Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ropirade 0.25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 0.285 mg ropinirole hydrochloride, equivalent to 0.25 mg of ropinirole.

Excipients with known effect:
One film-coated tablet contains 101.85 mg lactose.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White, round film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

ROPINIROLE is indicated for

- 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 therapy wears off or becomes inconsistent, and when fluctuations in the therapeutic effect occur ("end-of-dose" fluctuations or "on-off" type fluctuations).
- the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (RLS) (see section 5.1).

4.2 Posology and method of administration

Oral use.

Adults
ROPINIROLE may be taken with food, to improve gastrointestinal tolerance.

Individual dose titration against efficacy and tolerability is recommended.

Parkinson's disease:
Ropinirole should be taken three times a day.

Treatment initiation:
The initial dose of ropinirole should be 0.25 mg three times daily for 1 week. Thereafter, the dose of ropinirole can be increased in 0.25 mg three times daily increments, according to the following regimen

	Week			
	1	2	3	4
Unit dose (mg) of ropinirole	0.25	0.5	0.75	1.0
Total daily dose (mg) of ropinirole	0.75	1.5	2.25	3.0

Therapeutic regimen
After the initial titration, weekly increments of 0.5 to 1 mg three times daily (1.5 to 3 mg/day) of ropinirole may be given.
A therapeutic response may be seen between 3 and 9 mg/day. If sufficient symptomatic control is not achieved, or maintained after the initial titration as described above, the dose of ropinirole may be increased up to 24 mg/day.

Doses of ropinirole above 24 mg/day have not been studied.

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 according to the symptomatic response. In clinical trials, the levodopa dose was reduced gradually by around 20% in patients treated with ROPINIROLE as adjunct therapy. In patients with advanced Parkinson's disease receiving ropinirole in combination with levodopa, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the levodopa dose may ameliorate dyskinesia (see section 4.8).

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.

Restless Legs Syndrome:
Ropinirole should be taken just before bedtime, however the dose can be taken up to 3 hours before retiring.

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 remaining 5 days 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 (RLS) patients.

Dose titration

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

* To achieve optimal improvement in some patients.

The efficacy of ropinirole treatment has not been shown beyond 12 weeks (see section 5.1). The patient's response to ropinirole should be evaluated after 12 weeks treatment and the need for treatment continuation reconsidered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration as noted above.

General information for all therapeutic indications
Children and adolescents
ROPINIROLE 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 by approximately 15% in patients aged 65 years or above. Although a dose adjustment is not required, ropinirole dose should be individually titrated, with careful monitoring of tolerability, to the optimal clinical response.

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

The use of ropinirole in patients with severe renal impairment (creatinine clearance less than 30 ml/min) without regular haemodialysis has not been studied.

Parkinson' disease
A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis) has shown that a dose adjustment in these patients is required as follows: the initial dose of ROPINIROLE should be 0.25 mg three times a day. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose of ROPINIROLE is 18 mg/day in patients receiving regular haemodialysis. Supplemental doses after haemodialysis are not required (see section 5.2).

Restless Legs Syndrome
A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis) has shown that a dose adjustment in these patients is required as follows: the recommended initial dose of ROPINIROLE is 0.25 mg once daily. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose of ROPINIROLE is 3 mg/day in patients receiving regular haemodialysis. Supplemental doses after haemodialysis are not required (see section 5.2).

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe renal impairment (creatinine clearance <30 ml/min) without regular haemodialysis.
- Hepatic impairment.

4.4 Special warnings and precautions for use

Ropinirole has been associated with somnolence and episodes of sudden sleep onset particularly in patients with Parkinson' s disease (see section 4.8). Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported uncommonly, however, in Restless Legs Syndrome, this phenomenon is very rare. 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.

Impulse control disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Ropirade 0.25mg film-coated tablets. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

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).

Paradoxical worsening of Restless Legs Syndrome symptoms described as augmentation, (either earlier onset, increased intensity, or spread of symptoms to previously unaffected limbs), or early morning rebound (reoccurrence of symptoms in the early morning hours), have been observed during treatment with ropinirole. If this occurs, the adequacy of ropinirole treatment should be reviewed and dosage adjustment or discontinuation of treatment may be considered (see section 4.8).

Patients with major psychotic disorders or a history of major psychotic disorders should not be treated with dopamine agonists unless the potential benefits outweigh the risks.

Due to the risk of hypotension, blood pressure monitoring is recommended, particularly at the start of treatment, in patients with severe cardiovascular disease (in particular coronary insufficiency).

This medicinal product contains lactose monohydrate.
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 metabolised 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 Cmax 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, cimetidine or fluvoxamine, 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 hormone replacement therapy (HRT). In patients already receiving hormone replacement therapy, ropinirole treatment may be initiated in the usual 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.

There is no pharmacokinetic interaction between ropinirole and levodopa or domperidnone which would necessitate dosage adjustment of any of these medicinal products.

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.

In patients receiving the combination of vitamin K antagonists and ropinirole, cases of unbalanced INR have been reported. Increased clinical and biological surveillance (INR) is warranted.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

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

4.7 Effects on ability to drive and use machines

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 section 4.4).

4.8 Undesirable effects

The adverse drug reactions reported 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).

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.

Table 1 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.

Table 1
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

Table 2
Adverse drug reactions reported in other Restless Legs Syndrome clinical trials

Psychiatric disorders	
Uncommon	Hallucinations
Nervous system disorders	
Common	Augmentation, Early morning rebound (see section 4.4)

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.

Other experience with ropinirole
Ropinirole is also indicated for the treatment of Parkinson's disease. The adverse drug reactions reported in patients with Parkinson's disease on ropinirole monotherapy and adjunct therapy at doses up to 24 mg/day at an excess incidence over placebo are described below.

Table 3
Adverse drug reactions reported in Parkinson's disease clinical trials at doses up to 24 mg/day

Psychiatric disorders	
Common	Hallucinations, confusion
Uncommon	Increased libido
Nervous system disorders	
Very common	Syncope, dyskinesia, somnolence
Gastrointestinal disorders	
Very common	Nausea
Common	Vomiting, abdominal pain, heartburn
General disorders and administration site conditions	
Common	Leg oedema

Post marketing reports
Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus).

Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia have been reported.

Impulse control disorders
Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including ROPINIROLE (see section 4.4. 'Special warnings and precautions for use').

In Parkinson’s disease, ropinirole is associated with somnolence and has been associated uncommonly (≥1/1,000 to <1/100) with excessive daytime somnolence and sudden sleep onset episodes, however, in Restless Legs Syndrome, this phenomenon is very rare (<1/10,000).

Following ropinirole therapy, postural hypotension or hypotension has been reported uncommonly (≥1/1,000 to <1/100), rarely severe.

Very rare cases of hepatic reactions (<1/10,000), mainly increase of liver enzymes, have been reported.

Use of ropinirole in Parkinson's disease:
It is noted if these undesirable effects were reported in clinical trials as monotherapy or adjunct therapy to levodopa.

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

Immune system disorders
Not known Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus).

Psychiatric disorders
Common: hallucinations.
Uncommon: psychotic reactions (other than hallucinations) including delirium, delusion, paranoia.

Impulse control disorders
Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including ROPINIROLE (see section 4.4. 'Special warnings and precautions for use').

Use in adjunct therapy studies:
Common: confusion.

Nervous system disorders
Very common: somnolence
Common: dizziness (including vertigo).
Uncommon: sudden onset of sleep, excessive daytime somnolence.
Ropinirole is associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes.

Use in monotherapy studies:
Very common: syncope.

Use in adjunct therapy studies:
Very common: dyskinesia. In patients with advanced Parkinson's disease, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the levodopa dose may ameliorate dyskinesia (see section 4.2).

Vascular disorders
Uncommon: postural hypotension, hypotension.
postural hypotension or hypotension is rarely severe.

Gastrointestinal disorders
Very common: nausea.
Common: heartburn.

Use in monotherapy studies:
Common: vomiting, abdominal pain.

Hepatobiliary disorders
Not known: hepatic reactions, mainly increased liver enzymes.

General disorders
Use in monotherapy studies:
Common: leg oedema.

ROPINIROLE 3 mg film-coated tablets contain the colorant Sunset yellow aluminium lake which may cause allergic reactions.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the online reporting option (preferred method) accessible from the IMB homepage (www.imb.ie). A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost' (see details below). Alternatively, the traditional post-paid 'yellow card' option may also be used.FREEPOST Pharmacovigilance Section, Irish Medicines Board, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2 Tel: +353 1 6764971 Fax: +353 1 6762517 Website: http://www.imb.ie/ e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

The symptoms of ropinirole overdose are 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 agonists
ATC code: N04BC04.

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

Clinical efficacy in the treatment of Parkinson's disease
Ropinirole alleviates the dopamine deficiency which characterises Parkinson's disease by stimulating striatal dopamine receptors.

Clinical efficacy in the treatment of 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.

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; $p<0.0001$).

Long term efficacy was evaluated in a randomized, double-blind, placebo-controlled clinical trial of 26 weeks. Overall results were difficult to interpret due to significant centre treatment interaction and the high proportion of missing data.

No maintenance of efficacy at 26 weeks compared to placebo could be shown.

In clinical studies most patients were of Caucasian origin.

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

Study of the effect of ropinirole on cardiac repolarisation
A thorough QT study conducted in male and female healthy volunteers who received doses of 0.5, 1, 2 and 4 mg of ropinirole film-coated (immediate release) tablets once daily showed a maximum increase of the QT interval duration at the 1 mg dose of 3.46 milliseconds (point estimate) as compared to placebo. The upper bound of the one sided 95% confidence interval for the largest mean effect was less than 7.5 milliseconds. The effect of ropinirole at higher doses has not been systematically evaluated.
The available clinical data from a thorough QT study do not indicate a risk of QT prolongation at doses of ropinirole up to 4 mg/day. A risk of QT prolongation cannot be excluded as a thorough QT study at doses up to 24 mg/day has not been conducted.

5.2 Pharmacokinetic properties

Absorption
Bioavailability of ropinirole is approximately 50% (36-57%). Oral absorption of ropinirole film-coated (immediate-release) tablets is rapid with peak concentrations of ropinirole achieved at a median time of 1.5 hours post-dose. A high fat meal decreases the rate of absorption of ropinirole, as shown by a delay in median T_{max} by 2.6 hours and an average 25% decrease in C_{max}.

Distribution
Plasma protein binding of ropinirole is low (10 – 40 %).
Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approx 7 l/kg).

Biotransformation
Ropinirole is primarily cleared by the cytochrome P450 enzyme, CYP1A2, and its metabolites are mainly excreted in the urine. The major metabolite is at least 100 times less potent than ropinirole in animal models of dopaminergic function.

Elimination
Ropinirole is cleared from the systemic circulation with an average elimination half-life of approximately 6 hours. The increase in systemic exposure (C_{max} and AUC) to ropinirole is approximately proportional over the therapeutic dose range. No change in the oral clearance of ropinirole is observed following single and repeated oral administration. Wide inter-individual variability in the pharmacokinetic parameters has been observed.

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
Oral clearance of ropinirole is reduced by approximately 15% in elderly patients (65 years or above) compared to younger patients. Dosing adjustment is not necessary in the elderly.

Renal Impairment
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.

Parkinson's disease
In patients with end stage renal disease receiving regular haemodialysis, oral clearance of ropinirole is reduced by approximately 30%. Oral clearance of the metabolites SKF-104557 and SKF-89124 were also reduced by approximately 80% and 60%, respectively. Therefore, the recommended maximum dose is limited to 18 mg/day in these patients with Parkinson's disease (see section 4.2).

Restless Legs Syndrome
In patients with end stage renal disease receiving regular haemodialysis, oral clearance of ropinirole is reduced by approximately 30%. Oral clearance of the metabolites SKF-104557 and SKF-89124 were also reduced by approximately 80% and 60%, respectively**.** Therefore, the recommended maximum dose is limited to 3 mg/day in these patients with RLS (see section 4.2).

Paediatric population investigated for Restless Legs Syndrome
Limited pharmacokinetic data obtained in adolescents (12-17 years, n=9) showed that the systemic exposure following single doses of 0.125 mg and 0.25 mg was similar to that observed in adults (see also section 4.2; subparagraph "Children and adolescents).

5.3 Preclinical safety data

Toxicology
The toxicology profile is principally determined by the pharmacological activity of ropinirole: 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 the highest dose (50 mg/kg/day), and was 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/day there was no evidence of any carcinogenic effect in the mouse. In the rat, the only ropinirole -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
Parkinson's disease indication
Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg/day (approximately twice the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg/day (approximately 3 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg/day (approximately 5 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 4 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

Restless legs syndrome
Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg/day (approximately 15 times the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg/day (approximately 25 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg/day (approximately 40 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 30 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

Safety Pharmacology
Parkinson's disease indication
In vitro studies have shown that ropinirole inhibits hERG-mediated currents. The IC_{50} is 5-fold higher than the expected maximum plasma concentration in patients treated at the highest recommended dose (24 mg/day), see section 5.1.

Restless legs syndrome
In vitro studies have shown that ropinirole inhibits hERG-mediated currents. The IC_{50} is at least 30-fold higher than the expected maximum plasma concentration in patients treated at the highest recommended dose (4 mg/day), see section 5.1.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

Film coating:
Hypromellose
Macrogol 400
Titanium dioxide (E171)
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/Aclar/Aluminium blister: 2 years.

HDPE bottles: 18 months

Aluminium/Aluminium blister: 3 years.

6.4 Special precautions for storage

PVC/Aclar/Aluminium blister: Do not store above 25°C. In order to protect from moisture store in the original package.

HDPE bottles: Do not store above 30°C. In order to protect from moisture keep the bottle tightly closed.

Aluminium/Aluminium blister: Do not store above 30°C. In order to protect from moisture store in the original package.

6.5 Nature and contents of container

PVC/Aclar/Aluminium blister.
Packs of 7, 12, 21, 30, 50, 60, 84, 90, 126 or 210 film-coated tablets.

HDPE bottle with child-resistant PP-closure.
Bottle with 7, 12, 21, 30, 50, 60, 84, 90, 126 or 210 (2x105) film-coated tablets.

Aluminium/Aluminium blister.
Packs of 7, 12, 21, 30, 50, 60, 84, 90, 126 or 210 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/176/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th June 2008

Date of last renewal: 18th March 2013

10 DATE OF REVISION OF THE TEXT

November 2013