

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ropinirole Glenmark 5mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains ropinirole hydrochloride equivalent to 5.0 mg of ropinirole.

Ropinirole Glenmark 5 mg film-coated tablets:

Each film-coated tablet contains ropinirole hydrochloride equivalent to 5 mg of ropinirole

Excipient: 67.55 mg lactose (as lactose monohydrate and lactose anhydrous).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

5.0 mg Blue, circular, bevelled edged, biconvex film coated tablets with '259' debossed on one side and 'G' on the other 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.

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

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 of ropinirole. 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 Glenmark 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 Glenmark 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.

Children and adolescents

Ropinirole Glenmark 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 over 65 years of age. 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 30-50 ml/min) no change in the clearance of ropinirole was observed, indicating that no dosage adjustment is necessary.

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 three times a day. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose 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 listed in section 6.1.

Severe renal impairment (creatinine clearance <30ml/min) without regular haemodialysis.

Severe hepatic impairment.

4.4 Special warnings and precautions for use

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

particularly at the start of treatment, in patients with severe cardiovascular disease (in particular coronary insufficiency).

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.

Ropinirole should not be used to treat neuroleptic akathisia, taksikinesia (neuroleptic-induced compulsive tendency to walk), or secondary Restless Legs Syndrome (e.g. caused by renal failure, iron deficiency anaemia or pregnancy).

In patients with Parkinson's disease, ropinirole has been associated with somnolence and episodes of sudden sleep onset (see section 4.8). Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported uncommonly. Patients must be informed of this phenomenon and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered.

Patients with major psychiatric or psychotic disorders, or a history of these disorders, should only be treated with dopamine agonists if the potential benefits outweigh the risks.

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 ropinirole. Dose reduction/tapered discontinuation should be consistent if such symptoms develop.

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

This medicinal product also 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 L-dopa or domperidone (a medicinal product used to treat nausea and vomiting) that would necessitate dosage adjustment of either drug. Domperidone antagonises the dopaminergic actions of ropinirole peripherally and does not cross the blood-brain barrier. Hence its value as an anti-emetic in patients treated with centrally acting dopamine agonists.

Increased plasma concentrations of ropinirole have been observed in patients treated with high doses of oestrogens. In patients already receiving hormone replacement therapy (HRT), ropinirole treatment may be initiated in the normal manner. However, if HRT is stopped or introduced during treatment with ropinirole, dosage adjustment may be required, in accordance with clinical response.

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 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 (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.

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.

Breast feeding

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 also Section 4.4).

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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.

It is noted if these undesirable effects were reported in clinical trials as monotherapy or adjunct therapy to levodopa.

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 disordersUse in monotherapy studies:

Common: leg oedema.

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

The symptoms of ropinirole overdose are generally related to its dopaminergic activity. These symptoms may be alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Dopaminergic agents, dopamine agonists, ATC code: N04BC04.

Mechanism of action

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.

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 doses up to 24 mg/day has not been conducted.

5.2 Pharmacokinetic properties

Absorption

The bioavailability of ropinirole is about 50% (36% to 57%). Oral absorption of ropinirole film-coated (immediate release) tablets is rapid with peak concentrations achieved at a median time of 1.5 hours post dose. The increase in systemic exposure (C_{max} and AUC) to ropinirole is approximately proportional over the therapeutic dose range. 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).

Metabolism

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. 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. Dosage 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.

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

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 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/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.

Safety Pharmacology

In vitro studies have shown that ropinirole inhibits hERG-mediated currents. The IC₅₀ 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

Tablet Cores

Lactose, Anhydrous
Lactose Monohydrate
Cellulose, microcrystalline (E460)
Citric acid, anhydrous (E330)
Croscarmellose sodium (E468)
Magnesium Stearate (E572)

Film Coating

5.0 mg	Hypromellose (E464), Titanium dioxide (E171), Macrogol 400, Talc, Indigo carmine aluminium lake (E132), Brilliant blue FCF Aluminium lake (E133)
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6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30 °C.

Blisters

Store in the original package in order to protect from moisture.

Bottles

Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Blisters:

Plain Aluminium/Aluminium blisters; White, opaque Triplex(PVC/PE/Aclar)/Aluminium blisters.

Bottles:

White opaque HDPE bottle with polypropylene child-resistant closure

Pack Sizes

Blister: 21 and 84

Bottle: 84

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Ltd
Laxmi House
2 B Draycott Avenue
Kenton
Middlesex HA3 0BU
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1462/3/5

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 2010

10 DATE OF REVISION OF THE TEXT

July 2013