SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ropinirole 2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.28 mg ropinirole hydrochloride, equivalent to 2 mg ropinirole

Excipient(s) with known effect

Each film-coated tablet contains 103.19 mg lactose and 0.1575 mg lecithin (soya) (E322)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, round slightly arched film-coated tablets, debossed "R 2" on one side and plain on the other.

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 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

Posology

Parkinson's disease

Adults
Individual dose titration of ropinirole 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 ropinirole 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 ropinirole three times daily (1.5 to 3 mg/day) 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 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 as adjunct therapy. In patients with advanced Parkinson's disease receiving ropinirole in combination with levodopa, dyskinesia 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 also 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 (see section 4.4).

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

Restless Legs Syndrome

Adults
Individual dose titration against efficacy and tolerability is recommended. 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 the following table.

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

Dose titration

Week	2	3	4	5*	6*	7*
Dose (mg)/once daily	1.0	1.5	2.0	2.5	3.0	4.0

* 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.

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 (see section 4.4).

General information for all therapeutic indications

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.

Parkinson's disease
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.

Restless Legs Syndrome
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 once daily. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose of ropinirole is 3 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.

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.

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

Method of administration
Oral use.

4.3 Contraindications

- Hypersensitivity to the active substance, soya, peanut 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 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).

Augmentation (worsening of Restless Legs Syndrome)
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).

Somnolence and episodes of sudden sleep onset
In Parkinson's disease, ropinirole has been associated uncommonly with somnolence and episodes of sudden sleep onset during daily activities, in some cases without awareness or warning signs (see section 4.8). However, in Restless Legs Syndrome, this phenomenon is very rare. Nevertheless 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. A reduction of dosage or termination of therapy may be considered.

Psychiatric or psychotic disorders
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.

Mania
Patients should be regularly monitored for the development of mania. Patients and carers should be made aware that symptoms of mania can occur with or without the symptoms of impulse control disorders in patients treated with ropinirole. Dose reduction/tapered discontinuation should be considered if such symptoms develop

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).

Hypotension
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).

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.

Excipients

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

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, 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 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.

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. Ropinirole concentrations may gradually increase during pregnancy (see section 5.2).

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-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

Ropinirole has major influence on the ability to drive and use machines. Patients being treated with ropinirole and presenting with hallucinations, 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

Undesirable effects reported 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 data).

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

Use of ropinirole in Parkinson's disease
Undesirable effects 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.

Table below shows adverse drug reactions in Parkinson's disease

System Organ Class	Frequency			
	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Not known
Immune system disorders				Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus)
Psychiatric disorders		Hallucinations *Adjunct therapy*: Confusion	Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia	Aggression[1], dopamine dysregulation syndrome, mania (see section 4.4), impulse control disorders[2] (see section 4.4)
Nervous system disorders	Somnolence *Monotherapy*: Syncope *Adjunct therapy*: Dyskinesia[3]	Dizziness (including vertigo)	Sudden onset of sleep, excessive daytime somnolence[4]	
Vascular disorders			Postural hypotension, hypotension[5]	
Respiratory, thoracic and mediastinal disorders			Hiccups	
Gastro-intestinal disorders	Nausea	Heartburn *Monotherapy*: Vomiting, abdominal pain		
Hepatobiliary disorders				Hepatic reactions, mainly increased liver enzymes

Reproductive system and breast disorders				Spontaneous penile erection
General disorders and administration site conditions		*Monotherapy*: Oedema peripheral (including leg oedema)		Dopamine agonist withdrawal syndrome (including apathy, anxiety, depression, fatigue, sweating and pain)[6]

[1] Aggression has been associated with psychotic reactions as well as compulsive symptoms.

[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).

[3] In patients with advanced Parkinson's disease, dyskinesia 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).

[4] Ropinirole is associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes.

[5] Postural hypotension or hypotension is rarely severe.

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

Use of ropinirole in Restless Legs Syndrome

In Restless Legs Syndrome clinical trials the most common adverse drug reaction was 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 below lists the adverse drug reactions reported for ropinirole in the 12 week clinical trials at ≥1.0% above the placebo rate or those reported uncommonly but known to be associated with ropinirole

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

System Organ Class	Frequency		
	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Nervous system disorders		Syncope, somnolence, dizziness (including vertigo)	
Gastro-intestinal disorders	Vomiting,nausea	Abdominal pain	
Vascular disorders			Postural hypotension, hypotension
General disorders and administration site conditions		Fatigue	
Psychiatric disorders		Nervousness	Confusion

Adverse drug reactions reported in other Restless Legs Syndrome clinical trials

System Organ Class	Frequency	
	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Psychiatric Disorders		Hallucinations
Nervous system disorders	Augmentation, Early morning rebound (see section 4.4)	

Post marketing reports

System Organ Class	Frequency		
	Uncommon (≥1/1,000 to <1/100)	Very rare (<1/10,000)	Not known
Immune system disorders			Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus).
Psychiatric disorders			Psychotic reactions (other than hallucinations) including delirium, delusion and paranoia, aggression[1], dopamine dysregulation syndrome, mania (see section 4.4), impulse control disorders[2] (see section 4.4)
Nervous system disorders		Excessive daytime somnolence, sudden sleep onset episodes	
Vascular disorders	Postural hypotension or hypotension[3]		
Respiratory, thoracic and mediastinal disorders	Hiccups		
Hepatobiliary disorders		Hepatic reactions, mainly increase of liver enzymes	
Reproductive system and breast disorders			Spontaneous penile erection
General disorders and administration site conditions			Dopamine agonist withdrawal syndrome (including apathy, anxiety, depression, fatigue, sweating and pain)[4]

1. Aggression has been associated with psychotic reactions as well as compulsive symptoms.
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).
3. Postural hypotension or hypotension is rarely severe.
4. Non-motor adverse effects may occur when tapering or discontinuing dopamine agonists including ropinirole (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.

Lecithin (soya) may cause very rarely allergic reactions.

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 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 agonist.
ATC code: N04BC04

Mechanism of action
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.

Clinical efficacy

Restless Legs Syndrome
Ropinirole 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.

In clinical studies most patients were of Caucasian origin.

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%). Oral absorption of ropinirole film-coated (immediate-release) 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 Tmax 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

Elderly
Oral clearance of ropinirole is reduced by approximately 15% in elderly patients (65 years or above) compared to younger patients. Dosing 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 and 18 mg/day in these patients with Parkinson's disease (see section 4.2).

Paediatric population examined for Restless Legs Syndrome
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")

Pregnancy
Physiological changes in pregnancy (including decreased CYP1A2 activity) are predicted to gradually lead to an increased maternal systemic exposure of ropinirole (see section 4.6).

5.3 Preclinical safety data

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 twice the highest AUC at the Maximum Recommended Human Dose (MRHD) for Parkinson's disease and 15 times the highest AUC at the MRHD for Restless Legs Syndrome), increased foetal death at 90 mg/kg/day (approximately 3 times the highest AUC at the MRHD for Parkinson's disease and 25 times the highest AUC at the MRHD for Restless Legs Syndrome) and digit malformations at 150 mg/kg/day (approximately 5 times the highest AUC at the MRHD for Parkinson's disease and 40 times the highest AUC at the MRHD for Restless Legs Syndrome). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 4 times the highest AUC at the MRHD for Parkinson's disease and 30 times the highest AUC at the MRHD for Restless Legs Syndrome) and no indication of an effect during organogenesis in the rabbit when given alone at 20 mg/kg (9.5 times the mean human C_{max} at the MRHD). However, ropinirole at 10 mg/kg (4.8 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.

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.
Parkinson's disease: 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).
Restless Legs Syndrome: 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
Hydroxypropylcellulose
Croscarmellose sodium
Magnesium stearate

Tablet coating (Opadry II 85G34363)
Poly(vinyl alcohol) – partially hydrolyzed
Titanium dioxide (E171)
Macrogol 3350
Talc
Lecithin (soya) (E322)
Carmine (E120)
Iron oxide yellow (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above 30ºC. Store in the original container.

6.5 Nature and contents of container

OPA/Alu/PVC – aluminium blisters. The pack sizes available are:

15, 21, 28, 30, 60, 84, 90, 100 and 50 unit dose blisters (hospital pack).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited,
Ridings Point,
Whistler Drive,
Castleford,
WF10 5HX,
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1195

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