Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Raponer 2mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 2 mg ropinirole (as hydrochloride).

Excipient:
Each 2 mg prolonged-release tablet contains 64.97 mg lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

Pink, mottled, oval tablet, 16.0 x 8.20 mm, with 2x debossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of Parkinson's disease under the following conditions:
- Initial treatment as monotherapy, in order to delay the introduction of levodopa.
- In combination with levodopa, over the course of the disease, when the effect of levodopa wears off or becomes inconsistent and fluctuations in the therapeutic effect occur ("end of dose" or "on-off" type fluctuations).

4.2 Posology and method of administration

Oral use.

Adults
Individual dose titration against efficacy and tolerability is recommended. Raponer prolonged-release tablets should be taken once a day, at a similar time each day. The prolonged-release tablets may be taken with or without food (see section 5.2).

Raponer prolonged-release tablets must be swallowed whole and must not be chewed, crushed or divided.

Initial titration
The starting dose of ropinirole prolonged-release tablets is 2 mg once daily for the first week; this should be increased to 4 mg once daily from the second week of treatment. A therapeutic response may be seen at a dose of 4 mg once daily of ropinirole prolonged-release tablets.

Patients who initiate treatment with a dose of 2 mg/day of ropinirole prolonged-release tablets and who experience side effects that they cannot tolerate, may benefit from switching to treatment with ropinirole film-coated (immediate release) tablets at a lower daily dose, divided into three equal doses.

Therapeutic regimen
Patients should be maintained on the lowest dose of ropinirole prolonged-release tablets that achieve symptomatic control.

If sufficient symptomatic control is not achieved or maintained at a dose of 4 mg once daily of ropinirole prolonged-

release tablets, the daily dose may be increased by 2 mg at weekly or longer intervals up to a dose of 8 mg once daily of ropinirole prolonged-release tablets.

If sufficient symptomatic control is still not achieved or maintained at a dose of 8 mg once daily of ropinirole prolonged-release tablets, the daily dose may be increased by 2 mg to 4 mg at two weekly or longer intervals. The maximum daily dose of ropinirole prolonged-release tablets is 24 mg.

It is recommended that patients are prescribed the minimum number of ropinirole prolonged-release tablets that are necessary to achieve the required dose by utilising the highest available strengths of ropinirole prolonged-release tablets.

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

When Raponer prolonged-release tablets are administered as adjunct therapy to levodopa, it may be possible to reduce gradually the levodopa dose, depending on the clinical response. In clinical trials, the levodopa dose was reduced gradually by approximately 30% in patients receiving ropinirol prolonged-release tablets concurrently.
In patients with advanced Parkinson's disease receiving ropinirole prolonged-release tablets in combination with L-dopa, dyskinesias can occur during the initial titration of ropinirole prolonged-release tablets. In clinical trials it was shown that a reduction of the L-dopa dose may ameliorate dyskinesia (see also 4.8 Undesirable effects).

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 daily dose over the period of one week.

Switching from ropinirole film-coated (immediate-release) tablets to Raponer prolonged-release tablets Patients may be switched overnight from ropinirole film-coated (immediate-release) tablets to Raponer prolonged-release tablets. The dose of Raponer prolonged-release tablets should be based on the total daily dose of ropinirole film-coated (immediate-release) tablets that the patient was taking. The table below shows the recommended dose of Raponer prolonged-release tablets for patients switching from ropinirole film-coated (immediate-release) tablets:

Switching from ropinirole film-coated (immediate-release) tablets to Raponer prolonged-release tablets

Ropinirole film-coated (immediate-release) tablets Total daily dose (mg)	**Raponer prolonged-release tablets** Total daily dose (mg)
0.75 – 2.25	2
3 – 4.5	4
6	6
7.5 – 9	8
12	12
15 – 18	16
21	20
24	24

After switching to Raponer prolonged-release tablets, the dose may be adjusted depending on the therapeutic response (see “Initial titration” and “Therapeutic regimen” above).

Children and adolescents
Raponer prolonged-release tablets are not recommended for use in children and adolescents below 18 years of age 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. In patients aged 75 years and above, slower titration during treatment initiation may be considered.

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.

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 2 mg once daily. 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).

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- 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. 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. A reduction of dosage or termination of therapy may be considered.

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

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. 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).

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.

Raponer prolonged-release tablets contain castor oil. May cause stomach upset and diarrhea

4.5 Interaction with other medicinal products and other forms of interaction

There is no pharmacokinetic interaction between ropinirole and levodopa or domperidone which would necessitate dosage adjustment 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 should be avoided.

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 film-coated (immediate-release) tablet dose of 2 mg, three times a day) in Parkinson's disease patients, revealed that ciprofloxacin increased the C_{max} and AUC of ropinirole by 60% and 84% respectively, with a potential risk of adverse events. Hence, in patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when medicinal products known to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study in patients with Parkinson's disease between ropinirole (with a ropinirole film-coated (immediate-release) tablet 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.

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

4.6 Fertility, 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.

No human fertility data are available.

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

Undesirable effects reported are listed below by system organ class and frequency. It is noted if these undesirable effects were reported in clinical trials as monotherapy or adjunct therapy to levodopa.

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).

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

Adverse drug reactions reported in Parkinson's disease clinical trials with ropinirole prolonged−release tablets at doses up to 24 mg/day

	In monotherapy	**In adjunct therapy**
Psychiatric disorders		
Common	Hallucinations	Hallucinations
Nervous system disorders		
Very common	Somnolence	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).
Common	Dizziness (including vertigo)	Somnolence, dizziness (including vertigo)
Vascular disorders		
Common		Postural hypotension, hypotension
Uncommon	Postural hypotension, hypotension	
Gastrointestinal disorders		
Very common	Nausea	
Common	Constipation	Nausea, constipation
General disorders and administrative site conditions		
Common	Oedema peripheral	Oedema peripheral

In addition to the above adverse drug reactions, the following events have been reported with ropinirole film-coated (immediate-release) tablets in patients with Parkinson's disease during clinical trials (at doses up to 24 mg/day) and/or from post-marketing reports.

	In monotherapy	**In adjunct therapy**
Immune system disorders		
Not known	Hypersensitivity reactions (including urticaria, angiooedema, rash, pruritus).	
Psychiatric disorders		
Common		Confusion
Uncommon	Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia.	Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia.
Not known	Impulse control disorders including pathological gambling and hypersexuality and increased libido, have been reported in post marketing reports (see section 4.4)	

Nervous system disorders		
Very common	Syncope	Somnolence
Uncommon	Sudden onset of sleep, excessive daytime somnolence	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.	
Vascular disorders		
Uncommon	Postural hypotension or hypotension is rarely severe	
Gastrointestinal disorders		
Very common		Nausea
Common	Vomiting, heartburn, abdominal pain	Heartburn
Hepatobiliary disorders		
Not known	Hepatic reactions, mainly increased liver enzymes	
General disorders and administrative site conditions		
Common	Leg oedema	

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: **D**opaminergic agents, dopamine agonist, 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
A 36-week, double-blind, three-period crossover study, in monotherapy, conducted in 161 patients with early phase Parkinson’s disease demonstrated that ropinirole prolonged-release tablets were noninferior to ropinirole film-coated (immediate-release) tablets on the primary endpoint, the treatment difference in change from baseline in the Unified Parkinson’s Disease Rating Scale (UPDRS) motor score (a 3-point non-inferiority margin on the UPDRS motor score was defined). The adjusted mean difference between ropinirole prolonged-release tablets and ropinirole film-coated (immediate-release) tablets at study endpoint was -0.7 points (95% CI: [-1.51, 0.10], p=0.0842).

Following the overnight switch to a similar dose of the alternative tablet formulation, there was no difference in the adverse event profile and less than 3% of patients required a dose adjustment (all dose adjustments were increases by

one dose level. No patients required a dose decrease).

A 24-week, double-blind, placebo-controlled, parallel group study of ropinirole prolonged-release tablets in patients with Parkinson's disease who were not optimally controlled on levodopa demonstrated a clinically relevant and statistically significant superiority over placebo on the primary endpoint, change from baseline in awake time "off" (adjusted mean treatment difference -1.7 hours (95% CI: [-2.34, -1.09], p<0.0001). This was supported by secondary efficacy parameters of change from baseline in total awake time "on" (+1.7 hours (95% CI: [1.06, 2.33], p<0.0001) and total awake time "on" without troublesome dyskinesias (+1.5 hours (95% CI: [0.85, 2.13], p<0.0001). Importantly, there was no indication of an increase from baseline in awake time "on" with troublesome dyskinesias, either from diary card data or from the UPDRS items.

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%). Following oral administration of ropinirole prolonged-release tablets plasma concentrations increase slowly, with a median time to C_{max} generally achieved between 6 and 10 hours.

In a steady-state study in 25 Parkinson's disease patients receiving 12 mg of ropinirole prolonged release tablets once daily, a high fat meal increased the systemic exposure to ropinirole as shown by an average 20% increase in AUC and an average 44% increase in C_{max}. T_{max} was delayed by 3.0 hours. However, these changes are unlikely to be clinically relevant (e.g. increased incidence of adverse events).

The systemic exposure to ropinirole is comparable for ropinirole prolonged-release tablets and ropinirole film-coated (immediate-release) tablets based on the same daily dose.

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).

Metabolism
Ropinirole is primarily cleared by CYP1A2 metabolism 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 about 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. Following steady-state administration of ropinirole prolonged-release tablets, the inter-individual variability for C_{max} was between 30% and 55% and for AUC was between 40% and 70%.

Renal Impairment
There was no change observed in the pharmacokinetics of ropinirole in Parkinson's disease patients with mild to

moderate renal impairment.

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).

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 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.

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.

Safety Pharmacology
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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Croscarmellose sodium
Maltodextrin
Lactose monohydrate
Hydrogenated castor oil
Colloidal anhydrous silica
Magnesium stearate

Pigment Blend
Iron oxide red (E172)
Iron oxide yellow (E172)
Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Pack sizes:
Packs of 21, 28, 30, 42, 56, 84 and 90 prolonged-release tablets in blisters (aluminium/aluminium)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/110/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 03rd August 2012

10 DATE OF REVISION OF THE TEXT