# 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 mg of ropinirole (as hydrochloride).

Excipient with known effect:
Each film-coated tablet contains 54.25 mg lactose.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet

Ropinirole 2 mg: Light pink, 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)

- for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (see section 5.1)

## 4.2 Posology and method of administration

Oral use.

Adults
Individual dose titration against efficacy and tolerability is recommended.

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

*Treatment initiation*
The initial dose of ropinirole should be 0.25 mg three times daily for one week. Thereafter, the dose of ropinirole can be increased 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*
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 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, 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 holders guidance on discontinuation should be followed before initiating ropinirole therapy.

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).

Restless Legs Syndrome
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 0.25mg 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 carried out as above.

General information for the indications Parkinson’s disease and Restless Legs Syndrome

*Children and adolescents*

Ropinirole is not recommended for the use in children and adolescents below 18 years of age 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 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.

The use of ropinirole in patients with severe renal impairment (creatinine clearance less than 30 ml/min) without regular haemodialysis has not been studied.

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).

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).

## 4.3 Contraindications

- Hypersensitivity to ropinirole or to any of the excipients.
- Severe renal failure (creatinine clearance < 30 ml/min) and hepatic impairment.

## 4.4 Special warnings and precautions for use

**Somnolence and episodes of sudden sleep onset**
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 onset sleep 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 the treatment, in patients with severe cardiovascular disease (in particular coronary insufficiency).

**Neuroleptic akathisia, tasikinesia, secondary Restless Legs Syndrome**
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).

During treatment with ropinirole, paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed. If this occurs, treatment should be reviewed and dosage adjustment or discontinuation of treatment may be considered.

**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
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per 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 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 r ropinirole increased by 60% and 84% respectively,with a potential risk of adverse events. Hence, in patients already receiving ropinirole, the dose of ropinirole may have to be adjusted when medicinal products known to inhibit CYP1A2 (such as 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 CYP1A2

substrate) – 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

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 section 4.4).

## 4.8 Undesirable effect

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 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 2 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.

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

| | |
|---|---|
| **Psychiatric disorders** | |
| Common | Nervousness |
| Uncommon | Confusion |
| Not known | Dopamine dysregulation syndrome |
| **Nervous system disorders** | |
| Common | Syncope, somnolence, dizziness (including vertigo) |
| **Vascular disorders** | |
| Uncommon | Postural hypotension, hypotension |
| **Gastrointestinal disorders** | |
| Very common | Vomiting, nausea |
| Common | Abdominal pain |
| **General disorders and administration site conditions** | |
| Common | Fatigue |

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

| | |
|---|---|
| **Psychiatric disorders** | |
| Uncommon | Hallucinations |
| Not known | Dopamine dysregulation syndrome |
| **Nervous system disorders** | |
| 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.

Hallucinations were reported uncommonly in the open label long-term studies.

Paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed during treatment with ropinirole.

Use of ropinirole in Parkinson's disease

Ropinirole is also indicated for the treatment of Parkinson's disease. 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 (≥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 (cannot be estimated from the available data).

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 and paranoia.
Not known: aggression*, dopamine dysregulation syndrome, mania (see section 4.4.), impulse control disorders** (see section 4.4.).

* Aggression has been associated with psychotic reactions as well as compulsive symptoms.
** 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.).

*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.

Respiratory, thoracic and mediastinal disorders
Uncommon: hiccups

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.

Reproductive system and breast disorders
Not known: spontaneous penile erection

General disorders
*Use in monotherapy studies:*
Common: Oedema peripheral (including leg oedema).
Not known: Dopamine agonist withdrawal syndrome (including apathy, anxiety, depression, fatigue, sweating and pain).

**Dopamine agonist withdrawal syndrome**
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 at: www.mhra.gov.uk/yellowcard.

## 4.9 Overdose

The symptoms of ropinirole overdose are related to its dopaminergic activity.

These symptoms can be alleviated by appropriate treatment with dopamine antagonists, such as neuroleptics or metoclopramide.

## 5.1 Pharmacodynamic properties

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

*Mechanism of action*
Ropinirole is a non-ergoline $D_2/D_3$ dopamine agonist which stimulates striatal dopamine receptors.

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

Ropinirole acts in the hypothalamus and pituitary, to inhibit the secretion of prolactin.

Study of the effect of ropinirole on cardiac repolarisation
A thorough QT study conducted in male and female healthy volunteers who received doses of 0.5, 1, 2 and 4 mg of ropinirole film-coated (immediate release) tablets once daily showed a maximum increase of the QT interval duration at the 1 mg dose of 3.46 milliseconds (point estimate) as compared to placebo. The upper bound of the one sided 95% confidence interval for the largest mean effect was less than 7.5 milliseconds. The effect of ropinirole at higher doses has not been systematically evaluated.

The available clinical data from a thorough QT study do not indicate a risk of QT prolongation at doses of ropinirole up to 4 mg/day. A risk of QT prolongation cannot be excluded as a thorough QT study at doses up to 24 mg/day has not been conducted.

*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.

## 5.2 Pharmacokinetic properties

Absorption
Oral absorption of ropinirole is rapid. Bioavailability of ropinirole is approximately 50 % (36 to 57 %). Oral absorption of ropinirole film-coated (immediate release) tablets is rapid with 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 $T_{max}$ by 2.6 hours and an average 25% decrease in $C_{max}$.

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).

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. 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.

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 patients with RLS and 18 mg/day in 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").

Pregnancy
Physiological changes in pregnancy (including decreased CYP1A2 activity) are predicted to gradually lead to an increased maternal systemic exposure of ropinirole (see also 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)), increased foetal death at 90 mg/kg/day (approximately 3 times the highest AUC at the MRHD) and digit malformations at 150 mg/kg/day (approximately 5 times the highest AUC at the MRHD). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 4 times the highest AUC at the MRHD) and no indication of an effect during organogenesis in the rabbit when given alone at 20 mg/kg (9.5 times the mean human Cmax at the MRHD). However, ropinirole at 10 mg/kg (4.8 times the mean human Cmax 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. The $IC_{50}$ is 5-fold higher than the expected maximum plasma concentration in patients treated at the highest recommended dose (24 mg/day) (see section 5.1).

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Tablet core:
Cellulose, microcrystalline
Lactose monohydrate
Croscarmellose Sodium
Hypromellose
Magnesium stearate

Film coat:
Hypromellose
Titanium dioxide (E 171)
Macrogol
Iron oxide red (E 172)
Iron oxide yellow (E 172)

## 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

Ropinirole 2mg: 21, 28, 84 and 126 film-coated tablets

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd t/a Mylan
Station Close
Potters Bar
Hertfordshire
EN6 1TL
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/0815

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

04/04/2008

## 10 DATE OF REVISION OF THE TEXT

20/06/2023