

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Requip 0.25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.25 mg of ropinirole (as ropinirole hydrochloride).

Excipient with known effect

Each tablet contains 45.3 mg lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, pentagonal-shaped bevelled edge tablets marked SB on one side and 4890 on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Parkinson's disease under the following conditions:

- o Initial treatment as monotherapy, in order to delay the introduction of levodopa
- o 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)

4.2 Posology and method of administration

Oral use.

Adults

Individual dose titration against efficacy and tolerability is recommended.

Requip should be taken three times a day, preferably with meals to improve gastrointestinal tolerance.

Treatment initiation

The initial dose of ropinirole should be 0.25 mg three times daily for 1 week. Thereafter, the dose of ropinirole can be increased in 0.25 mg three times daily increments, according to the following regimen:

	Week			
	1	2	3	4
Unit dose (mg) of ropinirole	0.25	0.5	0.75	1.0
Total daily dose (mg) of ropinirole	0.75	1.5	2.25	3.0

Therapeutic regimen

After the initial titration, weekly increments of 0.5 to 1 mg three times daily (1.5 to 3 mg/day) of ropinirole may be given.

A therapeutic response may be seen between 3 and 9 mg/day of ropinirole. If sufficient symptomatic control is not achieved, or maintained after the initial titration as described above, the dose of ropinirole may be increased up to 24 mg/day.

Doses of ropinirole above 24 mg/day have not been studied.

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

When Requip 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 Requip as adjunct therapy. In patients with advanced Parkinson's disease receiving ropinirole in combination with levodopa, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the levodopa dose may ameliorate dyskinesia (see section 4.8).

When switching treatment from another dopamine agonist to ropinirole, the marketing authorisation holder's guidance on discontinuation should be followed before initiating ropinirole.

As with other dopamine agonists, it is necessary to discontinue ropinirole treatment gradually by reducing the number of daily doses over the period of one week (see section 4.4).

Children and adolescents

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

Elderly

The clearance of ropinirole is decreased by approximately 15% in patients aged 65 years or above. Although a dose adjustment is not required, ropinirole dose should be individually titrated, with careful monitoring of tolerability, to the optimal clinical response.

Renal impairment

In patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 mL/min) no change in the clearance of ropinirole was observed, indicating that no dosage adjustment is necessary in this population.

A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis) has shown that a dose adjustment in these patients is required as follows: the initial dose of Requip should be 0.25 mg three times a day. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose of Requip is 18 mg/day in patients receiving regular haemodialysis. Supplemental doses after haemodialysis are not required (see section 5.2).

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

4.3 Contraindications

Hypersensitivity to the active substance 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

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 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 Requip. 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 Requip. 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

This medicinal product also contains lactose.

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

Sodium

Each Requip film coated tablet 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 of oestrogens. In patients already receiving hormone replacement therapy (HRT), ropinirole treatment may be initiated in the normal manner. However, it may be necessary to adjust the ropinirole dose, in accordance with clinical response, if HRT is stopped or introduced during treatment with ropinirole.

Ropinirole is principally metabolised by the cytochrome P450 isoenzyme CYP1A2. A pharmacokinetic study (with a ropinirole dose of 2 mg, three times a day in patients with Parkinson's disease) revealed that ciprofloxacin increased the C_{max} and AUC of ropinirole by 60% and 84% respectively, with a potential risk of adverse events. Hence, in patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when medicinal products known to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study in patients with Parkinson's disease between ropinirole (at a dose of 2 mg, three times a day) and theophylline, a substrate of CYP1A2, revealed no change in the pharmacokinetics of either ropinirole or theophylline.

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.

Breastfeeding

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 effects

Undesirable effects reported are listed below by system organ class and frequency. It is noted if these undesirable effects were reported in clinical trials as monotherapy or adjunct therapy to levodopa.

Frequencies are defined as: very common ($\geq 1/10$); common $\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

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 Requip (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 HPRC Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

The symptoms of ropinirole overdose are related to its dopaminergic activity. These symptoms may be alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopaminergic agents, dopamine agonists

ATC code: N04BC04.

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

Mechanism of action

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.

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 T_{max} by 2.6 hours and an average 25% decrease in C_{max} .

Distribution

Plasma protein binding of ropinirole is low (10 – 40 %).

Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approx. 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.

Renal Impairment

There was no change observed in the pharmacokinetics of ropinirole in Parkinson's disease patients with mild to moderate renal impairment.

In patients with end stage renal disease receiving regular haemodialysis, oral clearance of ropinirole is reduced by approximately 30%. Oral clearance of the metabolites SKF-104557 and SKF-89124 were also reduced by approximately 80% and 60%, respectively. Therefore, the recommended maximum dose is limited to 18 mg/day in these patients with Parkinson's disease (see section 4.2).

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 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. 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 cores:

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate.

Film coating:

Hypromellose
Macrogol 400
Titanium dioxide (E171)
Polysorbate 80 (E433).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 °C

Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC/PE/PVdC-Aluminium/paper child-resistant blister or Aluminium(Alu)-Alu/paper child-resistant blister

Packs of 21, 84, 210 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited

12 Riverwalk

Citywest Business Campus

Dublin 24

Ireland

8 MARKETING AUTHORISATION NUMBER

PA1077/037/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 December 1996

Date of last renewal: 08 July 2006

10 DATE OF REVISION OF THE TEXT

July 2023