The discontinuation should be avoided.

Switching from ropinirole immediate release tablets to ropinirole prolonged-release tablets (Pharmacokinetics).

- Film-coated, symptomatic

Renal impairment

Levodopa clearance is decreased in patients with Parkinson’s disease, with an average decrease of 20% in patients with advanced Parkinson’s disease compared to patients with early PD. In clinical trials it was shown that a reduction of the L-dopa dose may ameliorate dyskinesia (see Dosage and Administration).

Contraindications

- Hypersensitivity to ropinirole or to any of the excipients.

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In patients with advanced Parkinson’s disease, dyskinesias can occur during the initial titration of ReQuip prolonged release formulations.

Use in monotherapy studies

Use in adjunct therapy studies:

- Hallucinations

- Constipation

- Abnormality in cognition, redistribution, sudden onset of sleep

Adverse drug reactions reported in clinical trials

- Fatigue

- Dizziness (including vertigo), somnolence, syncope

- Constipation

- Nausea, vomiting

- Abdominal pain

- Nausea

- Oedema peripheral

- Oedema perineal

- Post Marketing Data

- Psychotic reactions (other than hallucinations), including delusion, paranoia, delirium.

Post marketing data

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- Histrionic personality disorder.

- 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 PD treatment may be initiated in the normal manner. However, if HRT is stopped or introduced during treatment with ropinirole, dosage adjustment may be required.

- Sudden onset of sleep during daily activities, in some cases without awareness or control. The tablets may be taken with or without food. A high fat meal may double the AUC and Cmax in some individuals. (See Pharmacokinetics).

Effects on Ability to Drive and Use Machines

There are no data regarding 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 PD because of the possibility of somnolence and of dizziness (including vertigo).

Requiring dose adjustment of these drugs. No interaction has been seen between ropinirole and other drugs commonly used to treat Parkinson’s disease. Care should be taken when adding new medication(s). In a study in Parkinson’s patients receiving concurrent dopamine agonist, 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 Cmax and AUC of ropinirole by approximately 60% and 120% respectively. Hence, in patients already receiving REQUIP PD, the dose of ropinirole may need to be adjusted when drugs known to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin or fluoroquinolones, are introduced or withdrawn.

- Additional pain, corneal, dyspepsia, constipation

- Nausea, vomiting

- Abdominal pain

- Oedema perineal

- Oedema peripheral

- Psychotic reactions (other than hallucinations), including delusion, paranoia, delirium.

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Psychiatric disorders

Psychiatric disorders

- Uncommon

- Common

- Very common

- Abnormality in cognition, redistribution, sudden onset of sleep²

- Constipation

- Oedema perineal (including leg oedema)

- Oedema peripheral²

- Psychotic reactions (other than hallucinations), including delusion, paranoia, delirium.

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- Sudden onset of sleep²

- Nausea

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- Oedema peripheral

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- Sudden onset of sleep²

- Nausea

- Oedema perineal

- Oedema peripheral

- Psychotic reactions (other than hallucinations), including delusion, paranoia, delirium.
**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 awakening may be unaware of any tiredness prior to the sleep. In most cases the patients received concomitant medication with potential sedating properties.**

**Vascular disorders**

**Common**

Hypotension, postural hypotension

**Other adverse reactions:** anorexia, headache

**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 neostigmine or metoclopramide.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamics**

**ATC Code:** N04BC04

**Mechanism of Action**

Ropinirole is a potent, non-ergoline D2/D3 dopamine agonist.

Parkinson’s disease is characterized by a marked dopamine deficiency in the nigrostriatal system. Ropinirole alleviates this deficiency by stimulating endogenous dopamine receptors.

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

**Absorption**

Following oral administration of ropinirole PR, plasma concentrations increase directly, with a median time to Cmax of 6 hours. In a steady-state study in Parkinson’s disease patients receiving 12 mg of ropinirole PR once daily, a high first dose increased the systemic exposure to ropinirole as shown by an average 20% increase in AUC and an average 44% increase in Cmax. Tmax was delayed by 1 to 3 hours. However, in the studies that established the safety and efficacy of ropinirole PR, patients were instructed to take study medication without regard to food intake.

**Distribution**

Plasma protein binding of the drug is low (10 to 45%). 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 (Cmax 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 repeat 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 observed change in the pharmacokinetics of ropinirole in Parkinson’s disease patients with mild to moderate renal impairment.

In patients with end stage renal disease receiving regular dialysis, oral clearance of ropinirole is reduced by approximately 30%. Oral clearance of the metabolites SKF-105577 and SKF-89124 were also reduced by approximately 80% and 66% (see Dosage and Administration, Renal impairment).

In a simulation study, Ropinirole III 6 mg three times daily (18 mg/day) in patients with end stage renal disease was provided a similar exposure of ropinirole to patients receiving Ropinirole III 4 mg three times daily (12 mg/day) in patients with normal renal function, but the exposure to metabolites SKF-105577 and SKF-89124 significantly higher. There is no safety data in humans with higher exposure to the metabolites. Therefore, no dosage adjustment is needed even if exposure to the non-significant effect on exposure.

**Clinical Studies**

A 16-week, double-blind, three-period crossover study conducted in 161 patients compared the efficacy and safety of ropinirole prolonged release tablets and ropinirole immediate release tablets as monotherapy in subjects with early stage Parkinson’s disease.

The primary endpoint of this non-inferiority study was the treatment change in disease from baseline in the Unified Parkinson’s Disease Rating Scale (UPDRS) motor score to 5-point non-inferiority margin was defined. Ropinirole prolonged release was demonstrated to be non-inferior to ropinirole immediate release on the primary endpoint, the adjusted mean difference between ropinirole prolonged release and ropinirole immediate release at study endpoint was 0.7 points (0.95% CI [−0.35, 0.30]; p=0.844).

Following the occurrence in a switch to a similar dose of the alternative treatment formulation, there was no indication of worsened adverse event profile and less than 5% of patients required a dose adjustment (by increasing one dose level).

A 24-week double-blind, placebo-controlled, parallel group study evaluated the efficacy and safety of ropinirole PR in the treatment of Parkinson’s disease who were not optimally controlled with levodopa. Ropinirole PR demonstrated a clinically relevant and statistically significant superiority over placebo on the primary endpoint, change from baseline in “off” time-adjusted mean treatment difference of 1.9 hours (95% CI: 1.25–2.54; p<0.001).

The odds of ropinirole PR patients being a responder on the CGI-I Global improvement scale were more than 4 times the odds of a placebo patient (PR 42%; CI 34%–50%) (odds ratio 4.13 [1.94, 8.82]; p=0.001). The odds of a ropinirole PR patient being a responder on the composite endpoint of 20% reduction from baseline in both “on”-times and “off”-time were also more than 4 times that of a placebo patient (PR 54%; CI 30%–75%) (odds ratio 3.95 [1.73, 8.76]; p<0.001) while the odds of a ropinirole PR patient requiring reinstatement of L-dopa following a dose reduction were less than a placebo patient (PR 7% CI: 3%–17%) (odds ratio 0.62 [0.29, 1.30]; p=0.0004).

The results on the primary endpoint were supported by clinically meaningful and statistically significant superiority over placebo on all secondary endpoints including the proportion of patients with “on” time without troublesome dyskinesia at 5.8 hours (95% CI: 0.63, 3.30; p=0.008) and total “on” time without troublesome dyskinesia, either free of “off” time in patients with UPDRS scores.

At week 24 the mean dose of investigational product was 18.8 mg/day for ropinirole PR and 20.0 mg/day of placebo equivalent.

**Pre-clinical Safety Data**

**Carcinogenesis, mutagenesis, impairment of fertility**

Ropinirole was not genotoxic or clastogenic in the mouse and rat at doses up to 50 mg/kg. The mouse study did not reveal any carcinogenic effect. In the rat, the single oral-dosed lesion was Leydig cell hyperplasia/neoplasia in the testes resulting from the hypothyroidic 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. Carcinogenicity was not observed in a history of is x irradiation and in two tests.

**Reproductive toxicology**

In fertility studies in rats, effects were seen on implantation due to the predictable lowering effect of ropinirole. In humans, changes in gonadotropins, not preimplantation, is not essential for implantation in lincomycin or ethinyloestradiol mice or female. Administration of rapirole to pregnant rats at maximally tolerated doses resulted in decreased fetal body weight at 60 mg/kg, increased fetal deaths at 90 mg/kg and digital malformations at 150 mg/kg body weight (95% CI: 0.1–8.5%); p=0.005.

**Minimum Recommended Human Dose (MRHD)**

There was no teratogenic effect in the rat at 120 mg/kg (6.8 times the mean human AUC at the MRHD) and no indication of effect during organogenesis in the rabbit when given alone at 20 mg/kg (7.5 times the mean human AUC at the MRHD).

In rats, the MRHD administered to rabbits in combination with oral L-dopa (250 mg/kg) produced a higher incidence and severity of fetal malformations than L-dopa alone.

Ropinirole-related material was shown to transfer into the milk of lactating rats in small amounts (approximately 0.013% of the maternal dose).

**Animal toxicity and/or pharmacology**

Ropinirole caused no serious or toxicological toxicity in laboratory animals at 10mg/kg (monkey), 20 mg/kg (mouse) or 90mg/kg (rat). 5% or 28 times the mean human AUC at the MRHD. The toxicology profile is primarily determined by the pharmacological activity of the drug (behavioral changes, hypothyrocaemia, and decrease in blood pressure and heart rate, paws and salivation).

**PHARMACUTICAL PARTICULARS**

**List of Excipients**

Tablets contain: Lactose monohydrate 2206, hypromellose gester, cellulose tributyrate sodium, fowiclide, lactose, magnesium stearate, colloidal silicon dioxide, macrogel (4521), ferric oxide yellow (172), glycerol behenate.