IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0585/032/003
Case No: 2039486

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

Pliva Pharma Limited

Vision House, **Bedford Road**, **Petersfield**, **Hampshire GU32 3QB**, **United Kingdom**

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

Eironil 1mg film-coated 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 **12/12/2008** until **11/12/2013**.

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

Eironil 1 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mg film-coated tablet contains 1.0 mg of ropinirole (as hydrochloride).

Excipient(s):

Each 1 mg film-coated tablet contains 63.501mg of lactose (as monohydrate) and 0.0048mg of allura red AC (E129)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Eironil 1 mg Film-coated Tablets are pink, round, biconvex tablets embossed with „RO ” on one side and “1” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of Parkinson's disease under the following conditions:

Initial treatment as monotherapy, in order to delay the introduction of levodopa.

In combination with levodopa, over the course of the disease, when the effect of levodopa wears off or becomes inconsistent and fluctuations in the therapeutic effect occur ("end of dose" or "on-off" type fluctuations).

Ropinirole is also indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (see section 5.1).

4.2 Posology and method of administration

Oral use.

The tablets should be swallowed whole with fluid and preferably taken with meals.

Different strengths of this medicinal product are available in order to allow dosing according to the recommended treatment initiation and therapeutic regimens below. When the available range of strengths does not permit dose titration according to the treatment initiation regimen, Ropinirole should not be used in ropinirole naïve patients.

Treatment of idiopathic Parkinson's Disease:

Adults
Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken three times a day (t.i.d.), preferably with meals to improve gastrointestinal tolerance.

Treatment initiation: The initial dose should be 0.25 mg t.i.d. A guide for the titration regimen for the first four weeks of treatment is given in the table below:

Ripinirole	Week 1	Week 2	Week 3	Week 4
Unit dose (mg)	0.25	0.5	0.75	1.0
Total Daily dose (mg)	0.75	1.5	2.25	3.0

Therapeutic regimen: After the initial titration, weekly increments of up to 3 mg/day may be given. Ropinirole is usually given in divided doses three times per day.

The proposed titration regime is as follows:

Ripinirole	Week 5	Week 6	Week 7	Week 8
Unit dose (mg)	1.5	2.0	2.5	3.0
Total Daily dose (mg)	4.5	6.0	7.5	9.0

A therapeutic response may be seen between 3 and 9 mg/day, although adjunct therapy patients may require higher doses. If sufficient symptomatic control is not achieved, or maintained, the dose of ropinirole may be increased until an acceptable therapeutic response is established. Doses above 24 mg/day have not been investigated in clinical trials and this dose should not be exceeded.

If treatment is interrupted for one day or more re-initiation by dose titration should be considered (see above).

When ropinirole is administered as adjunct therapy to levodopa, the concurrent dose of levodopa may be reduced gradually by around 20% in total.

When switching treatment from another dopamine agonist to ropinirole, the manufacturer's guidance on discontinuation should be followed before initiating ropinirole.

Ropinirole should be discontinued gradually by reducing the number of daily doses over the period of one week.

Renal impairment: In parkinsonian patients with mild to moderate renal impairment (creatinine clearance 30-50 ml/min) no change in the clearance of ropinirole was observed, indicating that no dosage adjustment is necessary in this population.

Elderly: The clearance of ropinirole is decreased in patients over 65 years of age, but the dose of ropinirole for elderly patients can be titrated in the normal manner.

Children and adolescents: Parkinson's disease does not occur in children and adolescents. The use of ropinirole in this population has therefore not been studied and it should not be given to children.

Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.

Adults
Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken just before bed time, however the dose can be taken up to 3 hours before retiring. Ropinirole may be taken with food, to improve gastrointestinal tolerance.

Treatment initiation (week 1)
The recommended initial dose is 0.25 mg once daily (administered as above) for 2 days. If this dose is well tolerated the dose should be increased to 0.5 mg once daily for the remainder of week 1.

Therapeutic regimen (week 2 onwards)
Following treatment initiation, the daily dose should be increased until optimal therapeutic response is achieved. The average dose in clinical trials, in patients with moderate to severe Restless Legs Syndrome, was 2 mg once a day.

The dose may be increased to 1 mg once a day at week 2. The dose may then be increased by 0.5 mg per week over the next two weeks to a dose of 2 mg once a day. In some patients, to achieve optimal improvement, the dose may be increased gradually up to a maximum of 4 mg once a day. In clinical trials the dose was increased by 0.5 mg each week to 3 mg once a day and then by 1 mg up to the maximum recommended dose of 4 mg once a day as shown in the table below.

Doses above 4 mg once daily have not been investigated in Restless Legs Syndrome patients.

Dose titration

Week	2	3	4	5*	6*	7*
Dose (mg)/one daily	1	1.5	2	2.5	3	4

*To achieve optimal improvement in some patients

The patient's response to ropinirole should be evaluated after 3 months treatment (see section 5.1). At this time the dose prescribed and the need for continued treatment should be considered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above.

Renal impairment: No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min).

Elderly: The clearance of ropinirole is decreased in patients over 65 years of age. The increase in dosage should be gradual and titrated against the symptomatic response.

Children and adolescents: Ropinirole is not recommended for use in children and adolescents below 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications

Eironil 1 mg Film-coated Tablets
- Hypersensitivity to the active substance, allura red AC, or to any of the excipients
- Severe renal impairment (creatinine clearance <30 ml/min)
- Hepatic impairment

4.4 Special warnings and precautions for use

Due to the pharmacological action of ropinirole, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution due to the risk of hypotension; blood pressure monitoring is recommended, particularly at the beginning of treatment.

Co-administration of ropinirole with anti-hypertensive and anti-arrhythmic agents has not been studied. Caution should be exercised when these compounds are given concomitantly with ropinirole because of the unknown potential for the occurrence of hypotension, bradycardias or other arrhythmias.

Patients with a history or presence of psychiatric or psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks (see also section 4.5).

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

Ropinirole has been associated with somnolence and episodes of sudden sleep onset (see section 4.8), 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 ropinirole. 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.

Ropinirole should not be used to treat neuroleptic akathisia, tasikinesia (neuroleptic-induced compulsive tendency to walk), or secondary Restless Legs Syndrome (e.g. caused by renal failure, iron deficiency anaemia or pregnancy).

During treatment with ropinirole, paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed. If this occurs, treatment should be reviewed and dosage adjustment or discontinuation of treatment may be considered.

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

Ropinirole is principally metabolized by the cytochrome P450 isoenzyme CYP1A2. A pharmacokinetic study (with a ropinirole dose of 2 mg, three times a day) revealed that ciprofloxacin increased the C_{max} and AUC of ropinirole by 60% and 84% respectively, with a potential risk of adverse events. Hence, in patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when medicinal products known to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin, fluvoxamine or cimetidine, are introduced or withdrawn.

A pharmacokinetic interaction study between ropinirole (at a dose of 2 mg, three times a day) and theophylline, a substrate of CYP1A2, revealed no change in the pharmacokinetics of either ropinirole or theophylline. Therefore, it is not expected that ropinirole will compete with the metabolism of other medicinal products which are metabolised by CYP1A2.

Based on *in-vitro* data, ropinirole has little potential to inhibit cytochrome P450 at therapeutic doses. Hence, ropinirole is unlikely to affect the pharmacokinetics of other medicinal products, via a cytochrome P450 mechanism.

Smoking is known to induce CYP1A2 metabolism, therefore if patients stop or start smoking during treatment with ropinirole, dose adjustment maybe required.

Increased plasma concentrations of ropinirole have been observed in patients treated with high doses of oestrogens. In patients already receiving hormone replacement therapy (HRT), ropinirole treatment may be initiated in the normal manner. However, it may be necessary to adjust the ropinirole dose, in accordance with clinical response, if hormone replacement therapy is stopped or introduced during treatment with ropinirole.

No pharmacokinetic interaction has been seen between ropinirole and levodopa or domperidone (a medicinal product used to treat nausea and vomiting) which would necessitate dosage adjustment of either medicinal product. Domperidone antagonises the dopaminergic actions of ropinirole peripherally and does not cross the blood-brain barrier. Hence its value as an anti-emetic in patients treated with centrally acting dopamine agonists.

Neuroleptics and other centrally active dopamine antagonists, such as sulpiride or metoclopramide, may diminish the effectiveness of ropinirole and, therefore, concomitant use of these medicinal products with ropinirole should be avoided.

4.6 Pregnancy and lactation

There are no adequate data from the use of ropinirole in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). As the potential risk for humans is unknown, it is recommended that ropinirole is not used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the foetus.

Ropinirole should not be used in nursing mothers as it may inhibit lactation.

4.7 Effects on ability to drive and use machines

Ropinirole has major influence on the ability to drive and use machines.

Patients should be warned about the possibility of dizziness (including vertigo). Patients being treated with ropinirole 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 effects have resolved (see also Section 4.4).

4.8 Undesirable effects

Undesirable effects are listed below by system organ class and frequency. Frequencies are defined as: 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), not known (cannot be estimated from the available data).

Common and uncommon undesirable effects were generally determined from pooled safety data from clinical trial populations of ropinirole and are quoted as excess incidence over placebo. Rare and very rare undesirable effects were generally determined from post-marketing data and refer to reporting rate rather than true frequency.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse Drug Reactions Reported from Patients taking ropinirole in Parkinson's Disease:
The adverse drug reactions reported in patients with Parkinson's disease on ropinirole monotherapy and adjunct therapy at doses up to 24mg/day at an excess incidence over placebo are described below.

The most commonly reported undesirable effects are nausea, somnolence, dyskinesia and syncope.

Psychiatric disorders	
common	confusion[1] ,hallucinations
uncommon	Psychotic reactions (other than hallucinations), including delusion, paranoia, delirium.
Patients treated with dopamine agonists for treatment of Parkinson's disease, including ropinirole, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation[3].	
Nervous system disorders	
Very common	Syncope[2], dyskinesia[1], somnolence[2]
common	dizziness (including vertigo)[1,2]
uncommon	extreme daytime somnolence[3]sudden onset of sleep[3]
Vascular disorders	
uncommon	hypotension, postural hypotension
Gastrointestinal disorders	
Very common	nausea
common	vomiting[2], abdominal pain[2], heartburn[2]
General disorders and administrative site conditions	
common	leg oedema[2]
Hepatobiliary disorders	
not known	hepatic reactions, hepatic enzymes increased[3]

1 Adjunct therapy studies
2 Monotherapy studies
3 Post-marketing data (see Section 4.4)

Use of ropinirole in Restless Legs Syndrome
In Restless Legs Syndrome clinical trials the most common adverse drug reaction was nausea (approximately 30% of patients). Undesirable effects were normally mild to moderate and experienced at the start of therapy or on increase of dose and few patients withdrew from the clinical studies due to undesirable effects.

The table below lists the adverse drug reactions reported for ropinirole in the 12-week clinical trials at ≥1.0% above the placebo rate or those reported uncommonly but known to be associated with ropinirole.

Adverse drug reactions reported in 12-week Restless Legs Syndrome clinical trials (ropinirole n=309, placebo n=307)

Psychiatric disorders	
Common	Nervousness
Uncommon	Confusion
Nervous system disorders	
Common	Syncope, somnolence, dizziness (including vertigo)
Vascular disorders	
Uncommon	Postural hypotension, hypotension
Gastrointestinal disorders	
Very common	Vomiting, nausea
Common	Abdominal pain
General disorders and administration site conditions	
Common	Fatigue

Hallucinations were reported uncommonly in the open label long-term studies.

In post-marketing reports, extreme daytime somnolence and sudden onset of sleep have been reported very rarely in Restless Legs Syndrome.

Paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed during treatment with ropinirole.

Management of undesirable effects
Dose reduction should be considered if patients experience significant undesirable effects. If the undesirable effect abates, gradual up-titration can be re-instituted. Anti-nausea medicinal products that are not centrally active dopamine antagonists, such as domperidone, may be used, if required.

4.9 Overdose

There have been no incidences of intentional overdose with ropinirole in clinical trials. It is anticipated that the symptoms of ropinirole overdose will be related to its dopaminergic activity. These symptoms may be alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopamine agonist, ATC code: N04BC04.

Mechanism of action
Ropinirole is a non ergoline D2/D3 dopamine agonist which stimulates striatal dopamine receptors.

Parkinson's disease is characterised by a marked dopamine deficiency in the nigral striatal system. Ropinirole alleviates this deficiency by stimulating striatal dopamine receptors.

Ropinirole acts in the hypothalamus and pituitary to inhibit the secretion of prolactin.

Clinical efficacy in Restless Legs Syndrome
Ropinirole should only be prescribed to patients with moderate to severe idiopathic Restless Legs Syndrome. Moderate to severe idiopathic Restless Legs Syndrome is typically represented by patients who suffer with insomnia or severe discomfort in the limbs.

In the four 12-week efficacy studies, patients with Restless Legs Syndrome were randomised to ropinirole or placebo, and the effects on the IRLS scale scores at week 12 were compared to baseline. The mean dose of ropinirole for the moderate to severe patients was 2.0 mg/day. In a combined analysis of moderate to severe Restless Legs Syndrome patients from the four 12-week studies, the adjusted treatment difference for the change from baseline in IRLS scale total score at week 12 Last Observation Carried Forward (LOCF) Intention To Treat population was -4.0 points (95% CI -5.6, -2.4, $p<0.0001$; baseline and week 12 LOCF mean IRLS points: ropinirole 28.4 and 13.5; placebo 28.2 and 17.4).

A 12-week placebo-controlled polysomnography study in Restless Legs Syndrome patients examined the effect of treatment with ropinirole on periodic leg movements of sleep. A statistically significant difference in the periodic leg movements of sleep was seen between ropinirole and placebo from baseline to week 12.
Although sufficient data are not available to adequately demonstrate the long term efficacy of ropinirole in Restless Legs Syndrome (see section 4.2), in a 36-week study, patients who continued on ropinirole demonstrated a significantly lower relapse rate compared with patients randomised to placebo (33% versus 58%, $p=0.0156$).

A combined analysis of data from moderate to severe Restless Legs Syndrome patients, in the four 12-week placebo-controlled studies, indicated that ropinirole-treated patients reported significant improvements over placebo on the parameters of the Medical Outcome Study Sleep Scale (scores on 0-100 range except sleep quantity). The adjusted treatment differences between ropinirole and placebo were: sleep disturbance (-15.2, 95% CI -19.37, -10.94; $p<0.0001$), sleep quantity (0.7 hours, 95% CI 0.49, 0.94); $p<0.0001$), sleep adequacy (18.6, 95% CI 13.77, 23.45; $p<0.0001$) and daytime somnolence (-7.5, 95% CI -10.86, -4.23; $p<0.0001$).

A rebound phenomenon following discontinuation of ropinirole treatment (end of treatment rebound) cannot be excluded. In clinical trials, although the average IRLS total scores 7-10 days after withdrawal of therapy were higher in ropinirole-treated patients than in placebo-treated patients, the severity of symptoms following withdrawal of therapy generally did not exceed the baseline assessment in ropinirole-treated patients.

In clinical studies most patients were of Caucasian origin.

5.2 Pharmacokinetic properties

Absorption
The bioavailability of ropinirole is about 50% (36% to 57%), with C_{max} reached on average 1.5 hours after the dose. In the presence of food, C_{max} is delayed by about 2.6 hours and the peak plasma level is reduced by 25%, with no effect on the bioavailable quantity. The bioavailability of ropinirole varies greatly between individuals.

Distribution
The binding of ropinirole to plasma proteins is not high (<40%), with no effect on the distribution which is very extensive (volume of distribution in the order of 7 l/kg).

Metabolism
Ropinirole is mainly metabolised by the isoform CYP1A2 of cytochrome P450. None of the many metabolites formed are involved in the resulting activity of the product and the main metabolite is 100 times less potent than ropinirole in animal models examining dopaminergic function.

Elimination
Unchanged ropinirole and the metabolites are mainly excreted through the kidneys. The elimination half-life of ropinirole is 6 hours on average.

Linearity
The pharmacokinetics of ropinirole are linear overall (C_{max} and AUC) in the therapeutic range between 0.25 mg and 4 mg, after a single dose and after repeated dosing.

Population-related characteristics
In patients over 65 years of age, a reduction in the systemic clearance of ropinirole by about 30% is possible.

In patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min), no change in the pharmacokinetics of ropinirole is observed. No data are available in patients with severe renal impairment.

5.3 Preclinical safety data

Toxicology: The toxicology profile is principally determined by the pharmacological activity of the drug (behavioural changes, hypoprolactinaemia, decrease in blood pressure and heart rate, ptosis and salivation). In the albino rat only, retinal degeneration was observed in a long term study at a high dose (50 mg/kg), probably associated with an increased exposure to light.

Genotoxicity: Genotoxicity was not observed in the usual battery of *in vitro* and *in vivo* tests.

Carcinogenicity: From two-year studies conducted in the mouse and rat at dosages up to 50 mg/kg there was no evidence of any carcinogenic effect in the mouse. In the rat, the only drug-related lesions were Leydig cell hyperplasia and testicular adenoma resulting from the hypoprolactinaemic effect of ropinirole. These lesions are considered to be a species specific phenomenon and do not constitute a hazard with regard to the clinical use of ropinirole.

Reproductive Toxicity: Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg/day (approximately equivalent to the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg/day (approximately 2 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg/day (approximately 3 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 2.5 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Cellulose, microcrystalline
Maize starch
Silica colloidal anhydrous
Magnesium stearate

Opadry II 31F24239 Pink consisting of:
Hypromellose 15 cp (E464)
Lactose monohydrate
Titanium dioxide (E171)
Macrogol 4000
Iron oxide red (E172)
Allura red AC aluminum lake (E129)
Indigo carmine aluminum lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

18 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Al//PVC/Al/oPA foil blisters
1 mg: Packs of 21, 28 and 84 film-coated tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No Special Requirements.

7 MARKETING AUTHORISATION HOLDER

Pliva Pharma Limited
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8 MARKETING AUTHORISATION NUMBER

PA585/32/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th December 2008

10 DATE OF REVISION OF THE TEXT