Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cabergoline 0.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5mg cabergoline.

Excipient: lactose monohydrate 75mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

A white to off-white, capsule-shaped tablet, embossed with ‘C | 5’ on one side and ‘partial score >’ on the other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Inhibition 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

Cabergoline is to be administered by the oral route.

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

Treatment of hyperprolactinaemic disorders
The recommended initial dosage of cabergoline is 0.5mg per week given in one (single 0.5 mg) or two (separate 0.25 mg) doses (e.g. on Monday and Thursday) per week.

The weekly dose should be increased gradually, preferably by adding 0.5mg per week at monthly intervals until an optimal therapeutic response is achieved.

The therapeutic dosage is usually 1mg per week and ranges from 0.25mg to 2mg cabergoline per week.

Doses of cabergoline up to 4.5mg per week have been used in hyperprolactinaemic patients. The maximum daily dose should not exceed 3mg/day.

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

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

Use in children and adolescents
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 this strength of cabergoline is presently proposed, experience in the elderly is very limited. Available data do not indicate a special risk.

Renal Insufficiency
The assessment of safety and efficacy of cabergoline is limited in patients with renal disease. 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 Insufficiency
The assessment of safety and efficacy of cabergoline is limited in patients with hepatic disease. Cabergoline pharmacokinetics in patients with mild to moderate dysfunction (Child-Pugh score <10) were similar to those determined in previous studies in subjects with normal hepatic function. However, patients with the most severe dysfunction (Child-Pugh score >10) showed increased AUC values (>200%). These patients should be dosed with caution, and it is recommended that the dose should be limited to no more than 1mg/day.

4.3 Contraindications

- Hypersensitivity to cabergoline, any ergot alkaloid or to any of the excipients
- Pre-eclampsia, eclampsia
- Uncontrolled hypertension, post-partum hypertension
- History of pulmonary, pleural,, pericardial and retroperitoneal fibrotic disorders especially if associated with the use of dopamine agonists.
- Evidence of cardiac valvulopathy as determined by pretreatment echocardiography.
- History of psychosis or risk of post partum psychosis

4.4 Special warnings and precautions for use

General
As with other ergot alkaloids, cabergoline should be given with caution to subjects with cardiovascular disease, hypotension, Raynaud's syndrome, peptic ulcer or gastrointestinal bleeding.

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

Hypotension
Symptomatic hypotension can 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.

CNS
Somnolence: cabergoline has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported uncommonly. 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). Further, a reduction of dosage or termination of treatment 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

Treatment of hyperprolactinaemic disorders
Since hyperprolactinaemia with amenorrhoea and infertility may be associated with pituitary tumours, the underlying cause of the hyperprolactinaemia should be investigated 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.

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.

Before initiating long-term treatment:

All patients must undergo a cardiovascular evaluation, including echocardiogram, to assess the potential presence of asymptomatic valvular disease. It is also appropriate to perform baseline investigations of erythrocyte sedimentation rate or other inflammatory markers, lung function/chest X-ray and renal function prior to initiation of therapy.

In patients with valvular regurgitation, it is not known whether cabergoline treatment might worsen the underlying disease. If fibrotic valvular disease is detected, the patient should not be treated with cabergoline (see section 4.3).

During long-term treatment:

Fibrotic disorders can have an insidious onset and patients should be regularly monitored for possible manifestations of progressive fibrosis.
Therefore, during treatment, attention should be paid to the signs and symptoms of:
• Pleuro-pulmonary disease such as dyspnoea, shortness of breath, persistent cough or chest pain.
• Renal insufficiency or ureteral/abdominal vascular obstruction that may occur with pain in the loin/flank and lower limb oedema as well as any possible abdominal masses or tenderness that may indicate retroperitoneal fibrosis.
• Cardiac failure; cases of valvular and pericardial fibrosis have often manifested as cardiac failure. Therefore, valvular fibrosis (and constrictive pericarditis) should be excluded if such symptoms occur.

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

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

The need for other clinical monitoring (e.g. physical examination including, cardiac auscultation, Xray, 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.

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 Interaction with other medicinal products and other forms of interaction

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

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

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)

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.

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

4.6 Fertility, pregnancy and lactation

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

Cabergoline has been shown to cross the placenta in rats. It is not known whether this occurs in humans. Data on a limited number of pregnancies (n=100), generally taken during the first 8 weeks after conception, do not indicate cabergoline to be associated with an increased risk of abortion, premature delivery, multiple pregnancy or congenital abnormalities. To date, no other relevant epidemiological data are available. Animal studies indicate no direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development.

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.

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. When starting dopaminergic treatment, women must be warned that restoration of ovulation and fertility may be immediate (even before their first normal menstruation). Women not seeking pregnancy should be advised to use effective non-hormonal contraception during treatment and 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. Should pregnancy occur during treatment, cabergoline is to be discontinued. As a precautionary measure, women who become pregnant should be monitored to detect signs of pituitary enlargement since expansion of pre-existing pituitary tumours may occur during gestation.

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

Cabergoline should only be used during pregnancy if clearly indicated.

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

Breastfeeding should be avoided when taking 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 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 recurrent episodes and somnolence have resolved (see also section 4.4).

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 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%.

Post-marketing surveillance (including treatment with different strengths in Parkinson's Disease)

Fibrotic reactions
There have been reports of fibrotic and serosal inflammatory conditions, such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy and retroperitoneal fibrosis, in patients taking cabergoline (see 'Special warnings and special precautions for use').

The incidence of cardiac valvulopathy with cabergoline is not known. However based on recent studies of the prevalence of valvular regurgitation (the most sensitive echocardiogaphic marker for restrictive valvulopathy), the prevalence of regurgitation (virtually all cases asymptomatic) potentially attributable to cabergoline may be in the range of 20% or greater. There is limited information available on the reversibility of these reactions.

Somnolence
Cabergoline is associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes.

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).

The following undesirable effects have been observed 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) including isolated reports

Investigations Common	A fall in haemoglobin and haematocrit values, fall in the erythrocyte count, increases of triglycerides greater than 30% above the upper limit of the laboratory reference range (mostly transient)
Cardiac disorders Very common Common Uncommon	Orthostatic hypotension (mainly evident in the first weeks of therapy). Cardiac valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion). Angina, palpitations Erythromelalgia
Nervous system disorders Very common	Dyskinesia, dizziness, hyperkinesia.

Common	Drowsiness, Sleep disorders/somnolence, hallucinations, confusion, depression, headache, fatigue, paresthesia
Rare	Sudden sleep onset episodes
Not known (cannot be estimated from the available data)	Pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.
Eye disorders	
Uncommon	Hemianopia
Respiratory, thoracic and mediastinal disorders	
Common	Symptomatic pleural effusion/pulmonary fibrosis/pleuritis
Gastrointestinal disorders	
Very common	Nausea
Common	Vomiting, dyspepsia, gastritis, constipation. Gastric upset appeared more frequent in female than in male patients.
Not known (cannot be estimated from the available data)	Retroperitioneal fibrosis
Skin and subcutaneous tissue disorders	
Common	Facial redness
Musculoskeletal, connective tissue and bone disorders	
Rare	Cramp in fingers and calves
Vascular disorders	
Uncommon	Nose bleeding
Rare	Fainting
General disorders and administration site conditions	
Common	Peripheral oedema

4.9 Overdose

There is no clinical experience of overdosing, but observations from animal experiments suggest that symptoms resulting from overstimulation of dopamine receptors can be expected, such as nausea, vomiting, reduced blood pressure, confusion/psychosis or hallucinations. Where indicated, measures must be taken to restore blood pressure. In addition, with pronounced symptoms from the CNS (hallucinations), administration of a dopamine antagonist can be necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Prolactin inhibitor
ATC code: G02CB03

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 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 reached 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 was 6-allyl-8-carboxy-ergoline, which accounted for 4-6% of the dose. Three additional metabolites were identified in urine, which accounted overall for less than 3% of the dose. The metabolites have been found to be much less potent than cabergoline in inhibiting prolactin secretion “*in vitro”*.

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 cabergline 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 7mg 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

Lactose monohydrate
Leucine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package to protect from moisture.

6.5 Nature and contents of container

Type III amber glass bottles with a polypropylene screw cap.
A cylindrical tube or sachet containing desiccant (silica gel) is provided in each bottle.
Each bottle contains 2, 4, 8, 20, 28, 30, 40 & 80 tablets and is enclosed in an outer cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Arrow Generics Limited,
Unit 2, Eastman Way,
Stevenage,
Herts SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1130/014/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th February 2008
Date of last renewal: 13th March 2012

10 DATE OF REVISION OF THE TEXT

March 2013