Public Assessment Report

Decentralised Procedure

Cabergoline 0.5, 1, 2 & 4mg Tablets

UK/H/0955/01-04/DC

UK Licence No: PL 18909/0191-4

Arrow Generics Ltd
LAY SUMMARY

The MHRA today granted Arrow Generics Limited Marketing Authorisations (licences) for the medicinal products Cabergoline 0.5mg, 1mg, 2mg and 4mg tablets. This is a prescription-only medicine (POM).

Cabergoline 0.5mg tablets belong to a group of medicines known as prolactin inhibitors. Cabergoline prevents lactation (production of milk) by decreasing the level of a hormone known as prolactin. It is also used to reduce abnormal quantities of the hormone prolactin in the blood.

Cabergoline 1, 2 and 4mg tablets is one of a group of medicines known as dopamine agonists. Cabergoline acts in the same way as a chemical present in the nervous system called dopamine. Patients with Parkinson’s disease do not have enough of this chemical in their body. Cabergoline Tablets can be used either taken alone or in combination with levodopa, as second choice following non-ergot derived therapies.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Cabergoline tablets outweigh the risks, hence Marketing Authorisations have been granted.
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Steps taken after initial procedure
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<tr>
<td><strong>Type of Application</strong></td>
<td>Art 10.1</td>
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<tr>
<td><strong>Active Substance</strong></td>
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<td><strong>Form</strong></td>
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<td><strong>Strength</strong></td>
<td>0.5, 1, 2 and 4mg</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Arrow Generics Ltd, Unit 2, Eastman Way, Stevenage, Hertfordshire, UK</td>
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<td><strong>RMS</strong></td>
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Module 2

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.
Hyperprolactinaemic 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 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 single 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.
Anatomical evidence of cardiac valvulopathy of any valve (e.g., echocardiogram showing thickening of a valve leaflet, valvular stenosis and/or regurgitation).
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.

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson’s disease, including cabergoline.

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/Valvulopathy**

As with other ergot derivatives, pleural effusion/pulmonary fibrosis and valvulopathy have been reported following long-term administration of cabergoline. Some reports were in patients previously treated with ergotinic dopamine agonists. Following diagnosis of pleural effusion/pulmonary fibrosis or valvulopathy, the discontinuance of cabergoline has been reported to result in improvement of signs and symptoms.

In the event of new clinical symptoms of diseases in the respiratory system a pulmonary X-ray is recommended. Elevated erythrocyte sedimentation rate (ESR) has been observed in patients with pleural effusion/fibrosis. Consequently, a pulmonary X-ray is recommended in cases of abnormally elevated ESR without any apparent clinical explanation.

**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 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. 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 echocardiographic 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.
**Pathological gambling, increased libido and hypersexuality.** Patients treated with dopamine agonists for treatment of Parkinson’s disease, including cabergoline, especially at high doses, have been reported as showing pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

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.

<table>
<thead>
<tr>
<th>Investigations</th>
<th>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)</th>
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<tr>
<th>Cardiac disorders</th>
<th>Orthostatic hypotension (mainly evident in the first weeks of therapy)</th>
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<tbody>
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<td></td>
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<tr>
<td>Common</td>
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<tr>
<td>Uncommon</td>
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<tr>
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<tr>
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<th>Dyskinesia, dizziness, hyperkinesia.</th>
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<tr>
<td>Common</td>
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<tr>
<td>Rare</td>
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<tr>
<td>Not known (cannot be estimated from the available data)</td>
<td>Pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.</td>
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<th>Respiratory, thoracic and mediastinal disorders</th>
<th>Symptomatic pleural effusion/pulmonary fibrosis/pleuritis</th>
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<tbody>
<tr>
<td>Common</td>
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<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Nausea</th>
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<tr>
<td>Very common</td>
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<tr>
<td>Common</td>
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<tr>
<td>Not known (cannot be estimated from the available data)</td>
<td>Retroperitoneal fibrosis</td>
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<th>Facial redness</th>
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<thead>
<tr>
<th>Musculoskeletal, connective tissue and bone disorders</th>
<th>Cramp in fingers and calves</th>
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<tr>
<th>Vascular disorders</th>
<th>Nose bleeding</th>
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<tbody>
<tr>
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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-8β-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 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.
1 NAME OF THE MEDICINAL PRODUCT
Cabergoline 1mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 1mg cabergoline.

Excipient: lactose monohydrate 74.5mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet

A white to off-white, oval-shaped tablet, embossed with ‘C | 1’ 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
Treatment of Parkinson’s disease

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

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

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 is taken with meals for all therapeutic indications.

Adults and elderly patients
As expected for dopamine agonists, dose response for both efficacy and side effects appears to be linked to individual sensitivity.

Optimization of dose should be obtained through slow initial dose titration, from starting doses of 0.5mg cabergoline (de novo patients) and 1mg cabergoline (patients on L dopa) daily. The dosage of concurrent levodopa may be gradually decreased, while the dosage of cabergoline is increased, until the optimum balance is determined. In view of the long half-life of the compound, increments of the daily dose of 0.5-1mg cabergoline should be made at weekly (initial weeks) or bi-weekly intervals, up to optimal doses.

The recommended therapeutic dosage is 2 to 6mg cabergoline/day as adjuvant therapy to levodopa/carbidopa. Cabergoline should be given as a single daily dose.

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

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, to any of the excipients or to any other ergot alkaloids.
- 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.
- Anatomical evidence of cardiac valvulopathy of any valve (e.g., echocardiogram showing thickening of a valve leaflet, valvular stenosis and/or regurgitation).

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.

**Fibrosis and cardiac valvulopathy**

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 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.

**Before initiating treatment**

All patients should undergo cardiovascular evaluation, including an echocardiogram, to assess the potential presence of asymptomatic valvular disease. It may be appropriate to perform baseline investigations of ESR or other inflammatory markers, lung function/chest x-ray and renal function prior to initiation of therapy. If fibrotic valvular disease is detected, the patient should not be treated with cabergoline. (See section 4.3).

Valvulopathy was associated with cumulative doses.

**During 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 ureteric/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, as cases of pericardial fibrosis has often manifested as cardiac failure; constrictive pericarditis should be excluded if such symptoms appear.
- Cardiac failure, as cases of valvular fibrosis has often manifested as cardiac failure; valvular fibrosis should be excluded if such symptoms appear.
Clinical diagnostic monitoring for development of valvular disease or fibrosis, as appropriate, is recommended. Following treatment initiation, the first echocardiogram should 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 should 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, careful cardiac auscultation, X-ray, echocardiogram, CT scan) should be determined on an individual basis.

**Hypotension**
Symptomatic hypotension can occur within 6 hours following administration of cabergoline: particular attention should be paid when administering cabergoline concomitantly with other medical 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.

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

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 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. Furthermore a reduction of dosage or termination of therapy may be considered.

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson’s disease, including cabergoline.

**Other**
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, 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 interaction with L-Dopa or selegiline was observed in the studies carried out in parkinsonian patients.

**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 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 also 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 should only be used during pregnancy if clearly indicated.

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. 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.

Lactation

Cabergoline should not be administered to mothers who elect to breastfeed their infants since it prevents lactation. No information is available on the excretion of 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 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 and others at risk of serious injury or death, until such recurrent episodes and somnolence have resolved (see section 4.4)

4.8 Undesirable effects

Post-marketing surveillance

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 echocardiographic 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.

Pathological gambling, increased libido and hypersexuality. Patients treated with dopamine agonists for treatment of Parkinson’s disease, including cabergoline, especially at high doses, have been reported as showing pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

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.

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**Adjuvant therapy**

About 1070 parkinsonian patients have received cabergoline as adjuvant therapy to L-dopa in clinical studies; of these 74% 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.

**Nervous system disorders**

In the majority of cases (51%), events were related to the nervous system: most frequently reported events were dyskinesia, dizziness, hyperkinesia, hallucinations or confusion.

**Gastrointestinal disorders**

The gastrointestinal system was involved in 33% of cases: events most frequently reported were nausea, vomiting, dyspepsia and gastritis.

**Cardiac disorders**

The cardiovascular system was involved in 27% of cases, most frequently reported event being hypotension.

**Respiratory, thoracic and mediastinal disorders**

The respiratory system was involved in 13% of cases, symptomatic pleural effusion/fibrosis being reported with a frequency <2%.

**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: Antiparkinsonian drug, Dopamine agonist.

ATC Code: N04B C06

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

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

With regard to the endocrine effects of cabergoline not related to the antiprolactinaemic effect, available data from humans confirm the experimental findings in animals indicating that the test compound is endowed with a very selective action with no effect on basal secretion of other pituitary hormones or cortisol.

The pharmacodynamic actions of cabergoline not correlated with the therapeutic effect only relate to blood pressure decrease. The maximal hypotensive effect of cabergoline as single dose usually occurs
during the first 6 hours after active substance intake and is dose-dependent both in terms of maximal decrease and frequency.

5.2 Pharmacokinetic properties

**Absorption**
After oral administration cabergoline is rapidly absorbed from the gastrointestinal tract as the peak plasma concentration is 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 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 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 bottle with a polypropylene screw cap.

A cylindrical tube containing desiccant (silica gel) is provided in each bottle.

Each bottle contains 20, 30, 40, 60, 90 and 100 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, U.K.

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0192

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
13/03/2008

10 DATE OF REVISION OF THE TEXT
13/03/2008
1 **NAME OF THE MEDICINAL PRODUCT**
Cabergoline 2mg Tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each tablet contains 2mg cabergoline.

Excipient: lactose monohydrate 149mg.

For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**
Tablet

A white to off-white, capsule-shaped tablet, embossed with ‘CE | 2’ 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**
**Treatment of Parkinson’s disease**

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

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

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 is taken with meals for all therapeutic indications.

**Adults and elderly patients**
As expected for dopamine agonists, dose response for both efficacy and side effects appears to be linked to individual sensitivity.

Optimization of dose should be obtained through slow initial dose titration, from starting doses of 0.5mg cabergoline (de novo patients) and 1mg cabergoline (patients on L dopa) daily. The dosage of concurrent levodopa may be gradually decreased, while the dosage of cabergoline is increased, until the optimum balance is determined. In view of the long half-life of the compound, increments of the daily dose of 0.5-1mg cabergoline should be made at weekly (initial weeks) or bi-weekly intervals, up to optimal doses.

The recommended therapeutic dosage is 2 to 6mg cabergoline/day as adjuvant therapy to levodopa/carbidopa. Cabergoline should be given as a single daily dose.

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

**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, to any of the excipients or to any other ergot alkaloids.
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.
Anatomical evidence of cardiac valvulopathy of any valve (e.g., echocardiogram showing thickening of a valve leaflet, valvular stenosis and/or regurgitation).

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.

**Fibrosis and cardiac valvulopathy**
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 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.

**Before initiating treatment**
All patients should undergo cardiovascular evaluation, including an echocardiogram, to assess the potential presence of asymptomatic valvular disease. It may be appropriate to perform baseline investigations of ESR or other inflammatory markers, lung function/chest x-ray and renal function prior to initiation of therapy. If fibrotic valvular disease is detected, the patient should not be treated with cabergoline. (See section 4.3).

Valvulopathy was associated with cumulative doses.

**During 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 ureteric/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, as cases of pericardial fibrosis has often manifested as cardiac failure; constrictive pericarditis should be excluded if such symptoms appear.
• Cardiac failure, as cases of valvular fibrosis has often manifested as cardiac failure; valvular fibrosis should be excluded if such symptoms appear.

Clinical diagnostic monitoring for development of valvular disease or fibrosis, as appropriate, is recommended. Following treatment initiation, the first echocardiogram should 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 should 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, careful cardiac auscultation, X-ray, echocardiogram, CT scan) should be determined on an individual basis.

Hypotension
Symptomatic hypotension can occur within 6 hours following administration of cabergoline: particular attention should be paid when administering cabergoline concomitantly with other medical 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.

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

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 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. Furthermore a reduction of dosage or termination of therapy may be considered.

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson’s disease, including cabergoline.

Other
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, 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 interaction with L-Dopa or selegiline was observed in the studies carried out in parkinsonian patients.

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.

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

4.6 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 also 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.

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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 amenorrheic 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. 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.

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### Cardiac disorders

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### Respiratory, thoracic and mediastinal disorders

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### 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

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ATC Code: N04B C06

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

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

With regard to the endocrine effects of cabergoline not related to the antiprolactinaemic effect, available data from humans confirm the experimental findings in animals indicating that the test compound is endowed with a very selective action with no effect on basal secretion of other pituitary hormones or cortisol.
The pharmacodynamic actions of cabergoline not correlated with the therapeutic effect only relate to blood pressure decrease. The maximal hypotensive effect of cabergoline as single dose usually occurs during the first 6 hours after active substance intake and is dose-dependent both in terms of maximal decrease and frequency.

5.2 Pharmacokinetic properties

Absorption
After oral administration cabergoline is rapidly absorbed from the gastrointestinal tract as the peak plasma concentration is 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 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 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 bottle with a polypropylene screw cap.

A cylindrical tube containing desiccant (silica gel) is provided in each bottle.

Each bottle contains 20, 30, 60 and 100 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, U.K.

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0193

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
13/03/2008

10 DATE OF REVISION OF THE TEXT
13/03/2008
1 NAME OF THE MEDICINAL PRODUCT
Cabergoline 4mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 4mg cabergoline.

Excipient: lactose monohydrate 298mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet

A white to off-white, oval-shaped tablet, embossed with ‘CE | 4’ 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
Treatment of Parkinson’s disease

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

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

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 is taken with meals for all therapeutic indications.

Adults and elderly patients
As expected for dopamine agonists, dose response for both efficacy and side effects appears to be linked to individual sensitivity.

Optimization of dose should be obtained through slow initial dose titration, from starting doses of 0.5mg cabergoline (de novo patients) and 1mg cabergoline (patients on L dopa) daily. The dosage of concurrent levodopa may be gradually decreased, while the dosage of cabergoline is increased, until the optimum balance is determined. In view of the long half-life of the compound, increments of the daily dose of 0.5-1mg cabergoline should be made at weekly (initial weeks) or bi-weekly intervals, up to optimal doses.

The recommended therapeutic dosage is 2 to 6mg cabergoline/day as adjuvant therapy to levodopa/carbidopa. Cabergoline should be given as a single daily dose.

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

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, to any of the excipients or to any other ergot alkaloids.
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.
Anatomical evidence of cardiac valvulopathy of any valve (e.g., echocardiogram showing thickening of a valve leaflet, valvular stenosis and/or regurgitation).

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.

Fibrotic and cardiac valvulopathy
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 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.

Before initiating treatment
All patients should undergo cardiovascular evaluation, including an echocardiogram, to assess the potential presence of asymptomatic valvular disease. It may be appropriate to perform baseline investigations of ESR or other inflammatory markers, lung function/chest x-ray and renal function prior to initiation of therapy. If fibrotic valvular disease is detected, the patient should not be treated with cabergoline. (See section 4.3).

Valvulopathy was associated with cumulative doses.

During 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 ureteric/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, as cases of pericardial fibrosis has often manifested as cardiac failure; constrictive pericarditis should be excluded if such symptoms appear.

- Cardiac failure, as cases of valvular fibrosis has often manifested as cardiac failure; valvular fibrosis should be excluded if such symptoms appear.

Clinical diagnostic monitoring for development of valvular disease or fibrosis, as appropriate, is recommended. Following treatment initiation, the first echocardiogram should 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 should 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, careful cardiac auscultation, X-ray, echocardiogram, CT scan) should be determined on an individual basis.

**Hypotension**
Symptomatic hypotension can occur within 6 hours following administration of cabergoline: particular attention should be paid when administering cabergoline concomitantly with other medical 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.

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

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 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. Furthermore a reduction of dosage or termination of therapy may be considered.

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson’s disease, including cabergoline.

**Other**
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, 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 interaction with L-Dopa or selegiline was observed in the studies carried out in parkinsonian patients.

**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 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 also 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 should only be used during pregnancy if clearly indicated.

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 amenorrheic 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. 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.

**Lactation**

Cabergoline should not be administered to mothers who elect to breastfeed their infants since it prevents lactation. No information is available on the excretion of 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 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 and others at risk of serious injury or death, until such recurrent episodes and somnolence have resolved (see section 4.4)

4.8 Undesirable effects

**Post-marketing surveillance**

**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 echocardiographic 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.

**Pathological gambling, increased libido and hypersexuality.** Patients treated with dopamine agonists for treatment of Parkinson’s disease, including cabergoline, especially at high doses, have been reported as showing pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

**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.

<table>
<thead>
<tr>
<th>Investigations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>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)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Orthostatic hypotension (mainly evident in the first weeks of therapy)</td>
</tr>
<tr>
<td>Common</td>
<td>Angina, palpitations</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Erythromelalgia</td>
</tr>
<tr>
<td>Not known (cannot be estimated from the available data)</td>
<td>Cardiac valvulopathy (see above), pericarditis, pericardial effusion</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Dyskinesia, dizziness, hyperkinesia.</td>
</tr>
<tr>
<td>Common</td>
<td>Drowsiness, Sleep disorders/somnolence, hallucinations, confusion, depression, headache, fatigue, paresthesia</td>
</tr>
<tr>
<td>Rare</td>
<td>Sudden sleep onset episodes</td>
</tr>
<tr>
<td>Not known (cannot be estimated from the available data)</td>
<td>Pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hemianopia</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Symptomatic pleural effusion/pulmonary fibrosis/pleuritis</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Nausea</td>
</tr>
<tr>
<td>Common</td>
<td>Vomiting, dyspepsia, gastritis, constipation. Gastric upset appeared more frequent in female than in male patients.</td>
</tr>
<tr>
<td>Not known (cannot be estimated from the available data)</td>
<td>Retroperitoneal fibrosis</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Facial redness</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td></td>
</tr>
</tbody>
</table>
Rare | Cramp in fingers and calves
---|---
Vascular disorders | 
Uncommon | Nose bleeding
Rare | Fainting
General disorders and administration site conditions | 
Common | Peripheral oedema

Adjuvant therapy
About 1070 parkinsonian patients have received cabergoline as adjuvant therapy to L-dopa in clinical studies; of these 74% 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.

Nervous system disorders
In the majority of cases (51%), events were related to the nervous system: most frequently reported events were dyskinesia, dizziness, hyperkinesia, hallucinations or confusion.

Gastrointestinal disorders
The gastrointestinal system was involved in 33% of cases: events most frequently reported were nausea, vomiting, dyspepsia and gastritis.

Cardiac disorders
The cardiovascular system was involved in 27% of cases, most frequently reported event being hypotension.

Respiratory, thoracic and mediastinal disorders
The respiratory system was involved in 13% of cases, symptomatic pleural effusion/fibrosis being reported with a frequency <2%.

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: Antiparkinsonian drug, Dopamine agonist.
ATC Code: N04B C06

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

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

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during the first 6 hours after active substance intake and is dose-dependent both in terms of maximal decrease and frequency.

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

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

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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”.

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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 7mg per day.

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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
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Leucine

6.2 Incompatibilities
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6.5 Nature and contents of container
Type III amber glass bottle with a polypropylene screw cap.

A cylindrical tube containing desiccant (silica gel) is provided in each bottle.

Each bottle contains 15, 16, 20, 30, 50 and 100 tablets and is enclosed in an outer cardboard carton.

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8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0194

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
13/03/2008

10 DATE OF REVISION OF THE TEXT
13/03/2008
Module 3

Package leaflet: Information for the user
Cabergoline 0.5mg Tablets

cabergoline

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Cabergoline 0.5mg Tablets are and what they are used for
2. Before you take Cabergoline 0.5mg Tablets
3. How to take Cabergoline 0.5mg Tablets
4. Possible side effects
5. How to store Cabergoline 0.5mg Tablets
6. Further information.

1. WHAT CABERGOLINE 0.5MG TABLETS ARE AND WHAT THEY ARE USED FOR

Cabergoline belongs to a group of medicines known as prolactin inhibitors. Cabergoline prevents lactation (production of milk) by decreasing the level of a hormone known as prolactin.

Cabergoline 0.5mg Tablets are also used to reduce abnormal quantities of the hormone prolactin in the blood.

2. BEFORE YOU TAKE CABERGOLINE 0.5MG TABLETS

Do not take Cabergoline 0.5mg Tablets
- If you are allergic (hypersensitive) to cabergoline or other ergot alkaloids medicines (e.g. bromocriptine), or to any of the other ingredients of Cabergoline 0.5mg Tablets
- If you have uncontrolled high blood pressure
- If you have swelling of the hands, feet and high blood pressure during or after pregnancy (pre-eclampsia, eclampsia)
- If you have ever been treated for psychosis (lack of attention to or in the past) or if you are at risk of psychosis during pregnancy or after childbirth
- If you have ever been diagnosed in the past with problems described as thrombotic reactions affecting the lung, back of the abdomen and kidneys or heart.

Take special care with Cabergoline 0.5mg Tablets
If you have any of the following health problems you must inform your doctor before taking Cabergoline 0.5mg Tablets as the medicinal product may be unsuitable for you.
- Impaired kidney function
- Impaired liver function
- Cardiovascular disease
- Low blood pressure
- Raynaud’s syndrome (a painful condition where fingers or toes turn white, then bluish and finally red on exposure to cold or stress)
- Stomach ulcer or bleeding in the gastrointestinal tract (this can cause black faeces or vomiting with blood)

The use of cabergoline has been associated with pathological gambling, increased libido and hypersexuality.

Infertility can be reversed in women taking Cabergoline 0.5mg Tablets and pregnancy can occur before the menstrual cycle has normalized. Suitable means of contraception should therefore be used during treatment if necessary.

The safety and efficacy of Cabergoline 0.5mg Tablets has not been established in subjects less than 14 years of age.

Before you are given Cabergoline 0.5mg Tablets your doctor will arrange for you to have tests to assess the condition of your heart. Your doctor will continue to monitor your medical condition while taking Cabergoline 0.5mg Tablets.

Taking other medicines
Certain medicines used for reducing blood pressure and other medicinal products (e.g. phenothiazines, beta-blockers or diuretics) used for the treatment of psychological illness (schizophrenia or paranoia), if taken at the same time as Cabergoline 0.5mg Tablets can interfere with the effects of cabergoline. The treating doctor should therefore be aware of all medicines you may be taking.

There are other medicines such as other ergot alkaloids, medicines to stop you from feeling sick (such as metoclopramide), and macrolide antibiotics (such as erythromycin) that may affect the activity and tolerability of Cabergoline 0.5mg Tablets.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicinal products, including those obtained without a prescription and natural medical products/natural products.

Taking Cabergoline 0.5mg Tablets with food and drinks
Cabergoline 0.5mg Tablets should be taken by mouth, preferably with meals. This will decrease the risk of side effects like feeling sick.

The effect of alcohol on the tolerability of cabergoline is unknown and should be avoided while you are taking Cabergoline 0.5mg Tablets.

Pregnancy and breast-feeding
Pregnancy
There is only limited experience of the use of cabergoline during pregnancy. You should therefore consult your doctor if you are pregnant or plan to become pregnant before the treatment is started. If you are being treated with Cabergoline 0.5mg Tablets and become pregnant during this time you should discontinue the treatment and contact your doctor as soon as possible. Contraception should be continued for at least 4 weeks after stopping Cabergoline 0.5mg Tablets.

Infertility can be reversed in women taking Cabergoline 0.5mg Tablets and pregnancy can occur before the menstrual cycle has normalized. Suitable means of contraception should therefore be used during treatment if necessary.

Breast-feeding
You should not take Cabergoline 0.5mg Tablets if you wish to continue breastfeeding as it will affect lactation (milk production).

Ask your doctor for advice before taking any medicine.

Driving and using machines
Cabergoline 0.5mg Tablets can adversely affect the ability to react in some people and should therefore be considered in cases where a high level of alertness is required, e.g. driving a car and in precision work.

Cabergoline 0.5mg Tablets can cause tiredness (extreme drowsiness) and sudden sleep onset. Persons affected by this should therefore not drive or take part in activities in which reduced alertness could place them at risk of serious harm (e.g. using machines), until such recurrent episodes and tiredness have resolved. If affected, consult your doctor.

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Important information about some of the ingredients of Cabergoline 0.5mg Tablets
Cabergoline 0.5mg Tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE CABERGOLINE 0.5MG TABLETS

Always take Cabergoline 0.5mg Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The tablets should be taken with meals to reduce side effects such as nausea, vomiting and stomach pains.

Adults
The usual dose is as follows:
- To prevent lactation (production of milk): two tablets on the first day after giving birth.
- To reduce prolactin levels in other conditions: Treatment is started with one tablet once a week in one or two doses (e.g., half a tablet on a Monday and half a tablet on a Thursday). The dose may then be increased gradually as directed by your doctor up to a suitable maintenance dose. The usual maintenance dose is from 0.25 mg up to 2 mg per week.

If you take more Cabergoline 0.5mg Tablets than you should
It is important not to take too many tablets. Contact your nearest hospital Accident and Emergency department or a doctor for advice, if you have taken too many tablets or if you think a child has swallowed any. Symptoms of an overdose may include nausea, vomiting, reduced blood pressure, confusion/psychosis or hallucinations (seeing things). Take this leaflet and any tablets that you still have to show the doctor.

If you forget to take Cabergoline 0.5mg Tablets
If you forget to take a dose at the right time, you can take it as soon as you remember it. If it is almost time to take the next dose, skip the forgotten dose and take the next dose as usual.

If you stop taking Cabergoline 0.5mg Tablets
If you stop using Cabergoline 0.5mg Tablets the symptoms of your illness may become more severe and you should discuss with your doctor before you discontinue therapy. Cabergoline 0.5mg Tablets take many days to be cleared from the bloodstream and effects may worsen over a 2 week period.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cabergoline 0.5mg Tablets can cause side effects, although not everybody gets them.

Very common side effects (affecting more than one person in ten):
- Dizziness and lightheadedness on standing, involuntary/uncontrolled movements and nausea.

Common side effects (affecting less than 1 person in 10 but more than one person in 100):
- Vomiting, headaches, feeling tired or extreme tiredness, digestive disturbances, inflammation of the stomach lining (gastritis), stomach pain, constipation, redness of the skin, abnormal heart beat (palpitations), chest pain (angina), depression, hallucinations, confusion, crawling/prickling sensation in the body, swelling in the extremities of the arms and legs, coughing or pain when breathing, drop in red blood cells and changes in blood test results.

Uncommon side effects (affecting less than 1 person in 100 but more than one person in 1000):
- Partial blindness (hemianopsia), nose bleeds, redness and pain in the extremities of the arms and legs (erythromelalgia)

Rare (affecting less than one person in 1,000 but more than one person in 10,000):
- Episodes of sudden sleepiness, fainting and cramp in the fingers or calves.

Not known (cannot be estimated from the available data): A compulsive need to gamble and increase in your sexual drive.

Ergot related fibrosis has been reported. Ergot related fibrosis is an inflammatory condition of the inner lining of the body cavities possibly affecting the heart, lungs and kidneys. You should become aware of this as difficulty with breathing, chest pain, back pain, pelvic pain and swelling of the legs. Tell your doctor immediately if you experience such symptoms.

If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CABERGOLINE 0.5MG TABLETS

Keep out of the reach and sight of children.

Do not use Cabergoline 0.5mg Tablets after the expiry date which is stated on the bottle after Exp. The expiry date refers to the last day of that month.

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

Do not remove the tube containing the silica gel (desiccant) from the bottle, please refer to section 6 “Further information”.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Cabergoline 0.5mg Tablets contains
The active substance in cabergoline. Each tablet contains 0.5mg cabergoline.
- The other ingredients are lactose monohydrate and leucine.

What Cabergoline 0.5mg Tablets looks like and contents of the pack

Your medicine is in the form of a tablet. The tablets are white to off-white, capsule-shaped embossed with “C” on one side and “5” on the other side.

Cabergoline 0.5mg Tablets are packed in glass bottles with a polypropylene screw cap. Within each bottle is a tube which contains silica gel (desiccant) which helps protect your tablets against moisture.

Each bottle contains 2, 4, 8, 20, 28, 40 and 60 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Herts, SG1 4SZ, UK.

Manufacturer:

Arrow Pharma (Malta) Limited, 62 Hol For Industrial, Estate, Birzebbuga SB06, Malta

This leaflet was last approved in (MM/YYYY).
**Cabergoline 1mg, 2mg and 4mg Tablets**

**Cabergoline**

**Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet:**

1. What Cabergoline 1, 2 & 4mg Tablets are and what they are used for
2. Before you take Cabergoline 1, 2 & 4mg Tablets
3. How to take Cabergoline 1, 2 & 4mg Tablets
4. Possible side effects
5. How to store Cabergoline 1, 2 & 4mg Tablets
6. Further information.

**1. WHAT CABERGOLINE 1, 2 & 4MG TABLETS ARE AND WHAT THEY ARE USED FOR**

Cabergoline is one of a group of medicines known as dopamine agonists. Cabergoline acts in the same way as a chemical present in the nervous system called dopamine. Patients with Parkinson's disease do not have enough dopamine in their body. Cabergoline 1mg, 2mg and 4mg Tablets can be used either taken alone or in combination with levodopa, as second choice following non-ergot derived therapies. Treatment under a specialist is required.

**2. BEFORE YOU TAKE CABERGOLINE 1, 2 & 4MG TABLETS**

Do not take Cabergoline 1, 2 & 4mg Tablets if you:

- are allergic hypersensitive to cabergoline or other ergot alkaloid medicines (e.g. bromocriptine) or any of the other ingredients of Cabergoline 1, 2 & 4mg Tablets.
- have swelling of the hands, feet and high blood pressure during pregnancy (pre-eclampsia, eclampsia).
- have uncontrolled high blood pressure.
- have ever been diagnosed in the past with problems described as fibrotic reactions affecting the lungs, back of the abdomen and kidneys or heart.

Before you are given Cabergoline 1, 2 & 4mg Tablets your doctor will arrange for you to have tests to assess the condition of your heart. Your doctor will continue to monitor your medical condition while taking Cabergoline 1, 2 & 4mg Tablets.

**Take special care with Cabergoline 1, 2 & 4 mg Tablets**

If you have any of the following health problems you must inform your doctor before taking Cabergoline 1, 2 & 4mg Tablets as this medicinal product may be unsuitable for you:

- cardiovascular disease
- stomach ulcer or bleeding in the gastrointestinal tract (this can cause black faeces or vomiting with blood)
- impaired kidney function
- impaired liver function
- psychosis (currently or in the past) or if you are at risk of psychosis after childbirth
- Raynaud's syndrome (a painful condition where fingers or toes turn white, then bluish and finally red on exposure to cold or stress)
- low blood pressure
- serious chest complaints (currently or in the past) (such as difficulty in breathing).

The use of cabergoline has been associated with pathological gambling, increased libido and hyposexuality.

Infertility can be reversed in women taking Cabergoline 1, 2 & 4mg Tablets, and pregnancy can occur before the menstrual cycle has normalised. Suitable means of contraception should therefore be used during treatment if necessary.

**The safety and efficacy of Cabergoline 1, 2 & 4mg Tablets have not been established in subjects less than 16 years of age.**

**Taking other medicines**

Certain medicines used for reducing blood pressure and certain medicinal products (e.g. phenothiazines, sympathomimetics, tricyclics) used for the treatment of psychological illnesses (schizophrenia or psychosis), if taken at the same time as Cabergoline 1, 2 & 4mg Tablets can interfere with the effects of your tablets. The treating doctor should therefore be aware of all medicines you may be taking.

There are other medicines such as other ergot alkaloids, medicines to prevent vomiting (metoclopramide), medicines for reducing high blood pressure, and macrolide antibiotics (such as erythromycin) that may affect the activity and tolerability of Cabergoline 1, 2 & 4mg Tablets.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicinal products, including those obtained without a prescription and natural medical products/natural products.

**Taking Cabergoline 1, 2 & 4mg Tablets with food and drink**

Cabergoline 1, 2 & 4mg Tablets should be taken by mouth, preferably with meals.

The effect of alcohol on the tolerability of cabergoline is unknown and should be avoided while you are taking Cabergoline 1, 2 & 4mg Tablets.

**Pregnancy and breast-feeding**

**Pregnancy**

There is only limited experience of the use of cabergoline during pregnancy. You should therefore consult your doctor if you are pregnant or plan to become pregnant before the treatment is started. If you are being treated with Cabergoline 1, 2 & 4mg Tablets and become pregnant during this time you should discontinue the treatment and contact your doctor as soon as possible. Contraception should be continued for at least 4 weeks after stopping Cabergoline 1, 2 & 4mg Tablets.

**Breast-feeding**

It is not known whether cabergoline passes into breast milk. Cabergoline 1, 2 & 4mg Tablets should not be taken by mothers who intend to breast feed as it prevents lactation.

**Driving and using machines**

Cabergoline 1, 2 & 4mg Tablets can adversely affect the ability to react in some people and this should be considered in cases where a high level of alertness is required, e.g. driving a car and in precision work. Cabergoline 1, 2 & 4mg Tablets can cause somnolence (extreme drowsiness) and sudden sleep onset. Persons affected by this should therefore not drive or take part in activities in which reduced alertness could incur a risk of serious harm (e.g. using machines), until such recurrent episodes and somnolence have resolved. If affected, consult your doctor.
Important information about some of the ingredients of Cabergoline 1, 2 & 4mg Tablets

Cabergoline 1mg, 2mg and 4mg Tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3 HOW TO TAKE CABERGOLINE 1, 2 & 4MG TABLETS

Always take Cabergoline 1, 2 & 4mg Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The tablets should be taken with meals to reduce certain side effects such as nausea, vomiting and stomach pains.

Adults and elderly patients: The dose is determined by your doctor who will adjust it individually for you. The usual dose at the start of treatment is 0.5 - 1mg cabergoline daily. The dose is then increased gradually as directed by the doctor up to a suitable maintenance dose. The usual maintenance dose is from 2mg up to 8mg cabergoline daily.

If you take more Cabergoline 1, 2 & 4mg Tablets than you should
It is important not to take too many tablets. Contact your nearest hospital Accident and Emergency department or a doctor for advice, if you have taken too many tablets or if you think a child has swallowed any. Symptoms of overdose may include nausea, vomiting, reduced blood pressure, stomach pain, changes in behaviour, confusion or hallucinations (seeing things). Take this leaflet and any tablets that you still have to show the doctor.

If you forget to take Cabergoline 1, 2 & 4mg Tablets
If you forget to take a dose at the right time, you can take it as soon as you remember it. If it is almost time to take the next dose, skip the forgotten dose and take the next dose as usual.

If you stop taking Cabergoline 1, 2 & 4mg Tablets
If you stop using Cabergoline 1, 2 & 4mg Tablets the symptoms of your illness may become more severe and you should discuss with your doctor before you discontinue therapy. Cabergoline 1, 2 & 4mg Tablets may take many days to be cleared from the bloodstream and effects may worsen over a 2 week period resulting in worsening of symptoms of Parkinson's disease.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 POSSIBLE SIDE EFFECTS

Like all medicines, Cabergoline 1, 2 & 4mg Tablets can cause side effects, although not everybody gets them. Very common side effects (affecting more than one person in ten): Dizziness and lightheadedness on standing, involuntary/uncontrolled movements and nausea.

Common side effects (affecting less than 1 person in 10 but more than 1 person in 100): Vomiting, headache, feeling tired or extreme drowsiness, digestive disturbances, inflammation of the stomach lining (gastritis), stomach pain, constipation, redness of the skin, abnormal heart beat (palpitations), chest pain (angina), depression, hallucinations, confusion, crawling/prickling sensation in the body, swelling in the extremities of the arms and legs, coughing or pain when breathing, drop in red blood cells and changes in blood test results.

Uncommon side effects (affecting less than 1 person in 100 but more than 1 person in 1000): Partial blindness (hemianopia), nose bleeds, redness, and pain in the extremities of the arms and legs (erythromelalgia)

Rare (affecting less than one person in 1,000 but more than one person in 10,000): Episodes of sudden sleepiness, fainting and cramp in the fingers or calves.

Not known (cannot be estimated from the available data): A compulsive need to gamble and increase in your sexual drive.

Ergot related fibrosis has been reported. Ergot related fibrosis is an inflammatory condition of the inner lining of the body cavities possibly affecting the heart, lungs and kidneys. You should become aware of this as difficulty with breathing, chest pain, back pain, pelvic pain and swelling of the legs. Tell your doctor immediately if you experience such symptoms. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5 HOW TO STORE CABERGOLINE 1, 2 & 4MG TABLETS

Keep out of the reach and sight of children.

Do not use Cabergoline 1, 2 & 4mg Tablets after the expiry date which is stated on the bottle after Exp. The expiry date refers to the last day of that month.

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

Do not remove the tube containing the silica gel (desiccant) from the bottle. Please refer to section 6 “Further information”.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER INFORMATION

- The active substance is cabergoline. Each tablet contains 1mg, 2mg or 4mg cabergoline.
- The other ingredients are lactose monohydrate and leucine.

What Cabergoline 1, 2 & 4mg Tablets look like and contents of the pack

Cabergoline 1mg Tablets: A white to off-white, oval-shaped tablet, embossed with “C | 1” on one side and “partial score >” on the other side.

Cabergoline 2mg Tablets: A white to off-white, capsule-shaped tablet, embossed with “C | 2” on one side and “partial score >” on the other side.

Cabergoline 4mg Tablets: A white to off-white, oval-shaped tablet, embossed with “C | 4” on one side and “partial score >” on the other side.

Cabergoline Tablets are packed in glass bottles with a polypropylene screw cap. Within each bottle is a tube which contains silica gel (desiccant) which helps protect your tablets against moisture.

Each bottle of the 1mg strength contains 20, 30, 40, 60, 90 and 100 tablets, each bottle of the 2mg strength contains 20, 30, 60 and 100 tablets and each bottle of the 4mg strength contains 15, 16, 20, 30, 50 and 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder: Arrow Genomics Limited, Unit 2, Eastman Way, Stevenage, Herts SG1 4S2

Manufacturer: Arrow Pharma (Malta) Limited, 82 Hal Fatt Industrial Estate, Birebbuga B8506, Malta

This leaflet was last approved in (MM/YYYY).
Module 4

Labelling
For oral use. These tablets also contain lactose. Read the package leaflet before use. Do not store above 25°C. Store in the original package to protect from moisture. Keep out of the reach and sight of children.

Marketing Authorisation Holder: Arrow Genetics Ltd, Unit 2, Eastman Way, Stevenage, Herts, SG1 4SZ, U.K. PL 18909/0191

8 Tablets

Each tablet contains 0.5mg of cabergoline.
For oral use. These tablets also contain lactose. Read the package leaflet before use.

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

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Braille text reads as follows in English:
cabergoline
1 mg
tablets
PAR Cabergoline 0.5, 1, 2, and 4mg UK/H/955/1-4/DC

Cabergoline Tablets

Braile text reads as follows in English:
cabergoline
# 2 mg tablets

For oral use. These tablets also contain lactose. Read the package leaflet before use. Do not store above 25°C. Store in the original package to protect from moisture. Keep out of the reach and sight of children.

Marketing Authorisation Holder: Arrow Generics Ltd, Unit 2, Eastman Way, Stevenage, Herts, SG1 4SZ, U.K. PL 18906/0193

POM

Each tablet contains 2mg of cabergoline.
For oral use. These tablets also contain lactose. Read the package leaflet before use. Do not store above 25°C. Store in the original package to protect from moisture. Keep out of the reach and sight of children.

Marketing Authorisation Holder:
Arrow Generics Ltd, Unit 2, Eastman Way, Stevenage, Herts, SG1 4SZ, U.K. PL 189/09/0194

Cabergoline 4mg Tablets

cabergoline

16 Tablets

POM

Each tablet contains 4mg of cabergoline.
Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Cabergoline 0.5mg, 1mg, 2mg & 4mg Tablets, for the indications outlined in section 4.2 of the respective SPCs, could be approvable and Marketing Authorisations have been granted.

These are decentralised complex and standard abridged applications for Cabergoline 0.5mg, 1mg, 2mg and 4mg tablets.

Cabergoline 0.5mg tablets are a generic medicinal product of Dostinex 0.5mg tablets, marketed by Pfizer and authorised on 13 March 1992 in Sweden, which contains the same amount of active substance in the same pharmaceutical form.

Cabergoline 1mg, 2mg and 4mg tablets are generic medicinal product of Cabaser 1mg, 2mg and 4mg tablets (PL 00022/0169-171), respectively, authorised on 14 Feb 1996 and marketed by Pfizer, which contains the same amount of active substance in the same pharmaceutical form.

For UK/H/955/01-04/DC, the UK is the RMS and the following are CMS: BE, CZ, DE, DK, FI, IE, IT, MT, NL, NO, PL.

The submitted dossier was of acceptable standards.

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Cabergoline 0.5mg, 1mg, 2mg &amp; 4mg tablets</th>
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<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Cabergoline</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
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<td></td>
<td>N04B C06 – 1mg, 2mg &amp; 4mg</td>
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<td>Marketing Authorisation Number(s)</td>
<td>PL 18909/0191-4</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Arrow Generics Ltd, Unit 2, Eastman Way, Stevenage, Hertfordshire, UK</td>
</tr>
</tbody>
</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

Drug Substance

INN: Cabergoline

Chemical name: 1-\{(6-Allylgoline-8β-yl)carbonyl\}-1-[3-(dimethylamino)propyl]-3-ethylurea.

Ph Eur: 1-Ethyl-3-[3-(dimethylamino)propyl]-3-[[6aR,9R,10aR]-7-(prop-2-enyl)-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl]carbonyl]urea.

Molecular Weight: 451.62

Molecular Formula: C_{26}H_{37}N_{5}O_{2}

CAS No: 81409-90-7

Cabergoline is odourless white or almost white, crystalline powder. Practically insoluble in water, freely soluble in alcohol, very slightly soluble in hexane and 0.1M HCl.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

A valid Certificate of Suitability has been provided.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active cabergoline is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.
Batch analysis data are provided and comply with the proposed specification.

Acceptable justification of the proposed specifications are provided.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

The drug substance manufacturer commits to continuing long term stability studies and to stability test the first three commercial scale batches. This is acceptable.

**DRUG PRODUCT**

**Other ingredients**
Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate and leucine. All excipients used comply with their respective European Pharmacopoeia monograph.

Satisfactory specifications and Certificates of Analysis have been provided for all excipients. No materials of animal or human origin are contained in or used in the manufacture of this product. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

**Pharmaceutical development**
The applicant has provided a suitable product development rationale and data. Comparable dissolution and impurity profiles have been provided for batches of the proposed product versus reference product.

**Manufacture**
A description and flow-chart of the manufacturing method have been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches. The results are satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**
The product is packaged in Type III amber glass bottles with a polypropylene screw cap. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with storage conditions of “Do not store above 25 degree C”, “Protect from moisture” and “Store in the original package” are proposed. These are satisfactory.
SPC, PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

Specific non-clinical studies have not been performed, which is acceptable for these applications for generic products. The non-clinical overview provides a reasonable review of the known pharmacological and toxicological properties of cabergoline.
1. **INTRODUCTION**

These are decentralised complex and standard abridged applications for Cabergoline 0.5mg, 1mg, 2mg and 4mg tablets.

For Cabergoline 0.5mg tablets, the applicant claims essential similarity, under article 10(1), to Dostinex 0.5mg tablets, marketed by Pfizer and authorised on 13 March 1992 in Sweden, which contains the same amount of active substance in the same pharmaceutical form.

Cabergoline 1mg, 2mg and 4mg tablets are generic medicinal product of Cabaser 1mg, 2mg and 4mg tablets (PL 00022/0169-171), respectively, authorised on 14 February 1996 and marketed by Pfizer, which contains the same amount of active substance in the same pharmaceutical form.

For UK/H/955/01-04/DC, the UK is the RMS and the following are CMS: BE, CZ, DE, DK, FI, IE, IT, MT, NL, NO, PL

2. **BACKGROUND**

Cabergoline is a dopamine receptor agonist, derived from ergoline with potent, long-lasting prolactin-lowering activity and a high affinity for the D2 receptor. It is used in the treatment of Parkinson’s Disease and at a lower dose as a prolactin inhibitor to stop lactation. An elimination half-life of approximately 65 hours allows steady dopaminergic stimulation with once daily oral administration.

3. **INDICATIONS**

The applicant has submitted the following:

- Inhibition of lactation for medical reasons.
- Hyperprolactinaemic disorders.
- Prolactin secreting pituitary adenomas.
- Idiopathic hyperprolactinaemia.

**Treatment of Parkinson’s disease**

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

4. **DOSE & DOSE SCHEDULE**

The proposed posology is in line with currently agreed requirements and is therefore satisfactory.

5. **TOXICOLOGY**

No formal data are presented under this heading and none are required for this application.
6. **CLINICAL PHARMACOLOGY**

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.

Two comparative bioequivalence studies were carried out and the test and reference products shown to be bioequivalent (within the customary 90% confidence intervals) for the appropriate pharmacokinetic criteria.

**Biostudy 1**

A randomised, open-label, 2-way crossover, single dose, bioequivalence study of Arrow Cabergoline 0.5mg tablets (test) and Dostinex 0.5mg tablets (reference) in healthy non-smoking male and female volunteers under fed conditions.

<table>
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<tr>
<th></th>
<th>Arrow Cabergoline 0.5 mg</th>
<th>Dostinex 0.5 mg (Pharmacia)</th>
<th>Test/Ref Ratio</th>
<th>Test/Ref (90% CI)</th>
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<tr>
<td>AUC0-t (pg/ml h)</td>
<td>978.55 +/- 463.14</td>
<td>963.59 +/- 430.57</td>
<td>101.37%</td>
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<td>Cmax (pg/ml)</td>
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<td>T1/2 (h)</td>
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<td>94.63 +/- 27.49</td>
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<td>10.03 +/- 4.70</td>
<td></td>
<td></td>
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<tr>
<td>Kel (h)</td>
<td>0.0079 +/- 0.0026</td>
<td>0.0082 +/- 0.0033</td>
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</table>

**Biostudy 2**

A randomised, open-label, 2-way crossover, single dose, bioequivalence study of Arrow Cabergoline 1 mg tablets (test) and Carbaser 1 mg tablets (reference) in healthy non-smoking male and female volunteers under fed conditions.

<table>
<thead>
<tr>
<th></th>
<th>Arrow Cabergoline 1 mg</th>
<th>Carbaser 1 mg (Pharmacia)</th>
<th>Test/Ref Ratio</th>
<th>Test/Ref (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t (pg/ml h)</td>
<td>2170.51 +/- 986.88</td>
<td>1966.54 +/- 772.83</td>
<td>101.15%</td>
<td>83.92% to 121.92%</td>
</tr>
<tr>
<td>AUC0-inf (pg/ml h)</td>
<td>2515.15 +/- 1106.31</td>
<td>2234.76 +/- 969.07</td>
<td>111.89%</td>
<td>105.33% to 118.86%</td>
</tr>
<tr>
<td>Cmax (pg/ml)</td>
<td>36.61 +/- 15.26</td>
<td>32.38 +/- 10.83</td>
<td>110.44%</td>
<td>100.73% to 121.09%</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.89 +/- 0.89</td>
<td>1.63 +/- 0.79</td>
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<tr>
<td>T1/2 (h)</td>
<td>108.44 +/- 21.21</td>
<td>112.49 +/- 24.10</td>
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<tr>
<td>Residual area</td>
<td>10.49 +/- 6.25</td>
<td>10.70 +/- 4.52</td>
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<tr>
<td>Kel (h)</td>
<td>0.0066 +/- 0.0013</td>
<td>0.0065 +/- 0.0014</td>
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</tbody>
</table>

**Conclusions from both studies:** The design of the studies and the use of the fed state are considered appropriate. The 1 mg strength was selected for study in the volunteers because of the potential for side effects at greater doses.

The test products were accepted as bioequivalent in terms of rate and extent of absorption to the reference products [90% confidence intervals of the geometric mean ratio for AUC0-t, AUC0-inf and Cmax were within 80 and 125%].
Since cabergoline possesses linear pharmacokinetics over the range 0.5-7 mg and there is similarity quantitatively and qualitatively of the three formulations (1, 2 and 4 mg tablets), it may be inferred that the proposed 2mg and 4mg cabergoline tablets would also be bioequivalent to their originator counterparts.

7. **EFFICACY**
   No new data are submitted and none are required for these applications. The efficacy of cabergoline has been well documented.

8. **SAFETY**
   No new data are submitted and none are required for these applications.

9. **EXPERT REPORTS**
   A satisfactory clinical expert report has been submitted, which has been written by an appropriately qualified medical practitioner.

10. **SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**
    The summary of Product Characteristics are satisfactory.

11. **PATIENT INFORMATION LEAFLET (PIL)**
    The patient information leaflet is satisfactory.

12. **LABELLING**
    The labels are satisfactory

13. **APPLICATION FORM (MAA)**
    The MAAs are satisfactory

14. **CONCLUSION**
    The applicant compared Cabergoline 0.5mg tablets to Dostinex 0.5mg tablets and Cabergoline 1mg tablets to Carbaser 1mg tablets these products were shown to be bioequivalent. It is recommended that Marketing Authorisations should be granted for these applications.

    No new or unexpected safety concerns arise from these applications.

    The SPC, PIL and packaging are satisfactory and consistent with those for the reference product.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The important quality characteristics of Cabergoline 0.5mg, 1mg, 2mg, and 4mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

No new preclinical data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s product and the reference products.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator products.

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and the originator product are interchangeable. Extensive clinical experience with cabergoline is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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