IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0749/074/001
Case No: 2066318

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

Teva Pharma B.V.

Computerweg 10, **3542 DR Utrecht**, **Netherlands**

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

Ropinirole Teva 1 mg 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 **28/05/2009** until **12/02/2014**.

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

Ropinirole Teva 1 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ropinirole Teva 1 mg: Each film-coated tablet contains 1.14 mg ropinirole hydrochloride, equivalent to 1 mg ropinirole

Excipient(s):
Lactose and lecithin (soya) E322:
104.27 mg lactose & 0.1575 mg lecithin / 1 mg film-coated tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Ropinirole 1 mg: Green, round slightly arched film-coated tablets, debossed “R 1” on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ropinirole Teva is indicated for:

The 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).
- The symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (see section 5.1).

4.2 Posology and method of administration

For oral use.

Individual dose titration against efficacy and tolerability is recommended.

Adults

Parkinson’s Disease

Ropinirole Teva 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 three times daily for 1 week. Thereafter, the dose can be increased in 0.25 mg t.i.d increments, according to the following regimen.

	Week			
	1	2	3	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 0.5 to 1 mg t.i.d (1.5 to 3 mg/day) may be given. A therapeutic response may be seen between 3 and 9 mg/day. If sufficient symptomatic control is not achieved, or maintained, the dose of ropinirole may be increased up to a maximum of 24 mg/day. Doses above 24 mg/day have not been studied and this 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%.

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

As with other dopamine agonists, it is necessary to discontinue ropinirole treatment gradually by reducing the number of daily doses over the period of one week.

For doses not realisable/practicable with this medicinal product other strengths of this medicinal product are available

Restless Legs Syndrome

Ropinirole should be taken just before bedtime; 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 for 2 days (administered as above). 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 following table.

Week	2	3	4	5*	6*	7*
Dose (mg)/once daily	1.0	1.5	2.0	2.5	3.0	4.0

* To achieve optimal improvement in some patients.

Doses above 4 mg once daily have not been investigated in Restless Legs Syndrome 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 reinitiated by dose titration carried out as above.

General information for all therapeutic indications

Children and Adolescents

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

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.

Renal Impairment

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

4.3 Contraindications

Hypersensitivity to ropinirole, soya, peanut or to any of the excipients.
Severe renal impairment (creatinine clearance <30 ml/min).
Hepatic impairment.

4.4 Special warnings and precautions for use

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.

In Parkinson's disease, ropinirole has been associated uncommonly with somnolence and episodes of sudden sleep onset (see section 4.8) however, in Restless Legs Syndrome, this phenomenon is very rare. 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 phenomenon 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.

Patients with major psychiatric or psychotic disorders should not be treated with dopamine agonists unless the potential benefits outweigh the risks (see also section 4.5).

Pathological gambling, hypersexuality and increased libido have been reported in patients treated with dopamine agonists for Parkinson’s disease, including Ropinirole Teva (see section 4.8).

Impulse control disorders including pathological gambling and hypersexuality, and increased libido, have been reported in patients treated with dopamine agonists, including ropinirole, principally for Parkinson's disease (see section 4.8).

Due to the risk of hypotension, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution. Blood pressure monitoring is recommended, particularly at the start of treatment (due to the risk of postural hypotension).

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

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.

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 HRT is stopped or introduced during treatment with ropinirole.

Ropinirole is principally metabolised by the cytochrome P450 isoenzyme CYP1A2. A pharmacokinetic study (with a ropinirole dose of 2 mg, three times a day) in Parkinson patients revealed that ciprofloxacine 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. ciprofloxacine, enoxacin or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study in Parkinson patients between ropinirole (at a dose of 2mg, 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.

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.

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.

No information is available on the potential for interaction between ropinirole and alcohol. As with other centrally active medications, patients should be cautioned against taking ropinirole with alcohol.

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 machine. 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 recurrent episodes and somnolence 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 events were generally determined from pooled safety data from clinical trial populations 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.

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.
Table below lists the adverse drug reactions reported for ropinirole in the 12 week clinical trials at 1% above the placebo rate or those reported uncommonly but known to be associated with ropinirole (ropinirole n=309, placebo n=307).

Organ Class System	Frequency		
	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Nervous system disorders		Syncope, somnolence and dizziness (including vertigo)	
Gastro-intestinal disorders	Vomiting and nausea	Abdominal pain	
Vascular disorders			Postural hypotension and hypotension
General disorders and administration site conditions		Fatigue	
Psychiatric disorders		Nervousness	Confusion

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

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.

Parkinson's Disease

Organ Class System	Monotherapy or Adjunct therapy	Frequency			
		Very Common (≥1/10)	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1,000 to <1/100)	Not known
Nervous system disorders	Both	Somnolence	Dizziness (including vertigo)	Excessive daytime somnolence and sudden onset of sleep	
	Monotherapy	Syncope			
	Adjunct therapy	Dyskinesia			
Gastro-intestinal disorders	Both	Nausea	Heartburn		
	Monotherapy		Abdomnial pain, vomiting		
Vascular disorders	Both			Hypotension and postural hypotension (rarely severe)	
General disorders and administration site conditions	Monotherapy		Leg oedema		
Heptobiliary disorders	Both				Hepatic reactions and increased liver enzymes
Psychiatric disorders	Both		Hallucinations	Psychotic reactions (other than hallucinations) including delirium, delusion, and paranoia	
	Adjunct therapy		Confusion, hallucination		

Both: Monotherapy and adjunct therapy

Patients treated with dopamine agonists for treatment of Parkinson's disease, including Ropinirole Teva, have been reported as exhibiting signs of pathological gambling, hypersexuality and increased libido. Those disorders were reported especially at high doses and were generally reversible upon reduction of the dose or treatment discontinuation (see section 4.4).

Lecithin (soya) may cause very rarely allergic reactions

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: Dopaminergic agents, dopamine agonists; ATC code: N04BC04

Ropinirole is a non-ergoline D2/D3 dopamine agonist, which stimulates striatal dopamine receptors.

Ropinirole alleviates the dopamine deficiency which characterises Parkinson's disease 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

Oral absorption of ropinirole is rapid. 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 low (10 – 40 %).

Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (mean value 6.7 l/kg, range 3.4 - 19.5 l/kg) and is cleared from the systemic circulation with an average elimination half-life of approximately 6 hours (range 3.4 - 10.2 h) and an apparent oral clearance of 58.7 l/h (range 18.5 - 132 l/h).

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.
Wide inter-individual variability in the pharmacokinetic parameters has been seen and the increase in systemic exposure (C_{max} and AUC) to ropinirole with an increase in dose over the therapeutic dose range is proportional after single administration.

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 (approximately 15 times the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg (approximately 25 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg (approximately 40 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg (approximately 30 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
Microcrystalline cellulose
Hydroxypropylcellulose
Croscarmellose sodium
Magnesium stearate

Tablet coating (Opadry II 85G11948) for Ropinirole Teva 1 mg:
Poly(vinyl alcohol) – partially hydrolyzed
Titanium dioxide (E171)
Macrogol 3350
Talc
Lecithin (soya) (E322)
FD&C Blue #2/ Indigo Carmine Aluminium (E132)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

18 months.

6.4 Special precautions for storage

Ropinirole Teva 1 mg: Do not store above 30ºC. Store in the original container.

6.5 Nature and contents of container

OPA/Alu/PVC – aluminium blisters. The pack sizes available are:

Ropinirole Teva 1 mg: 15, 21, 30, 60, 84, 90 and 100 and 50 unit dose blisters (hospital pack).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10,
3542DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA749/74/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th February 2009

10 DATE OF REVISION OF THE TEXT

May 2009