SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cabergonicht 0.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5 mg cabergoline.

Excipient with known effect:
Each tablet contains 75.8 mg lactose
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, oval-shaped, flat bevelled tablets containing 0,5 mg cabergoline. Each tablet is scored on one side and has “CBG” on one side and “0,5” on the other side of the break line.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Inhibition/supression of lactation for medical reasons.
Hyperprolactimaemic disorders
Prolactin secreting pituitary adenomas
Idiopathic hyperprolactinaemia

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

4.2 Posology and method of administration

Posology

The maximum dose is 3 mg cabergoline per day.
Adults:

Treatment of hyperprolactinaemic disorders:

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. 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.

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 cabergoline per week are to be given since the tolerability of doses greater than 1 mg cabergoline 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.

Inhibition of lactation:
Cabergoline should be administered within the first 24 hours post-partum. The recommended therapeutic dosage is 1 mg cabergoline given as a single dose.

Suppression of established lactation:
The recommended therapeutic dosage regimen is 0.25 mg (one-half 0.5 mg tablet) every 12 hours for two days (1 mg total dose). This dosage regimen should not be exceeded in nursing women treated for suppression of established lactation to avoid potential postural hypotension.

Hepatic or renal impairment
Use in patients with hepatic insufficiency and renal insufficiency see section 4.4

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

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.

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 active substance, 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).
Risk of postpartum psychosis.

4.4 Special warnings and precautions for use

General:

The assessment of safety and efficacy of cabergoline is limited in patients with renal and hepatic disease. As with other ergot derivatives, cabergoline should be given with caution to patients with

severe cardiovascular disease, hypotension, Raynaud's syndrome, peptic ulcer or gastrointestinal bleeding, or with a history of serious, particularly psychotic, mental disorders or where there is a risk of post-partum psychosis.
The effects of alcohol on overall tolerability of cabergoline are currently unknown.

Symptomatic hypotension may occur with cabergoline, particularly when taken concomitantly with other medicinal products known to lower blood pressure.
Monitoring of treatment with regular checks of blood pressure is recommended in the first 3-4 days after initiation of treatment.

Inhibition/suppression of physiologic lactation
As with other ergot derivatives,Cabergoline should not be used in women with pregnancy-induced hypertension, for example, preeclampsia or post-partum hypertension unless the potential benefit is judged to outweigh the possible risk.
A single dose of 0.25 mg cabergoline should not be exceeded in nursing women treated for suppression of established lactation to avoid potential postural hypotension (see section 4.2).

Treatment of hyperprolactinemic disorders:
Since hyperprolactinaemia with amenorrhoea/galactorrhoea and infertility may be associated with pituitary tumours, a complete evaluation of the pituitary is indicated investigating the underlying cause of the hyperprolactinaemia before treatment with cabergoline is commenced.

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.

Cabergoline restores ovulation and fertility in women with hyperprolactinemic 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 Cabergonicht 0.5 mg Tablets 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 amenorrheic period and, once menses are reinitiated, every time a menstrual period is delayed by more than 3 days. Women who wish to avoid pregnancy should be advised to use mechanical contraception during treatment with cabergoline and after discontinuation of cabergoline until recurrence of anovulation. As a precautionary measure, women who become pregnant should be monitored to detect signs of pituitary enlargement since expansion of pre-existing pituitary tumors may occur during gestation.

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 (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 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 treatment may be considered.

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.

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; these patients should be treated with caution.

Hepatic impairment:
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, 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.

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

Concomitant use not recommended:
Elevated plasma levels of bromocriptine have been observed in combination with macrolide antibiotics (such as erythromycin). Effects of macrolide antibiotics on cabergoline's plasma levels when administered simultaneously have not been studied. The combination should be avoided, as it may result in elevated cabergoline plasma levels.

Cabergoline acts through direct stimulation of dopamine receptors. Consequently, it should not be combined with medicinal products with a dopamine antagonistic effect (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, 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.

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

<u>Pregnancy</u>

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 has been shown to cross the placenta in rats. It is not known whether this occurs in humans.
Because of the limited experience of the use of cabergoline in pregnancy, cabergoline should be withdrawn before a planned pregnancy. If the patient becomes pregnant during treatment, cabergoline shall be immediately withdrawn. During pregnancy, these patients must be carefully monitored for any pregnancy-induced pituitary enlargement.

Contraception should be continued for at least 4 weeks after stopping cabergoline.

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. 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.

Cabergoline should only be used during pregnancy if clearly indicated and after an accurate benefit/risk evaluation. (See section 4.4 Special warning and precautions for use – Treatment of Hyperprolactinemic Disorders).
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.

Breast-feeding
Cabergoline should not be administered to mothers with hyperprolactinemic disorders who elect to breastfeed their infants since it prevents lactation. No information is available on the excretion of the active substance in maternal milk but in rats cabergoline and/or its metabolites are excreted in the milk.

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

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. 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 being treated with cabergoline and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death(e.g., operating machines), until such episodes and somnolence have resolved (see section 4.4 - Somnolence/sudden sleep onset).

4.8 Undesirable effects

The undesirable effects are usually dose-dependent, and can be reduced by decreasing the dose gradually.

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).

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Cardiac disorders	**Very Common**	Valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion)
	Common	Chest pain
	Uncommon	Palpitations
	Not Known	Angina pectoris
Respiratory, thoracic and mediastinal disorders	**Uncommon**	Dyspnea, 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, paresthesia
	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	**Common**	Facial redness
	Uncommon	Rash, alopecia
Musculoskeletal and connective tissue disorders	**Uncommon**	Leg cramps
	Rare	Cramp in fingers
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/supression of lactation
** Common in patients treated for hyperprolactinaemin disorders; Uncommon in patients treated for inhibition/supression of lactation
*** Very common in patients treated for hyperprolactinaemin disorders; Uncommon in patients treated for inhibition/supression of lactation

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.

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

There is no clinical experience of overdose, but observations from animal experiments suggest that symptoms resulting from overstimulation of dopamine receptors can be expected, such as nausea, vomiting, gastric complaints, postural hypotension, reduced blood pressure, confusion/psychosis or hallucinations. Where indicated, supportive measures must be taken to remove unabsorbed drug and to restore blood pressure. 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 0.5mg 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.
Non-clinical 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 30ºC. 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, 4, 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.

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 THE TEXT
2016-11-14