

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ropinirole 5mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One Ropinirole 5 mg film-coated tablet contains 5 mg of ropinirole (as hydrochloride).

Excipient with known effect:  
54.250 mg lactose/film-coated tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Blue coloured, capsule shaped biconvex, film-coated tablets with break-line on both sides.  
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the 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.

Individual dose titration is recommended, based on efficacy and tolerability.

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

Treatment initiation

The initial dose should be 0.25 mg Ropinirole three times daily for one week. Thereafter, the dose can be increased upwards in 0.25 mg increments three times daily 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*

Following initial dose titration, the Ropinirole dose may be increased by weekly increments of 0.5 to 1 mg three times daily (1.5 to 3 mg/day)

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 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 L-dopa, the concurrent dose of L-dopa 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 L-dopa, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the Ldopa dose may ameliorate dyskinesia (see also section 4.8).

When switching treatment from another dopamine agonist to Ropinirole, the manufacturer's guidelines on discontinuation should be followed prior to initiating Ropinirole therapy.

As with other dopamine agonists, Ropinirole should be tapered off gradually, by reducing the number of daily doses over a 1-week period.

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

*Children and adolescents*

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

*Elderly patients*

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 of 30-50 ml/min), no change in ropinirole clearance 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 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 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 < 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. There have been (uncommon) reports of sudden sleep onset during daily activities. In some cases, such episodes occurred without any warning signs or awareness by the patient. 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 dose reduction or discontinuation of therapy should 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 considered if such symptoms develop.

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

This 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

No pharmacokinetic interaction between ropinirole and L-dopa 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 with ropinirole should be avoided.

Elevated ropinirole plasma levels have been observed in patients receiving high-doses of oestrogen. 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 Ropinirole therapy, adjustment of the Ropinirole dose may be required, depending on the response to treatment.

Ropinirole is mainly metabolised by the cytochrome P450 isoenzyme CYP1A2. A pharmacokinetic study on patients with Parkinson's disease (who were given a 2 mg ropinirole dose three times a day.) revealed that, following concomitant administration of ciprofloxacin,  $C_{max}$  and AUC values for ropinirole increased by 60% and 84% respectively. There is hence a potential risk of adverse effects. Therefore, in patients already receiving Ropinirole, the Ropinirole dose may have to be reduced, if active substances that inhibit CYP1A2 (such as ciprofloxacin, enoxacin or fluvoxamine) are concomitantly administered. This also applies when such medicinal products are being withdrawn.

A pharmacokinetic interaction study on Parkinson patients between ropinirole (at a dose of 2 mg three times a day.) and theophylline (a CYP1A2 substrate) – revealed no changes in the pharmacokinetics of either ropinirole or theophylline.

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

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 of sudden sleep onset and somnolence have resolved (see also section 4.4).

4.8 Undesirable effects

Undesirable effects 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: frequency cannot be estimated from the available.

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

		<u>In monotherapy studies</u>	<u>In adjunct therapy studies</u>
Immune system disorders			
Not known	Hypersensitivity reactions including urticarial, angioedema, rash, pruritus		
Psychiatric disorders			
Common	Hallucinations		Confusion
Uncommon	Psychotic reactions (other hallucinations) including delirium, delusion, paranoia.  Impulse control disorders including pathological gambling and hypersexuality, and increased libido, have been reported in postmarketing reports (see section 4.4).		
Nervous system disorders			
Very common	Somnolence	Syncope	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)		
Uncommon	Excessive daytime somnolence, sudden onset of sleep  Ropinirole is associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes.		
Vascular disorders			
Uncommon	Hypotension, postural hypotension  Hypotension or postural hypotension is rarely severe		
Gastrointestinal disorders			
Very common	Nausea		
Common	Heartburn	Vomiting, abdominal pain	
Hepatobiliary disorders			
Not known	Hepatic reactions, mainly increased liver enzymes		
General disorders and administration site conditions			
Common		Leg oedema	

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’)

4.9 Overdose

It is anticipated that the symptoms of ropinirole overdose will be related to the dopaminergic activity. These symptoms can be alleviated by appropriate treatment with dopamine antagonists, such as a neuroleptic or metoclopramide.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: dopaminergic agents, dopamine agonist.

ATC code: N04BC04.

#### *Mechanism of action*

Ropinirole is a non-ergoline D<sub>2</sub>/D<sub>3</sub> dopamine agonist which stimulates striatal dopamine receptors.

Ropinirole alleviates the symptoms of dopamine deficiency, which characterises Parkinson's disease, by stimulating dopamine receptors in the striatum.

Due to its action in the hypothalamus and pituitary, ropinirole inhibits prolactin secretion.

#### 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 4mg/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

Oral absorption of ropinirole is rapid. Bioavailability of ropinirole is approximately 50 % (36 to 57 %) and average peak concentrations of ropinirole are 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<sub>max</sub> by 2.6 hours and an average 25% decrease in C<sub>max</sub>.

#### Distribution

The binding of ropinirole to plasma proteins 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. The increase in systemic exposure (C<sub>max</sub> 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.

#### 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 18mg/day in these patients with Parkinson's disease (see section 4.2).

### 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 a high 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*

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.

#### Safety Pharmacology

*In vitro* studies have shown that ropinirole inhibits hERG-mediated currents. The IC<sub>50</sub> 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:

Cellulose, Microcrystalline  
Lactose Monohydrate  
Croscarmellose Sodium  
Hypromellose  
Magnesium stearate

Film Coat

Hypromellose  
Titanium Dioxide (E171)  
Macrogol 400  
Polysorbate 80  
Indigo Carmine Aluminium (E132)

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

3 years.

## **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions

## **6.5 Nature and contents of container**

HDPE multidose container with child resistant closure (PP)

Silica gel canister

Ropinirol 5 mg: 21, 28, 84 and 126 film-coated tablets

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

No special requirements for disposal.

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

## **7 MARKETING AUTHORISATION HOLDER**

McDermott Laboratories  
t/a Gerard Laboratories  
Baldoyle Industrial Estate  
Grange Road  
Dublin 13

## **8 MARKETING AUTHORISATION NUMBER**

PA 577/94/4

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 1st August 2008

Date of last renewal: 8th March 2012

## **10 DATE OF REVISION OF THE TEXT**

June 2013