IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0436/044/003
Case No: 2036252

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

Norton Waterford Limited

T/A IVAX Pharmaceuticals Ireland, **IDA Industrial Park**, **Waterford**, **Ireland**

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

Eflavex 4 mg 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 **09/07/2008** until **28/02/2013**.

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

Eflavex 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4 mg cabergoline.

Excipient: lactose 301.2 mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

The tablet can be divided into equal halves.

White, oval, biconvex tablets with scores on both sides. One side is debossed with ‘CBG’ and ‘4’ 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, eflavex 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

Eflavex is to be administered by the oral route. In order to reduce the risk of gastrointestinal undesirable effects it is recommended that eflavex 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 eflavex (de novo patients) and 1 mg eflavex (patients on L dopa) daily. The dosage of concurrent levodopa may be gradually decreased, while the dosage of eflavex 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 eflavex should be done at weekly (initial weeks) or bi-weekly intervals, up to optimal doses.
The recommended therapeutic dosage is 2 to 6 mg eflavex /day as adjuvant therapy to levodopa/carbidopa. Eflavex should be given as a single daily dose.

Use in children and adolescents:
The safety and efficacy of eflavex 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

Hypersensitivity to eflavex, other ergot alkaloids or to any of the excipients.
Pre-eclampsia, eclampsia
Uncontrolled hypertension.
History of pulmonary, pericardial and retroperitoneal fibrotic disorders.
Anatomical evidence of cardiac valvulopathy of any valve (e.g., echocardiogram showing valve leaflet thickening, valve restriction, valve mixed restriction-stenosis).

4.4 Special warnings and precautions for use

General

The assessment of safety and efficacy of eflavex is limited in patients with renal and hepatic disease. As with other ergot alkaloids, eflavex 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 eflavex are currently unknown.

Eflavex 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

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 eflavex. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of eflavex.
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.

Before initiating treatment:
All patients should undergo a cardiovascular evaluation, including 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 eflavex. (See Section 4.3).

Valvulopathy was associated with cumulative doses.

<u>During treatment:</u>
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, as cases of pericardial fibrosis have often manifested as cardiac failure; constrictive pericarditis should be excluded if such symptoms appear.

• Cardiac failure, as cases of valvular fibrosis have 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.

Eflavex 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 eflavex: particular attention should be paid when administering eflavex 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: Eflavex 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 eflavex. 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 eflavex were observed in moderate to severe renal disease. The pharmacokinetics of eflavex 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: Eflavex 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 eflavex.

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 eflavex’s plasma levels when administered simultaneously have not been studied. The combination should be avoided, as it may result in elevated eflavex plasma levels.

Eflavex 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 eflavex and other ergot alkaloids. Therefore, long-term treatment with eflavex 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 eflavex.

4.6 Pregnancy and lactation

Pregnancy

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

Eflavex 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 eflavex 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 eflavex in pregnancy, eflavex should be withdrawn before a planned pregnancy. If the patient becomes pregnant during treatment, eflavex shall be immediately withdrawn. During pregnancy, these patients must be carefully monitored for any pregnancy-induced pituitary enlargement.

Eflavex should only be used during pregnancy if clearly indicated.

Eflavex 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 eflavex withdrawal. Because of limited experience on the safety of foetal exposure to eflavex, it is advisable that women seeking pregnancy conceive at least one month after eflavex discontinuation given that ovulatory cycles persist in some patients for 6 months after withdrawal. Should pregnancy occur during treatment, eflavex 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 eflavex.

Lactation
Eflavex 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 eflavex and/or its metabolites are excreted in the milk.

Lactation should be avoided when taking eflavex.

4.7 Effects on ability to drive and use machines

Eflavex 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 eflavex 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 eflavex 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 eflavex (see 'Special warnings and special precautions for use'). The incidence of valvulopathy with eflavex 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 eflavex 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 eflavex) 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 eflavex treatment.
Alterations in standard laboratory tests are uncommon during long term therapy with eflavex. 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 eflavex-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 eflavex. 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.

Disorders in the central and peripheral nervous system Very common (≥ 1/10) Common (≥ 1/100 and < 1/10) Rare (≥ 1/10,000 and < 1/1000)	Dyskinesia, dizziness, hyperkinesia. Drowsiness, Sleep disorders, hallucinations, confusion Episodes where the patient suddenly falls asleep
Cardiac disorders Very common (≥ 1/10) Common (≥ 1/100 and < 1/10) Uncommon (≥ 1/1000 and <1/100)	Orthostatic hypotension Angina Erythromelalgia
Disorders of the respiratory tract, thorax and mediastinum Common (≥ 1/100 and < 1/10)	Symptomatic pleural exudate/pulmonary fibrosis
Gastrointestinal disorders Very common (≥ 1/10) Common (≥ 1/100 and < 1/10)	Nausea Vomiting, dyspepsia, gastritis, constipation.
General symptoms and disorders at the site of application Common (≥ 1/100 and < 1/10)	Peripheral oedemas
Examinations Common (≥ 1/100 and < 1/10)	A fall in haemoglobin and haematocrit values, fall in the erythrocyte count

Post-marketing Surveillance:
Eflavex 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 eflavex, 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 eflavex:
Valvulopathy and fibrosis. (See section 4.4) – Fibrosis/Valvulopathy).
Hallucinations

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

Common (>1/100, <1/10)
Nervous system disorders: Depression, headache, fatigue, paresthesia, somnolence.
Cardiac disorders: Palpitations
Gastrointestinal disorders: Constipation
Skin and subcutaneous tissue disorders: Facial redness

Uncommon (>1/1000, <1/100)
Eye disorders: Hemianopsia
Vascular disorders: Nose bleeding

Rare (>1/10000, <1/1000)
Vascular disorders: Fainting
Musculoskeletal, connective tissue and bone disorders: Cramp in fingers and calves

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: N04B C06

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

With regard to the endocrine effects of eflavex 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 eflavex not correlated with the therapeutic effect only relate to blood pressure decrease. The maximal hypotensive effect of eflavex 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 eflavex 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 eflavex.

Distribution
"In-vitro" experiments showed that eflavex 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 eflavex in inhibiting prolactin secretion "in-vitro".

Elimination
The elimination half-life of eflavex, 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 eflavex obtained after a single dose (37 ± 8 pg/ml) and after a 4 week multiple-regimen (101 ± 43 pg/ml) for 0.5 eflavex dose.

Ten days after administration about 18% and 72% of the dose is recovered in urine and faeces, respectively. Unchanged eflavex 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 eflavex indicate a large safety margin for this compound in rodents and in monkeys, as well as a lack of teratogenic, mutagenic or carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous lactose
L-Leucin
Magnesium stearate (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

The drying capsule 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 with silica gel. The brown glass bottle has an induction-sealed childproof aluminium membrane and a childproof HDPE 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
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8 MARKETING AUTHORISATION NUMBER

PA 436/44/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th February 2008

10 DATE OF REVISION OF THE TEXT