SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ropinirole 5 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Ropinirole 5 mg Film-Coated Tablets are blue, round (10.5mm in diameter), biconvex, and embossed with R5 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of idiopathic Parkinson's Disease:

Ropinirole may be used alone (without levodopa) in the treatment of idiopathic Parkinson's disease.

Addition of ropinirole to levodopa may be used to control "on-off" fluctuations and permit a reduction in the total daily dose of levodopa.

4.2 Posology and method of administration

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

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. A guide for the titration regimen for the first four weeks of treatment is given in the table below:

	Week			
	1	**2**	**3**	**4**
Unit dose (mg)	0.25	0.5	0.75	1.0
Unit dose presentation (mg)	0.25	0.5	0.25, 0.5	1.0
Total daily dose (mg)	0.75	1.5	2.25	3.0

Therapeutic regimen: After the initial titration, weekly increments of up to 3 mg/day may be given. Ropinirole is usually given in divided doses three times per day.

A therapeutic response may be seen between 3 and 9 mg/day, although adjunct therapy patients may require higher doses. 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.

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 L-dopa, the concurrent dose of L-dopa may be reduced gradually by around 20% in total. 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 L-dopa dose may ameliorate dyskinesia (see also section 4.8).

When switching treatment from another dopamine agonist to ropinirole, the manufacturer’s guidance on discontinuation should be followed before initiating ropinirole.

Ropinirole should be discontinued gradually by reducing the number of daily doses over the period of one week.

Treatment discontinuation
Abrupt discontinuation of dopaminergic therapy can lead to the development of a neuroleptic malignant syndrome (see section 4.4).

In parkinsonian 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.

The use of ropinirole in patients with severe renal (creatinine clearance <30 ml/min) or hepatic impairment has not been studied. Administration of ropinirole to such patients is not recommended.

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.

Children: Parkinson's disease does not occur in children. The use of ropinirole in this population has therefore not been studied and it should not be given to children.

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 (see section 4.4).

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.

Hepatic impairment.

4.4 Special warnings and precautions for use

Due to the pharmacological action of ropinirole, patients with severe cardiovascular disease should be treated with caution.

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).

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.

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. Furthermore, a reduction of dosage or termination of therapy may be considered.

Ropinirole Film-Coated Tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Neuroleptic malignant syndrome
Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy. Therefore it is recommended to taper treatment (see section 4.2).

Dopamine agonist withdrawal syndrome (DAWS)
DAWS has been reported with dopamine agonists, including ropinirole (see section 4.8). To discontinue treatment in patients with Parkinson's disease, ropinirole should be tapered off (see section 4.2). Limited data suggests that patients with impulse control disorders and those receiving high daily dose and/or high cumulative doses of dopamine agonists may be at higher risk for developing DAWS. Withdrawal symptoms may include apathy, anxiety, depression, fatigue, sweating and pain and do not respond to levodopa. Prior to tapering off and discontinuing ropinirole, patients should be informed about potential withdrawal symptoms. Patients should be closely monitored during tapering and discontinuation. In case of severe and/or persistent withdrawal symptoms, temporary re-administration of ropinirole at the lowest effective dose may be considered.

Hallucinations
Hallucinations are known as a side effect of treatment with dopamine agonists and levodopa. Patients should be informed that hallucinations can occur.

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 medicinal products with ropinirole should be avoided.

No pharmacokinetic interaction has been seen between ropinirole and L-dopa or domperidone which would necessitate dosage adjustment of either drug. 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 of Parkinsonian patients receiving concurrent digoxin, no interaction was seen which would require dosage adjustment.
It has been established from in vitro experiments that ropinirole is metabolised by the cytochrome P450 enzyme CYP1A2. There is, therefore, the potential for an interaction between ropinirole and substrates (such as theophylline) or inhibitors (such as ciprofloxacin, fluvoxamine and cimetidine) of this enzyme. In patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when these drugs are introduced or withdrawn.

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.

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.

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

In patients receiving the combination of vitamin K antagonists and ropinirole, cases of unbalanced INR have been reported. Increased clinical and biological surveillance (INR) is warranted.

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-related material was shown to transfer into the milk of lactating rats. It is unknown whether ropinirole and its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded.

Ropinirole should not be used in nursing mothers as it may inhibit lactation.

Fertility
There are no data on the effects of ropinirole on human fertility. In female fertility studies in rats, effects were seen on implantation but no effects were seen on male fertility (see Section 5.3).

4.7 Effects on 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 drug reactions are listed below by system organ class and frequency. Frequencies are defined as: Very Common (> 1/10), Common (> 1/100, < 1/10), Uncommon (> 1/1000, < 1/100), Rare (> 1/10,000, < 1/1000), Very Rare (<1/10,000) or not known (frequency cannot be estimated from the data) including isolated reports.

Common and uncommon events 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 events were generally determined from post-marketing data and refer to reporting rate rather than the true frequency.

The most commonly reported undesirable effects are nausea, somnolence, dyskinesia and syncope.

Adverse drug reactions reported from patients taking ropinirole

Immune system disorders	
Very Rare:	Hypersensitivity reactions (including urticaria, angioedema, rash, pruritis)[3]
Psychiatric Disorders	
Common:	Confusion[1], Hallucinations
Uncommon:	Psychotic reactions (other than hallucinations) including delusion, and paranoia, delirium.
Not known	Dopamine dysregulation syndrome
Nervous System Disorders	
Very Common:	Somnolence[2], Dyskinesia[1*]
Common:	Dizziness (including vertigo)[1,2], syncope[2]
Uncommon:	Extreme somnolence[3], Sudden onset of sleep[3]
Vascular Disorders	
Common:	Hypotension, Postural hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Hiccups[3]
Gastrointestinal Disorders	
Very Common:	Nausea
Common:	Abdominal pain[2], Vomiting[2], Dyspepsia[2]
Reproductive system and breast disorders	
Not known:	Spontaneous penile erection[3]
General Disorders and Administration Site Conditions	
Common:	Oedema peripheral (including leg oedema[2])
Hepatobiliary Disorders	
Very Rare:	Hepatic enzymes increased[3]

1 Adjunct therapy studies
2 Monotherapy studies
3 Post-marketing data (see Section 4.4)

* 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 L-dopa dose may ameliorate dyskinesia (see also section 4.2)

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').

General Disorders and Administration Site Conditions
Not known: Dopamine agonist withdrawal syndrome including apathy, anxiety, depression, fatigue, sweating and pain.

Non-motor adverse effects may occur when tapering or discontinuing dopamine agonists including ropinirole (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: *Dopamine agonist* ATC code: *N04BC04*

Mechanism of action

Ropinirole is a non-ergoline dopamine agonist.

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.

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. 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).

Biotransformation
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/non-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 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
In fertility studies in female rats, effects were seen on implantation due to the prolactin-lowering effect of ropinirole. It should be noted that prolactin is not essential for implantation in humans.

Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg/day (mean AUC in rats approximately 15 times the highest AUC at the Maximum Recommended Human Dose (MRHD)), increased foetal death at 90 mg/kg/day (approximately 25 times the highest AUC at the MRHD) and digit malformations at 150 mg/kg/day (approximately 40 times the highest AUC at the MRHD).

There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 30 times the maximum AUC at the MRHD) and no indication of an effect during organogenesis in the rabbit when given alone at 20 mg/kg (60 times the mean human C_{max} at the MRHD). However, ropinirole at 10 mg/kg (30 times the mean human C_{max} at the MRHD) administered to rabbits in combination with oral L-dopa produced a higher incidence and severity of digit malformations than L-dopa alone.

Safety Pharmacology
In vitro studies have shown that ropinirole inhibits hERG-mediated currents. The IC_{50} 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:

Lactose monohydrate

Microcrystalline cellulose

Pregelatinised starch

Magnesium stearate

Film coating:

Opadry II 85F20521 (Polyvinyl alcohol, Titanium dioxide, Macrogol 3350, Talc, Indigo carmine aluminium lake)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25°C

Store in the original package in order to protect from light

HDPE tablet containers only:

Keep the container tightly closed in order to protect from moisture

6.5 Nature and contents of container

Aluminium/Aluminium blister or induction sealed HDPE tablet containers of 2, 5, 7, 10, 12, 14, 20, 21, 28, 30, 50, 56, 60, 84, 100, 126 and 210 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
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8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0649

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