsia, eclampsia
- Post-partum hypertension or uncontrolled hypertension
- 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
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, or with a history of serious, particularly psychotic, mental disorders.

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

Hypotension
Symptomatic and postural 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 3-4 days after initiation of treatment.

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 treatment may be considered. (see section 4.7)

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.

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.

<u>Before initiating long-term treatment</u>
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).

<u>During long-term treatment</u>

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 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 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 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 or valve leaflet thickening. (see section 4.3).

The need for supplementary 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 fibrotic disorder.

Psychiatric
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.

Inhibition/Suppression of physiologic lactation
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).

Serious adverse reactions in postpartum women
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 during 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 evaluated promptly.

Treatment of hyperprolactinaemic disorders
Because hyperprolactinaemia accompanied with amenorrhoea/galactorrhoea and infertility may be associated with pituitary tumour, 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. Once menses are reinitiated a pregnancy test is recommended every time a menstrual period is delayed by more than 3 days.
Women should be advised to use mechanical contraception during treatment with cabergoline and for at least one month after discontinuation of cabergoline.
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.

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

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.

No information is available about possible interactions between cabergoline and other ergot alkaloids. Therefore, the concomitant use of these medications during long-term treatment with cabergoline is not recommended.

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

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

No pharmacokinetic interactions with L-dopa or selegiline have been observed in studies of patients with Parkinson’s disease. 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.

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.

Effective non-hormonal contraception is recommended during treatment and for at least 4 weeks after stopping treatment with cabergoline.

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

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.

Breastfeeding
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 breastfeed in case of failed lactation inhibition/suppression by cabergoline. Since it prevents lactation, cabergoline should not be administered to mothers with hyperprolactinaemic disorders who wish to breastfeed their infants.

Fertility
In rats, for whom prolactin is important for implantation, cabergoline has shown expected effect on fertility (impaired implantation).
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 (see section 4.4). Women 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.

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 present 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).

4.8 Undesirable effects

The undesirable effects are usually dose-dependent. In patients with known intolerance to dopaminergic drugs, undesirable effects can be reduced by starting treatment with cabergoline gradually (e.g. 0.25 mg once a week) and then gradually increasing the dose until the therapeutic dose is reached. Once persistent or severe undesirable effects have occurred, they can be reversed by temporarily reducing the dose, followed by a more gradual increase (e.g. in increments of 0.25 mg weekly every 14 days).

Inhibition of lactation: Approximately 14% of the patients experience undesirable effects. The most common are low blood pressure (12%), dizziness (6%) and headaches (5%). Long-term treatment increases the frequency of undesirable effects to approximately 70%.

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)	**Rare** (≥1/10,000 to ≤1/1,000)	**Very rare** (< 1/10,000)	**Not known** (cannot be estimated from the available data)
Immune system disorders			Hypersensitivity reaction			
Psychiatric disorders		Depression	Increased libido			Aggression, delusions, hypersexuality, pathological gambling, psychotic disorder, hallucinations
Nervous system disorders	Headache*, dizziness/vertigo*	Somnolence	Transient hemianopsia, syncope, paraesthesia			Sudden sleep onset (see section 4.4), tremor
Eye disorders						Visual impairment
Cardiac disorders	Valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion)		Palpitations			Angina pectoris
Vascular disorders		Cabergoline generally exerts a hypotensive	Digital vasospasm, fainting			

System organ class	Very common (≥ 1/10)	Common (≥ 1/100 < 1/10)	Uncommon (≥ 1/1,000 < 1/100)	Rare (≥1/10,000 to ≤1/1,000)	Very rare (< 1/10,000)	Not known (cannot be estimated from the available data)
		effect in patients on long-term treatment; Postural hypotension (see section 4.4), hot flushes/facial redness**				
Respiratory, thoracic and mediastinal disorders			Dyspnoea, pleural effusion, fibrosis, (including pulmonary fibrosis), epistaxis		Pleural fibrosis	Respiratory disorder, respiratory failure, pleurisy, chest pain
Gastrointestinal disorders	Nausea*, dyspepsia, gastritis, abdominal pain*	Constipation, vomiting**		Epigastric pain		
Hepatobiliary disorders						Hepatic function abnormal
Skin and subcutaneous tissue disorders			Rash, alopecia			
Musculoskeletal and connective tissue disorders			Leg cramps			
Reproductive system and breast disorders		Breast pain				
General disorders and administration site conditions	Asthenia***, fatigue		Oedema, peripheral oedema			
Investigations		Asymptomatic decreases in blood pressure (> 20 mmHg systolic and > 10 mmHg diastolic)	A decrease in haemoglobin values have been observed in amenhorrhoeic women during the first few months after menses			Blood creatinine phosphokinase increased, liver function tests abnormal

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

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

Hypotension
Low blood pressure (≥ 20 mmHg systolic and ≥ 10 mmHg diastolic) has been reported in the 3-4 days following a single dose of 1 mg cabergoline in post-partum studies. The undesirable effects generally occur in the first two weeks, and then decline or disappear. 3% of the patients had their treatment discontinued on account of the undesirable effects.

Somnolence/sudden sleep onset
Cabergoline is associated with somnolence and in less common cases has been associated with excessive somnolence during the day as well as with sudden sleep attacks (see section 4.7).

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, e.g. nausea, vomiting, gastric complaints, postural hypotension, reduced blood pressure, 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: Prolactin inhibitor
ATC code: G02CB03

Mechanism of action
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.

Pharmacodynamic effects
The prolactin-reducing effect is dose-dependent, starting within 3 hours and remaining for 2-3 weeks. The long-acting effect means that a single dose is generally sufficient to stop the initiation of milk secretion. In treatment of hyperprolactinaemia, the serum prolactin levels are generally normalised within two to four weeks of the optimal dose being attained. Prolactin can still be significantly reduced several months after withdrawal of the treatment.

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 mg 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

There are no non-clinical data of relevance for the safety assessment, which are not already included in other relevant sections of this Summary of Product Characteristics.

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 tablets.

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 NUMBER

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 07th May 2004

Date of last renewal: 07th May 2009

10 DATE OF REVISION OF THE TEXT

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