Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ropinirole Actavis 4mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 4 mg ropinirole (as hydrochloride).

Excipient:
Ropinirole Actavis 4 mg film-coated tablet contains 173.440 mg lactose (as lactose monohydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Ropinirole Actavis 4mg film-coated tablet is round (9.5 mm in diameter), orange and biconvex embossed with R4 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of Parkinson's Disease:
- as monotherapy in early phase in order to delay levodopa therapy.
- in combination with levodopa in later stage of the disease when the effect of levodopa is decreased or varies and fluctuations are seen (“end of dose” or “on-off” fluctuations)

For 0.25, 0.5, 1, 2, 3, 4 mg strengths:
Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in dosages up to 4 mg daily (see section 5.1).

4.2 Posology and method of administration

Oral use.
Individual dose titration of ropinirole against efficacy and tolerability is recommended.

Adults

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

Treatment initiation: The initial dose is 0.25 mg ropinirole three times per day for one week. Then the dose is gradually increased by 0.25 mg three times per day in accordance to table 1 below:

Table 1 – Ropiniriole dose titration (Parkinson’s Disease)

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 mg to 1 mg ropinirole three times per day (1.5

to 3 mg/day) may be given.

A therapeutic response may be seen between 3 and 9 mg/day of ropinirole. If sufficient symptomatic control is not achieved, or maintained, the dose of ropinirole may be increased to 24 mg/day. Doses above 24 mg/day have not been investigated and this dose should not be exceeded.

If treatment is stopped for one or more days it should be considered to re-initiate the treatment by dose titration (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.

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

Idipopathic Resless Leg 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 ropinirole once daily (administered as above) for 2 days. If this dose is well tolerated the dose should be increased to 0.5 mg ropinirole 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 ropinirole once a day.
The dose may be increased to 1 mg ropinirole 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 ropinirole once a day. In some patients, to achieve optimal improvement, the dose may be increased gradually up to a maximum of 4 mg ropinirole 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 ropinirole once a day as shown in table 2. Doses above 4 mg once daily have not been investigated in Restless Legs Syndrome patients.

Table 2 – Ropiniriole dose titration (Restless Leg 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.

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

General information for all therapeutic indications

Children and adolescents

Ropinirole Actavis 4mg is not recommended for use in children and adolescents under 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).

Hepatic impairment

Ropinirole Actavis 4mg is contraindicated in patients with hepatic impairment (see section 4.3).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Severe renal impairment (creatinine clearance <30 ml/min).
Hepatic impairment.

4.4 Special warnings and precautions for use

In Parkinson's disease, ropinirole has been associated uncommonly with somnolence and episodes of sudden sleep onset during daily activities, in some cases without awareness or warning signs (see section 4.8). However, in Restless Legs Syndrome, this phenomenon is very rare. Nevertheless, all 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 psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks.

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.

Due to the risk of hypotension, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution and it is recommended to check blood pressure, particular at the start of treatment.

Impulse control disorders including pathological gambling and hypersexuality, and increased libido, have been reported in patients treated with dopamine agonists, including ropinirole, principally for Parkinsons's disease, Those disorders were reported especially at high doses and were generally reversible upon reduction of the dose or treatment discontinuation (see section 4.8).

Ropinirole Actavis 4mg 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 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.

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. 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 hormone replacement therapy is stopped or introduced during treatment with ropinirole.

No pharmacokinetic interaction has been seen between ropinirole and levodopa or domperidone that would necessitate dosage adjustment of either medicinal product.

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.

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.

Co-administration of ropinirol with antihypertensive and anti-arrhytmic agents has not been studied.
In study in patients with Parkinson’s disease receiving digoxine, no interaction was seen which would require dosage adjustment.

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 Actavis 4mg may have 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

Adverse drug reactions are listed below by system organ class and frequency. The frequencies are defined as: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/1/100), rare (≥1/10,000, <1/1000), very rare

(<1/10,000), not known (cannot be estimated from the available data).

Use of 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 24 mg/day at an excess incidence over placebo are described below as well as from post marketing data.

Table 3 – Adverse drug reactions in Parkinson's disease

Psychiatric disorders	
Common	Hallucinations Adjunct therapy: Confusion
Uncommon	Psychic reactions (other than hallucinations) including delirium, delusion, paranoia.
Not known	Pathological gambling, hypersexuality and increased libido, (see section 4.4)
Nervous system disorders	
Very common	Somnolence. Monotherapy: Syncope Adjunct therapy: Dyskinesia
Common	Dizziness (including vertigo)
Uncommon	Sudden sleep onset, marked somnolens during daytime. Ropinirole may cause somnolence and has (uncommonly) been associated with pronounced fatigue, during daytime and episodes where the patient suddenly falls asleep.)
Vascular disorder	
Uncommon	Postural hypotension, hypotension, which are rarely severe
Gastrointestinal disorders	
Very common	Nausea
Common	Heartburn Monotherapy: Abdominal pain, vomiting
Hepatobiliary disorders	
Not known	Hepatic reactions, particularly increased hepatic enzymes
General disorders and administration site conditions	
Common	Monotherapy: 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. Table 4 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.

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.

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

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 agonists, ATC code: N04BC04.

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

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.

Restless leg syndrome
Ropinirole Actavis 4mg 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 (10-40%), 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.

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

Elimination
Unchanged ropinirole and the metabolites are mainly excreted through the kidneys. The elimination half-life of ropinirole is 6 (3-10) 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.

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).

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
Pregelatinised maize starch
Magnesium stearate

Film-coating:
Polyvinyl alcohol
Titanium dioxide E 171
Macrogol 3350
Talc

Iron oxide yellow (E172), iron oxide red (E172), iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/Aclar/Aluminium blisters: **2 years**
Aluminium/Aluminium blisters: **2 years**

Tablet containers: **2 years**

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blisters: PVC/Aclar/Aluminium blisters; Aluminium/Aluminium blisters.
Tablet containers: Container made of HDPE with child- resistant screw cap made of HDPE and PP with aluminium foil.

Blister: 20, 21, 30, 50, 60, 84 and 100 film-coated tablets
Tablet container: 84 and 100 film-coated tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjördur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA 1380/4/6

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st November 2008

10 DATE OF REVISION OF THE TEXT

August 2012