# REQUIP

**Ropinirole**

## QUALITATIVE AND QUANTITATIVE COMPOSITION

Ropinirole hydrochloride equivalent to 0.25 mg, 1.0 mg, 2.0 mg or 5.0 mg ropinirole free base.

## PHARMACEUTICAL FORM

Film-coated, pentagonal-shaped tablets for oral administration. The tablet strengths are distinguished by colour and debossing;

0.25 mg: white, pentagonal-shaped, film-coated tablets marked "SB" on one side and "4890" on the other.

1.0 mg: green, pentagonal-shaped, film-coated tablets marked "SB" on one side and "4892" on the other.

2.0 mg: pink, pentagonal-shaped, film-coated tablets marked "SB" on one side and "4893" on the other.

## CLINICAL PARTICULARS

### Indications

REQUIP is indicated for the treatment of idiopathic Parkinson's disease:

- REQUIP may be used alone (without levodopa [L-Dopa]) in the treatment of idiopathic Parkinson's disease.
- Addition of REQUIP to levodopa may be used to control "on-off" fluctuations and permit a reduction in the total daily dose of L-Dopa.

REQUIP is indicated for the treatment of moderate to severe primary Restless Legs Syndrome (RLS).

### Dosage and Administration

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

Individual dose titration against efficacy and tolerability is recommended.

Patients should be down-titrated if they experience disabling somnolence at any dose level. For other adverse events, down-titration followed by more gradual up-titration has been shown to be beneficial.

***Parkinson's Disease***

- **Adults**

REQUIP should be taken three times a day and may be taken with or without food (*see Pharmacokinetics*).

***Treatment initiation:*** The initial dose should be 0.25 mg t.i.d (three times a day). 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 |
| 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. REQUIP is usually given in divided doses three times per day.

A therapeutic response may be seen between 3 mg and 9 mg/day, although adjunct therapy patients may require higher doses. If sufficient symptomatic control is not achieved or maintained after the initial titration period, as described above, the dose of REQUIP may be increased until an acceptable therapeutic response is established.

The safety and efficacy of doses above 24 mg/day have not been established and this dose should not be exceeded.

When REQUIP is given as adjunct therapy to L-dopa, it may be possible to reduce gradually the L-dopa dose, depending on the clinical response. In clinical trials, the L-dopa dose was reduced gradually by approximately 20% in patients receiving ropinirole concurrently. In patients with advanced Parkinson's disease receiving REQUIP in combination with L-dopa, dyskinesias can occur during the initial titration of REQUIP. In clinical trials it was shown that a reduction of the L-dopa dose may ameliorate dyskinesia (*see Adverse Reactions*).

As with other dopamine agonists, REQUIP should be discontinued gradually by reducing the number of daily doses over the period of one week.

If treatment is interrupted for one day or more, re-initiation by dose titration should be considered (see above).

***Restless Legs Syndrome***

REQUIP should be taken once-daily before bedtime, however the dose can be taken up to 3 hours before retiring. REQUIP may be taken with or without food.

<u>Treatment Initiation (Week 1)</u>

The recommended initial dose is 0.25 mg once daily for 2 days. If this dose is well tolerated the dose may 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 can be increased according to the regimen below until optimal therapeutic response is achieved.

| Week | Dose (mg)/once daily |
|---|---|
| 2 | 1 |
| 3 | 1.5 |
| 4 | 2 |
| 5 | 2.5 |
| 6 | 3 |
| 7 | 4 |

First signs of a response can be anticipated after one week of treatment in some patients, although further titration to achieve optimal effect is likely to be required. The mean daily dose in clinical trials was 2 mg/day.

The safety and efficacy of doses above 4 mg/day have not been established.

As with other dopamine agonists, it is necessary to discontinue ropinirole treatment gradually by reducing the daily dose.

If treatment is interrupted for one day or more, re-initiation by dose titration should be considered (see above).

- **Elderly**

The clearance of ropinirole is decreased in patients aged 65 years or above, but the dose of REQUIP for elderly patients can be titrated in the normal manner.

- **Children and Adolescents**

The safety and efficacy of ropinirole have not been established in patients under 18 years of age, therefore REQUIP is not recommended for use in patients within this age group.

- **Renal impairment**

In 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.

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: For patients with Restless Legs Syndrome, the recommended initial dose of REQUIP is 0.25 mg once daily. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose is 3 mg/day in patients receiving regular dialysis. Supplemental doses after dialysis are not required. For patients with Parkinson's Disease, the initial dose of REQUIP 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 dialysis. Supplemental doses after dialysis are not required.

The use of ropinirole in patients with severe renal impairment (creatinine clearance <30 mL/min) without regular dialysis has not been studied.

- **Hepatic impairment**

The use of ropinirole in patients with hepatic impairment has not been studied. Administration of REQUIP to such patients is not recommended.

## Contraindications

Hypersensitivity to ropinirole or to any of the listed excipients.

## Warnings and Precautions

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. As with other dopaminergic drugs, caution should be exercised when these compounds are given concomitantly with REQUIP 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. REQUIP should not be used in the treatment of patients with neuroleptic induced akathisia.

Impulse control symptoms including compulsive behaviours (including pathological gambling, hypersexuality, compulsive shopping and binge eating) have been reported in patients treated with dopaminergic agents, including ropinirole (*see Adverse Reactions – Post Marketing Data*). These were generally reversible upon dose reduction or treatment discontinuation. In some ropinirole cases, other factors were present such as a history of compulsive behaviours or concurrent dopaminergic treatment.

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.

## Interactions

Neuroleptics and other centrally active dopamine antagonists, such as sulpiride or metoclopramide, may diminish the effectiveness of ropinirole and, therefore, concomitant use of these drugs with REQUIP 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. In a study in Parkinsonian patients receiving concurrent digoxin, no interaction was seen which would require dosage adjustment.

Ropinirole is principally metabolised by the cytochrome P450 enzyme CYP1A2. A pharmacokinetic study in Parkinson's patients revealed that ciprofloxacin increased the $C_{max}$ and AUC of ropinirole by approximately 60% and 84% respectively. Hence, in patients already receiving REQUIP, the dose of REQUIP may need to be adjusted when drugs known to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study in Parkinson's patients between ropinirole and theophylline, as representative of substrates of CYP1A2, revealed no change in the pharmacokinetics of either ropinirole or theophylline. Hence, changes in ropinirole pharmacokinetics following coadministration with other substrates of CYP1A2 are not expected.

Increased plasma concentrations of ropinirole have been observed in patients treated with high doses of oestrogens. In patients already receiving hormone replacement therapy (HRT), REQUIP treatment may be initiated in the normal manner. However, if HRT is stopped or introduced during treatment with REQUIP, 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 REQUIP with alcohol.

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

## Pregnancy and 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 (see *Pre-Clinical Safety Data*). No effects were seen on male fertility in rats.

### Pregnancy

There are no adequate and well-controlled studies of ropinirole in pregnant women. Ropinorole concentrations may gradually increase during pregnancy (see *Pharmacokinetics*). Studies in animals have shown embryo-foetal toxicity (see *Pre-Clinical Safety* Data).

It is recommended that REQUIP is not used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the foetus.

### Lactation

There are no data regarding the excretion of ropinirole in human milk. Ropinirole has been detected in rat milk (see *Pre-Clinical Safety Data*).

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

## Effects on Ability to Drive and Use Machines

No data are available on the effect of ropinirole on the ability to drive or use machinery. Patients should be cautioned about their ability to drive or operate machinery whilst taking REQUIP because of the possibility of somnolence and of dizziness (including vertigo).

Patients should be informed about the possibility of sudden onset of sleep without any prior warning or apparent daytime somnolence (*see Adverse Reactions*), which has primarily been observed in patients with Parkinson's disease, and should be cautioned that their safety and that of others is at risk should this happen when driving or operating machinery. If patients develop significant daytime sleepiness or episodes of falling asleep during activities that require active participation, patients should be told not to drive and to avoid other potentially dangerous activities.

## Adverse Reactions

Adverse reactions are tabulated below according to the indication. The overall safety profile of ropinirole comprises adverse reactions from all indications from clinical trial data and from post-marketing experience.

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), including isolated reports.

### Clinical Trial Data

The tables below list the adverse drug reactions reported at a higher rate with ropinirole than placebo or a higher or comparable rate to comparator in clinical trials.

**Adverse Drug Reactions Reported from Patients with Parkinson's Disease**

Unless otherwise indicated, the data in the following table was observed with both immediate release and prolonged release formulations.

| | **Use in monotherapy studies** | **Use in adjunct therapy studies:** |
|---|---|---|
| **Psychiatric disorders** | | |
| Common | Hallucinations | Hallucinations, confusion[1] |
| **Nervous system disorders** | | |
| Very common | Somnolence, syncope[1] | Dyskinesia[3] |
| Common | Dizziness (including vertigo), sudden onset of sleep[2] | Somnolence[2], dizziness (including vertigo), sudden onset of sleep[2] |
| **Vascular disorders** | | |
| Common | | Postural hypotension[2], hypotension[2] |
| Uncommon | Postural hypotension[2], hypotension[2] | |
| **Gastrointestinal disorders** | | |
| Very common | Nausea | |
| Common | Abdominal pain[1], vomiting[1], dyspepsia[1], constipation[2] | Nausea, constipation[2] |
| **General disorders and administrative site conditions** | | |
| Common | Oedema peripheral (including leg oedema) | Oedema peripheral[2] |

[1]Immediate release clinical trials data

[2] Prolonged release clinical trials data

[3] In patients with advanced Parkinson's disease, dyskinesias can occur during the initial titration of REQUIP. In clinical trials it was shown that a reduction of the L-dopa dose may ameliorate dyskinesia (*see Dosage and Administration*).

**Adverse Drug Reactions Reported During Clinical Trials in Patients with Restless Legs Syndrome**

| | |
|---|---|
| **Psychiatric disorders** | |
| Common | nervousness |
| **Nervous system disorders** | |
| Common | dizziness (including vertigo), somnolence, syncope<br>Augmentation[#], early morning rebound |
| [#] 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. (*see Warnings and Precautions*). | |
| **Gastrointestinal disorders** | |
| Very common | nausea, vomiting |
| Common | abdominal pain |
| **General disorders and administrative site conditions** | |
| Common | fatigue |

**Post Marketing Data**

| | |
|---|---|
| **Immune system disorders** | |
| Very rare | Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus). |
| **Psychiatric disorders** | |
| Uncommon | Psychotic reactions (other than hallucinations) including delusion, paranoia, delirium.<br>Impulse control symptoms, increased libido including hypersexuality, pathological gambling, compulsive shopping, binge eating (*see Warnings and Precautions*).<br>Aggression* |
| *****Aggression has been associated with psychotic reactions as well as compulsive symptoms. | |
| **Nervous system disorders** | |
| Very rare | extreme somnolence, sudden onset of sleep† |

| | |
|---|---|
| †As with other dopaminergic therapies, extreme somnolence and sudden onset of sleep have been reported primarily in Parkinson's disease. Patients experiencing sudden onset of sleep cannot resist the urge to sleep, and on waking may be unaware of any tiredness prior to the sleep. Where data from post-marketing reports were available, patients had recovered after down titration or on withdrawal of the drug. In most cases the patients received concomitant medication with potential sedating properties. | |
| ***Vascular disorders*** | |
| Common | hypotension, postural hypotension |
| As with other dopamine agonists, hypotension including postural hypotension has been observed with ropinirole treatment. Occasionally, severe symptomatic hypotension and bradycardia may occur. | |

## 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.

# PHARMACOLOGICAL PROPERTIES

## Pharmacodynamics

### *ATC Code*

N04BC04

#### Mechanism of Action

Ropinirole is a non-ergoline D2/D3 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.

Although not fully understood, the pathophysiology of Restless Legs Syndrome is thought to be a result of a dopaminergic deficiency, such as a reduction in the synthesis of dopamine and/or D2 receptor density in the striatum. Neuropharmacological evidence suggests primary dopaminergic system involvement and possibly other neurotransmitter systems. Furthermore, evidence from Positron Emission Tomography (PET) studies show that a mild striatal pre-synaptic dopaminergic dysfunction may be involved.

### *Pharmacodynamic Effects*

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

## Pharmacokinetics

The pharmacokinetics of ropinirole are consistent between healthy volunteers, Parkinson's disease patients and patients with Restless Legs Syndrome.

Wide inter-individual variability in the pharmacokinetic parameters has been seen. Bioavailability of ropinirole is approximately 50% (36 to 57%).

### *Absorption*

Oral absorption of ropinirole is rapid with peak concentrations of the drug achieved at a median time of 1.5 hours post dose.

The bioavailability of ropinirole was similar in both the fed and fasted state. However, 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 $C_{max}$.

As expected for a drug being administered approximately every half life, there is, on average, two-fold higher steady-state plasma concentrations of ropinirole following the recommended t.i.d. regimen compared to those observed following a single oral dose.

### *Distribution*

Plasma protein binding of the drug is low (10 to 40%). Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approx. 7 L/kg).

### *Metabolism*

Ropinirole is primarily cleared by CYP1A2 metabolism 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 about 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.

**Special Patient Populations**

**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:**
There was no change observed in the pharmacokinetics of ropinirole in Parkinson's

disease patients with mild to moderate renal impairment (creatinine clearance between 30 to 50 mL/min).

In patients with end stage renal disease receiving regular dialysis, oral clearance of ropinirole is reduced by approximately 30%. The recommended maximum dose is limited to 3 mg/day in patients with Restless Legs Syndrome and 18 mg/day in patients with Parkinson's Disease.

**Pregnancy:**
Physiological changes in pregnancy (including decreased CYP1A2 activity) are predicted to gradually lead to an increased maternal systemic exposure of ropinirole (reaching an approximate 2-fold increase by the third trimester based on physiologically based pharmacokinetic modelling).

## Clinical Studies

***Parkinson's Disease***

A double-blind 5-year study in 268 patients compared ropinirole and L-dopa in the treatment of early Parkinson's disease. The incidence of dyskinesias in patients receiving ropinirole (either alone or following subsequent L-dopa supplementation) was markedly lower than for patients receiving L-dopa (with or without additional L-dopa supplementation). Patients randomised to ropinirole were 4 times less likely to develop dyskinesias than those on L-dopa (odds ratio 3.8: 95% CI [2.1, 6.9]; $p<0.0001$); the incidence of dyskinesia was 20% and 46% for ropinirole and L-dopa patients, respectively. In those patients who completed the study without the need for supplemental L-dopa, ropinirole patients were 15-times less likely to develop dyskinesia than L-dopa patients (odds ratio 15.2: 95%CI [6.2, 36.9]; $p<0.0001$); the incidence of dyskinesia was 5% and 36% for ropinirole and L-dopa patients, respectively.

In the patients who completed the 5-year study, there was no significant difference in efficacy between those who received either ropinirole or L-dopa. A difference of 1.5 (95% CI [-0.1, 3.2] from baseline to completion in the Activities of Daily Living (ADL) score on the Unified Parkinson's Disease Rating Scale (UPDRS), was observed. Thirty-four percent (34%) of ropinirole patients who completed the 5-year study remained on monotherapy at study endpoint. The mean dose of ropinirole at study endpoint was 16.5 mg for all patients and 15.0 mg for those on monotherapy.

***Restless Legs Syndrome***

Restless Legs Syndrome is classed as a neurological condition that has a profound impact on sleep and is characterised by distressing sensations deep in the lower limbs and an urge to move the affected limbs in order to relieve symptoms. Approximately 80% of patients with Restless Legs Syndrome experience periodic leg movements of sleep, which are repetitive stereotypic movements that affect one or both legs and may wake the patient several times during the night. As these movements frequently disrupt sleep they contribute significantly to the morbidity of Restless Legs Syndrome.

In the three pivotal, 12-week efficacy studies, Restless Legs Syndrome patients were randomised to ropinirole or placebo, and the effects on the International Restless Legs Syndrome (IRLS) scale and Clinical Global Impression (CGI) scores at Week-12 were compared to baseline. The mean dose of ropinirole at Week 12 was 2.0 mg/day. At week 12, statistically significant differences between ropinirole and placebo were seen in all three studies. In addition, statistically significant differences in IRLS total score and CGI score between ropinirole and placebo were seen as early as 1-week of treatment.

Short and long term efficacy study

Short (12-week) and longer term (26-week) efficacy was evaluated in a randomized, double-blind, placebo-controlled clinical trial; this trial was designed to evaluate efficacy in a moderate-to-severe RLS patient population (baseline IRLS $\geq$ 24) as well as explore longer-term safety. Patients were randomised to ropinirole (N=197) or placebo (N=207), and efficacy was evaluated using the IRLS scale total score at weeks 12 and 26. The primary efficacy end point for the ITT population in adjusted mean change from baseline to Week 12 showed a treatment difference (95% CI) of -2.1 (-4.0, -0.1) in favour of ropinirole (p=0.039). Similarly, the secondary efficacy end point for ITT population in adjusted mean change from baseline to Week 26 showed a treatment difference (95% CI) of -2.5 (-4.6, -0.3) in favour of ropinirole (p=0.023). The magnitude of change observed on the IRLS scale is lower than expected, based on three previous 12-week clinical efficacy trials (SK&F-101468\190, SK&F-101468\194, SK&F-101468\249) of ropinirole that evaluated patients with a baseline IRLS score $\geq$ 15. There were considerable variations in treatment effects across centre groups in this trial. The treatment differences (95% CI) observed at week 12 ranged from 2.8 (-3.8, 9.3) to -11.0 (-17.4, -4.5); those at week 26 ranged from 0.8 (-7.1, 8.6) to -15.9 (-22.0, -9.9). The proportion of subjects who were withdrawn prematurely from the trial at the conclusion of the double-blind treatment period was 39% in the group receiving ropinirole versus 29% in the placebo group. The adverse events across the trial were consistent with the known safety profile of ropinirole; the rates of confirmed augmentation, confirmed 'clinically meaningful' augmentation and early morning rebound as assessed by an independent Adjudication Board were 4%, 3% and 2%, respectively, during the 66-week duration of study.

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 and periodic leg movements of sleep that lead to arousal from sleep. Statistically significant differences in both the periodic leg movements of sleep (p=<0.001) and the periodic leg movements leading to arousal index (p=0.0096) were seen between ropinirole and placebo from baseline to Week 12.

Long-term maintenance of efficacy was demonstrated in a 36-week study. Patients continued on ropinirole demonstrated a significantly lower relapse rate compared with patients randomised to placebo (33% Vs 58%, p=0.0156).

Ropinirole patients reported significant improvements compared to placebo in sleep disturbance, sleep quantity, sleep adequacy and daytime somnolence.

## Pre-clinical Safety Data

### Carcinogenesis, mutagenesis

Two-year studies have been conducted in the mouse and rat at dosages up to 50 mg/kg. The mouse study did not reveal any carcinogenic effect. In the mouse, there was an increase in benign uterine endometrial polyps at a dose of 50 mg/kg/day (10 times the maximum recommended human dose on a $mg/m^2$ basis). In the rat, the only drug-related lesions were Leydig cell hyperplasia/adenoma in the testis 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.

Genotoxicity was not observed in a battery of *in vitro* and *in vivo* tests.

### Reproductive toxicology

In fertility studies in rats, effects were seen on implantation due to the prolactin-lowering effect of ropinirole. In humans, chorionic gonadotropin, not prolactin, is essential for implantation in females. No effects were seen on male fertility.

Parkinson's Disease

Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg, increased foetal death at 90 mg/kg and digit malformations at 150 mg/kg (3.4, 5.1, 8.5 times the mean human AUC at the Maximum Recommended Human Dose (MRHD)). There was no teratogenic effect in the rat at 120 mg/kg (6.8 times the mean AUC at 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 $C_{max}$ 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.

Restless Legs Syndrome

Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg, increased foetal death at 90 mg/kg and digit malformations at 150 mg/kg (33, 49 and 81 times the mean human AUC at the MRHD). There was no teratogenic effect in the rat at 120 mg/kg (65 times the mean human 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.

Ropinirole-related material was shown to transfer into the milk of lactating rats in small amounts (approximately 0.01% of the dose per pup).

**Animal toxicology and/or pharmacology**

Ropinirole caused no serious or irreversible toxicity in laboratory animals at 15mg/kg (monkey), 20 mg/kg (mouse) or 50 mg/kg (rat); 0.9, 0.4 and 2.8 times (for PD) or 8.8, 3.5 and 27 times (for RLS) the mean human AUC at MRHD. The toxicology profile is principally determined by the pharmacological activity of the drug (behavioural changes, hypoprolactinaemia, and decrease in blood pressure and heart rate, ptosis and salivation).

# PHARMACEUTICAL PARTICULARS

## List of Excipients

***Tablet cores***: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate.

***Film coats:***

| | Tablet strength (mg) and colour | | |
|---|---|---|---|
| | 0.25 | 1.0 | 2.0 |
| Tablet Colour | White | Green | Pink |
| Hydroxypropylmethyl cellulose | ✓ | ✓ | ✓ |
| Polyethylene glycol 400 | ✓ | ✓ | ✓ |
| Titanium Dioxide | ✓ | ✓ | ✓ |
| Iron Oxide Yellow | | ✓ | ✓ |
| Iron Oxide Red | | | ✓ |
| Indigo Carmine Aluminium Lake E132 (FD&C Blue No. 2) | | ✓ | |
| Polysorbate 80 | ✓ | | |

## Incompatibilities

None known.

## Shelf Life

The expiry date is indicated on the packaging.

## Special Precautions for Storage

This product should be stored in a dry place at or below 25ºC.

## Nature and Contents of Container

Cold form blister (*Al/Al*)
Cold form child-resistant blister (*Al-Al/paper*)
PVC/PCTFE/PVC/Aluminium Blister

0.25 mg tablet: blister pack of 21 and/or 210 tablets

1 mg, and 2 mg tablets: blister pack of 21 tablets

Not all presentations are marketed locally.

**Version number: GDS33 / IPI18SI (PD) & IPI19SI (RLS)**

**Date of issue: 12 December 2017**

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[GSK logo]