

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ropinirole 0.5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.50 mg Ropinirole (as hydrochloride).

Excipient (s) with known effect: Each 0.50 mg film-coated tablet contains 48.43 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Round biconvex, plain on both sides, yellow.

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).

Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (see section 5.1).

4.2 Posology and method of administration

Oral use.

Parkinson's disease

Adults

Individual dose titration against efficacy and tolerability is recommended.

Ropinirole tablets 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 tablet 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 tablets 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.

In Restless Legs Syndrome

Adults

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 once daily (administered as above) for 2 days. If this dose is well tolerated the dose should be increased to 0.5 mg 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 once a day.

The dose may be increased to 1 mg 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 once a day. In some patients, to achieve optimal improvement, the dose may be increased gradually up to a maximum of 4 mg 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 once a day as shown in table 1.

Doses above 4 mg once daily have not been investigated in Restless Legs Syndrome patients.

Table 1 Dose titration

| | | | | | | |
|----------------------|---|-----|---|-----|----|----|
| 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 efficacy of ropinirole treatment has not been shown beyond 12 weeks (see Section 5.1). Patient response should be evaluated after 12 weeks treatment and the need for treatment continuation reconsidered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration as noted above.

Children and adolescents

Ropinirole tablet is not recommended for use in children 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.

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 initial dose of Ropinirole tablets should be 0.25 mg three times a day. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose of Ropinirole tablets 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 ropinirole 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

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 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 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, tasikinesia (neuroleptic-induced compulsive tendency to walk) or secondary Restless Legs Syndrome (e.g. caused by renal failure, iron deficiency anaemia or pregnancy).

Paradoxical worsening of Restless Legs Syndrome symptoms described as augmentation (either earlier onset, increased intensity, or spread of symptoms to previously unaffected limbs), or early morning rebound (reoccurrence of symptoms in the early morning hours) have been observed during treatment with ropinirole. If this occurs, the adequacy of ropinirole treatment should be reviewed and dosage adjustment or discontinuation of treatment may be considered (see section 4.8).

Ropinirole should be administered with care to patients with moderate liver failure. The onset of adverse 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

In a study in parkinsonian patients receiving concurrent digoxin, no interaction was seen which would require dosage adjustment.

There is no pharmacokinetic interaction between ropinirole and levodopa or domperidone (a medicinal product used to treat nausea and vomiting) which would necessitate dosage adjustment of these medicinal products. 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.

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 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.

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 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.

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 ($\geq 1/10$); 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).

Use of ropinirole in Parkinson's disease

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

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.

Use of ropinirole in Restless Legs Syndrome

In Restless Legs Syndrome clinical trials the most common adverse drug reaction is 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 2 lists the adverse drug reactions reported for ropinirole in the 12-week clinical trials at $\geq 1.0\%$ above the placebo rate or those reported uncommonly but known to be associated with ropinirole.

Table 2 Adverse drug reactions reported in 12-week Restless Legs Syndrome clinical trials (ropinirole n=309, placebo n=307)

| | |
|---|---|
| <i>Psychiatric disorders</i> | |
| Common | Nervousness |
| Uncommon | Confusion |
| <i>Nervous system disorders</i> | |
| Common | Syncope, somnolence, dizziness (including vertigo) |
| <i>Vascular disorders</i> | |
| Uncommon | Postural hypotension, hypotension |
| <i>Gastrointestinal disorders</i> | |
| Very common | Vomiting, nausea |
| Common | Abdominal pain |
| <i>General disorders and administration site conditions</i> | |
| Common | Fatigue |

Table 3 Adverse drug reactions reported in other Restless Legs Syndrome clinical trials

| | |
|---------------------------------|---|
| <i>Psychiatric Disorders</i> | |
| Uncommon | Hallucinations |
| <i>Nervous system disorders</i> | |
| Common | Augmentation, Early morning rebound (see section 4.4) |

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 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.

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

Parkinson's disease

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.

Restless Legs Syndrome

Clinical efficacy

Ropinirole tablets 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.

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; $p < 0.0001$).

Long term efficacy was evaluated in a randomised, double-blind, placebo-controlled clinical trial of 26 weeks. Overall results were difficult to interpret due to significant centre treatment interaction and the high proportion of missing data. No maintenance of efficacy at 26 weeks compared to placebo could be shown.

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 tablets once daily showed a maximum increase of the QT interval duration at the 1mg 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.

In clinical studies most patients were of Caucasian origin.

5.2 Pharmacokinetic properties

Absorption

Bioavailability of ropinirole is approximately 50% (36-57%). Oral absorption of ropinirole tablets is rapid with peak concentrations of ropinirole 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_{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. 7l/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_{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.

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).

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

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 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

Lactose monohydrate
Cellulose microcrystalline
Croscarmellose sodium
Magnesium stearate

Film coating

OPADRY yellow (03B82930): hypromellose, titanium dioxide (E171), macrogol 400, iron oxide yellow (E172), indigo carmine aluminium lake (E132), iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Ropinirole Tablets are packed in Alu-Alu blisters
Each blister strip contains 7 tablets.
Pack-sizes of 21 or 42 tablets

Ropinirole Tablets are also packed in HDPE bottles with PPCTC closure. Each bottle contains 21 or 84 tablets and a silica gel canister.

Not all pack sizes or pack type may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House
319 Pinner Road
North Harrow
Middlesex HA1 4HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1390/052/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 24th February 2012

10 DATE OF REVISION OF THE TEXT

October 2013