IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1130/010/003
Case No: 2044852

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Arrow Generics Limited

Unit 2, Eastman Way, **Stevenage**, **Hertfordshire**, **SG1 4SZ**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Caberex 4mg Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **10/06/2008** until **07/02/2013**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Caberex 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.

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 a 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 echocardiogaphic marker for restrictive valvulopathy), the prevalence of regurgitation (virtually all cases asymptomatic) potentially attributable to cabergoline may be in the range of 20% or greater. There is limited information available on the reversibility of these reactions.

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

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.

Investigations Common	A fall in haemoglobin and haematocrit values, fall in the erythrocyte count, increases of triglycerides greater than 30% above the upper limit of the laboratory reference range (mostly transient)
Cardiac disorders Very common	Orthostatic hypotension (mainly evident in the first weeks of therapy)
Common	Angina, palpitations
Uncommon	Erythromelalgia

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

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 15, 16, 20, 30, 50, 60 (3 x 20), 100 and 100 (5 x 20) 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

PA1130/010/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8th February 2008

10 DATE OF REVISION OF THE TEXT

June 2008