Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ropinirole 1mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1.14mg of ropinirole hydrochloride equivalent to 1mg of ropinirole
Excipient: 47mg of lactose
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Green, raised pentagon shaped coated tablet with ‘RI’ over ‘1’ on one side and ‘>’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Parkinson's Disease with the following conditions:

- Initial treatment as monotherapy to delay treatment with levodopa
- Association with levodopa during the evolution of the disease when the effect of the treatement with levodopa runs short or becomes inconstant, and that fluctuations of the therapeutic effect appear (fluctuations type “end-of-dose” or "on-off").

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

4.2 Posology and method of administration

Individual dose titration against efficacy and tolerability is recommended.

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

In the treatment of Parkinson’s Disease

Ropinirole should be taken three times a day, preferably with meals to improve gastrointestinal tolerance.

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

Table 1: Dose titration for treatment of Parkinson’s disease

	Week **1**	**2**	**3**	**4**
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 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, 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.

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.

In the treatment of Restless Leg Syndrome

Individual dose titration against efficacy and tolerability is recommended. 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 (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 table 1. Doses above 4 mg once daily have not been investigated in Restless Legs Syndrome patients.
Table 2: Dose titration for treatment of Restless Legs Syndrome

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 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.

As with other dopamine agonists, ropinirole should be discontinued gradually by reducing the number of daily doses over the period of one week.

General instructions

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

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

Renal impairment:
In 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

4.3 Contraindications

Hypersensitivity to ropinirole or to any of the excipients.

Severe renal impairment (creatinine clearance <30 ml/min)

Severe hepatic impairment.

4.4 Special warnings and precautions for use

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

Ropinirole should be administered with caution to patients with moderate hepatic impairment. Undesirable effects should be closely monitored.

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 major 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. Those disorders were reported especially at high doses and were generally reversible upon reduction of the dose or treatment discontinuation. Risk factors such as a history of compulsive behaviours were present in some cases (see section 4.8).

Ropinirole has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's Disease, 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 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.

Lactose
The 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

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

No pharmacokinetic interaction has been seen between ropinirole and levodopa or domperidone 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 with centrally acting agonists.

No interaction has been seen between ropinirole and other drugs commonly used to treat Parkinson's disease but, as is common practice, care should be taken when adding a new drug to a treatment regimen. Other dopamine agonists may be used with caution.

In a study in parkinsonian patients receiving concurrent digoxin, no interaction was seen which would require dosage adjustment.

Ropinirole is principally metabolised by the cytochrome P450 enzyme CYP1A2. A pharmacokinetic study (with a ropinirole dose of 2 mg, three times a day in patients with Parkinson’s disease) 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 or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study in patients with Parkinson’s disease 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.
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, if HRT is stopped or introduced during treatment with ropinirole, dosage adjustment may be required.

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

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 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.

Lactation:
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 recurrent episodes and somnolence have resolved (see also Section 4.4).

4.8 Undesirable effects

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000) very rare (<1/10,000); not known (cannot be estimated from the available data). Common and uncommon reactions 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 reactions were generally determined from post-marketing data and refer to reporting rate rather than true frequency.

Use of Ropinirole in Parkinson's disease
Psychiatric disorders:
Common: 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.

Use in adjunct therapy studies:
Common: confusion

Nervous system disorders:
Very Common: somnolence
Common: dizziness (including vertigo)
Uncommon: excessive daytime solmnolence, sudden onset of sleep
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: hypotension, postural 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:
Very rare: hepatic enzymes increased

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

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.

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 are summarised below. These adverse drug reactions were 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.

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 (see Section 4.4).

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: N04B C04

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

Clinical efficacy in the treatment of Parkinson's disease
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 the treatment of Restless Leg 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 and essentially complete. Bioavailability of ropinirole is approximately 50% (36 to 57%) and average peak concentrations (Cmax) of the drug are achieved at a median time of 1.5 hours post-dose. Wide inter-individual variability in the pharmacokinetic parameters has been seen but, overall, there is a proportional increase in the systemic exposure (Cmax and AUC) to the drug with an increase in dose, over the therapeutic dose range.

Distribution
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 about six hours (range 3.4-10.2 h) and an apparent oral clearance of 58.7 L/h (range 18.5-132 L/h). Plasma protein binding of the drug is low (10-40%).

Metabolism
The cytochrome P450 isoenzyme CYP1A2 is primarily responsible for the oxidative metabolism of ropinirole. Ropinirole is mainly excreted in the urine as metabolites. The major metabolite is at least 100 times less potent than ropinirole in animal models of dopaminergic function.

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

Paediatric population
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

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.

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 a high dose (50 mg/kg/day), and was probably associated with an increased exposure to light

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

Carcinogenicity: Two-year studies have been conducted in the mouse and rat at dosages up to 50 mg/kg. The mouse study did not reveal any carcinogenic effect. In the rat, the only drug-related lesions were Leydig cell hyperplasia/adenoma in the testis 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium Stearate

Film-coating
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Indigo Carmine (E132)
Iron Oxide Yellow (E172)

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

HDPE bottle: Do not store above 25°C. Keep the bottle tightly closed in order to protect from light and moisture.

6.5 Nature and contents of container

PCTFE/PVC/PVC/Aluminium foil blisters
In Blisters of 12, 14, 21, 28, 42, 63, 84, 105, 126, 147, 210 film-coated tablets

HDPE Bottles with a PP closure and tamper proof induction inner seal
84 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

Arrow Generics Limited
Unit 2, Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1130/19/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st May 2010

10 DATE OF REVISION OF THE TEXT

September 2011