

IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0436/044/002

Case No: 2078465

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

Norton Waterford

T/A IVAX Pharmaceuticals Ireland, Unit 301, IDA Industrial Park, Cork Road, Waterford, Ireland

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

Eflavex, 2 Milligram

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 **09/02/2010**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Eflavex 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg cabergoline.

Excipient: lactose 150.6 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

The tablet can be divided into equal halves.

White, capsule-shaped, biconvex tablets with scores on both sides. One side is debossed with 'CBG' and '2' on either side of the score.

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 sections 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 undesirable 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 1 mg 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 0.5-1 mg cabergoline should be done at weekly (initial weeks) or bi-weekly intervals, up to optimal doses.

The recommended therapeutic dosage is 2 to 3 mg cabergoline /day as adjuvant therapy to levodopa/carbidopa. The maximum dose of 3 mg/day of cabergoline must not be exceeded. 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.

Use in patients with hepatic or renal dysfunction

For patients with severe hepatic dysfunction or end stage renal failure see section 4.3 and 4.4.

4.3 Contraindications

Pre-eclampsia, eclampsia

Post-partum hypertension or uncontrolled hypertension.

Hypersensitivity to cabergoline, other ergot alkaloids or to any of the excipients.

Severe impairment of liver function.

History of adverse pulmonary reactions, such as pleuritis and fibrosis, associated with use of dopamine agonists

History of pericardial and retroperitoneal fibrotic disorders.

History of psychosis or risk of post-partum psychosis

For long term treatment, evidence of cardiac valvulopathy of any valve as determined by pre-treatment echocardiography

4.4 Special warnings and precautions for use

General

The assessment of safety and efficacy of cabergoline is limited in patients with renal and hepatic disease. As with other ergot 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 overall tolerability of cabergoline are currently unknown.

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.

Fibrosis and Cardiac Valvulopathy and possibly related clinical phenomena:

Fibrotic and serosal inflammatory disorders such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy involving one or more valves (aortic, mitral and tricuspid) or retroperitoneal fibrosis have occurred after prolonged usage of ergot derivatives with agonist activity at the serotonin 5HT_{2B} receptor, such as cabergoline. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of cabergoline. Erythrocyte sedimentation rate (ESR) has been found to be abnormally increased in association with pleural effusion/fibrosis. Chest x-ray examination is recommended in cases of unexplained ESR increases to abnormal values.

Serum creatine measurements can also be used to help in the diagnosis of fibrotic disorder.

Valvulopathy has been associated with cumulative doses, therefore, patients should be treated with the lowest effective dose. At each visit, the risk benefit profile of cabergoline treatment for the patient should be reassessed to determine the suitability of continued treatment with cabergoline.

Before initiating long term treatment:

All patients should undergo a cardiovascular evaluation, including echocardiogram, to assess the potential presence of asymptomatic valvular disease. It is also appropriate to perform baseline investigations of erythrocyte sedimentation rate or other inflammatory markers, lung function/chest x-ray and renal function prior to initiation of therapy. In patients with valvular regurgitation, it is not known whether cabergoline treatment might worsen the underlying disease. If fibrotic valvular disease is detected, the patient should not be treated with cabergoline. (See Section 4.3).

During long term treatment:

Fibrotic disorders can have an insidious onset and patients should be regularly monitored for possible manifestations of progressive fibrosis. Therefore during treatment, attention should be paid to the signs and symptoms of:

- Pleuropulmonary disease, such as dyspnoea, shortness of breath, persistent cough, or chest pain.
- Renal insufficiency or ureteral/abdominal vascular obstruction that may occur with pain in the loin/flank, and lower limb oedema, as well as any possible abdominal masses or tenderness that may indicate retroperitoneal fibrosis.
- Cardiac failure cases of valvular and pericardial fibrosis have often manifested as cardiac failure. Therefore, valvular fibrosis (and constrictive pericarditis) should be excluded if such symptoms occur.

Clinical diagnostic monitoring for development of fibrotic disease, as appropriate, is essential. Following treatment initiation, the first echocardiogram must occur within 3-6 months, thereafter, the frequency of echocardiographic monitoring should be determined by appropriate individual clinical assessment with particular emphasis on the above-mentioned signs and symptoms, but must occur at 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 including cardiac auscultation, X-ray, CT scan) should be determined on an individual basis.

Additional appropriate investigations such as erythrocyte sedimentation rate, and serum creatinine measurements should be performed if necessary to support a diagnosis of fibrotic disorder.

Hypotension:

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

Renal Insufficiency: 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: 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 daily dose should be limited to no more than 1 mg.

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

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.

Precautions

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

No pharmacokinetic interactions with L-dopa or selegiline have been observed in studies of patients with Parkinson's disease. Pharmacokinetic interactions with other medicinal products cannot be predicted based on available information about the metabolism of cabergoline.

4.6 Pregnancy and lactation

Pregnancy

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

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 is 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.

Lactation 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 or others at risk of serious injury or death, until such recurrent episodes and somnolence have resolved (see section 4.4).

4.8 Undesirable effects

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%.

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 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.

Other adverse events expected for the pharmacological class, in view of the vasoconstrictive properties, include angina (reported in about 1% of the patients on cabergoline) and erythromelalgia (observed in 0.4% of the patients). Similarly expected for the pharmacological class, peripheral oedema occurred in 6% of patients.

Gastric upset was more frequent in female than in male patients, while CNS events were more frequent in the elderly.

A blood pressure decrease of clinical relevance was observed mainly on standing in a minority of patients. The effect was mainly evident in the first weeks of therapy. Neither modification of heart rate nor consistent changes of ECG tracing were observed during cabergoline treatment.

Alterations in standard laboratory tests are uncommon during long term therapy with cabergoline. In clinical studies, increases of triglycerides greater than 30% above the upper limit of the laboratory reference range were observed in 6.8% of the cabergoline-treated patients who had values within the normal range at baseline. In most cases the increases were transient. No clear indications of increases over time or significant shifts from normal to abnormal values were observed in the overall group of patients treated with cabergoline. A clinically relevant decrease in haemoglobin, haematocrit and/or red blood cell count (>15% Vs baseline) was observed at least once in 6.8% of clinical study patients with normal values at entry; normalization was observed in one third of these patients.

Cardiac disorders Very common ($\geq 1/10$) Common ($\geq 1/100$ to $< 1/10$) Uncommon ($\geq 1/1000$ to $< 1/100$)	Orthostatic hypotension Cardiac valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion) Angina Erythromelalgia
Blood and lymphatic system disorders Common ($\geq 1/100$ to $< 1/10$)	A fall in haemoglobin and haematocrit values, fall in the erythrocyte count
Nervous system disorders Very common ($\geq 1/10$) Common ($\geq 1/100$ to $< 1/10$) Rare ($\geq 1/10,000$ to $< 1/1000$)	Dyskinesia, dizziness, hyperkinesia. Drowsiness, Sleep disorders, hallucinations, confusion Episodes where the patient suddenly falls asleep
Respiratory, thoracic and mediastinal disorders Common ($\geq 1/100$ to $< 1/10$)	Symptomatic pleural exudate/pulmonary fibrosis
Gastrointestinal disorders Very common ($\geq 1/10$) Common ($\geq 1/100$ to $< 1/10$)	Nausea Vomiting, dyspepsia, gastritis, constipation.

General disorders and administration site conditions Common ($\geq 1/100$ to $< 1/10$)	Peripheral oedemas
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Post-marketing Surveillance:

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

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 events have been reported in association with cabergoline:

Hallucinations

Other:

Adverse events have been reported with lower doses of cabergoline (0.25 – 2 mg per week) that are not listed above including:

Cardiac disorders Common ($\geq 1/100$ to $< 1/10$)	Palpitations
Nervous system disorders Common ($\geq 1/100$ to $< 1/10$)	Depression, headache, fatigue, paresthesia, somnolence.
Eye disorders Uncommon ($\geq 1/1000$ to $< 1/100$)	Hemianopsia
Gastrointestinal disorders Common ($\geq 1/100$ to $< 1/10$)	Constipation
Skin and subcutaneous tissue disorders Common ($\geq 1/100$ to $< 1/10$)	Facial redness
Musculoskeletal and connective tissue disorders Rare ($\geq 1/10000$ to $< 1/1000$)	Cramp in fingers and calves
Vascular disorders Uncommon ($\geq 1/1000$ to $< 1/100$) Rare ($\geq 1/10000$ to $< 1/1000$)	Nose bleeding Fainting

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: Dopamine agonist

ATC code: N04BC06

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 at an average dose of 4 mg/day following titration (up to 5-6 mg 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 received within 0.5 to 4 hours.

Food does not appear to affect absorption and disposition of cabergoline.

Distribution

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

Biotransformation

In urine, the main metabolite identified is 6-allyl-8β-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 7 mg per day.

5.3 Preclinical safety data

Almost all the findings noted throughout the series of preclinical safety studies are a consequence of the central dopaminergic effects or the long-lasting inhibition of PRL in species (rodents) with a specific hormonal physiology different to man.

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**

Anhydrous lactose
L-Leucine
Magnesium stearate (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. The drying capsule or bag with silica gel must not be removed from the bottle.

6.5 Nature and contents of container

Brown glass bottles (type III) that contain a desiccation capsule or bag with silica gel. The brown glass bottle has an induction-sealed childproof aluminium membrane and a childproof HDPE or Polypropylene top. External box.

Packaging sizes: 2, 8, 14, 15, 16, 20, 28, 30, 32, 40, 48, 50, 60, 90, 96, 100.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Norton Waterford
trading as IVAX Pharmaceuticals Ireland
Unit 301
IDA Industrial Park
Cork Road
Waterford
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 436/44/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 February 2008

Date of last renewal: 7 May 2009

10 DATE OF REVISION OF THE TEXT

January 2010