

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1077/037/007

Case No: 2068088

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

GlaxoSmithKline (Ireland) Limited

Stonemasons Way, Rathfarnham, Dublin 16, Ireland

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Requip Modutab 3 mg Prolonged-Release Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **21/12/2009** until **31/01/2013**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Requip Modutab 3 mg Prolonged-Release Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 3 mg of ropinirole (as hydrochloride).

Excipients: 42.9 mg lactose, 0.005 mg sunset yellow FCF (E110)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tabs

Purple capsule-shaped, film-coated, marked "GS" on one side and "TYH" on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of Parkinson's disease under the following conditions:

- Initial treatment as monotherapy, in order to delay the introduction of levodopa
- In combination with levodopa, over the course of the disease, when the effect of levodopa 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-Modutab prolonged-release tablets should be taken once a day, at a similar time each day. The prolonged-release tablets may be taken with or without food (see section 5.2).

Requip-Modutab prolonged-release tablets must be swallowed whole and must not be chewed, crushed or divided.

Initial titration

The starting dose of ropinirole prolonged-release tablets is 2 mg once daily for the first week; this should be increased to 4 mg once daily from the second week of treatment. A therapeutic response may be seen at a dose of 4 mg once daily of ropinirole prolonged-release tablets.

Patients who initiate treatment with a dose of 2 mg/day of ropinirole prolonged-release tablets and who experience side effects that they cannot tolerate, may benefit from switching to treatment with ropinirole film-coated (immediate release) tablets at a lower daily dose, divided into three equal doses.

Therapeutic regimen

Patients should be maintained on the lowest dose of ropinirole prolonged-release tablets that achieve symptomatic control.

If sufficient symptomatic control is not achieved or maintained at a dose of 4 mg once daily of ropinirole prolonged-release tablets, the daily dose may be increased by 2 mg at weekly or longer intervals up to a dose of 8 mg once daily of ropinirole prolonged-release tablets.

If sufficient symptomatic control is still not achieved or maintained at a dose of 8 mg once daily of ropinirole prolonged-release tablets, the daily dose may be increased by 2 mg to 4 mg at two weekly or longer intervals. The maximum daily dose of ropinirole prolonged-release tablets is 24 mg.

It is recommended that patients are prescribed the minimum number of ropinirole prolonged-release tablets that are necessary to achieve the required dose by utilising the highest available strengths of ropinirole prolonged-release tablets.

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

When Requip-Modutab prolonged-release tablets are administered as adjunct therapy to levodopa, it may be possible to reduce gradually the levodopa dose, depending on the clinical response. In clinical trials, the levodopa dose was reduced gradually by approximately 30% in patients receiving Requip-Modutab prolonged-release tablets concurrently. In advanced Parkinson's disease, in combination treatment with levodopa, dyskinesias can occur during the initial titration of Requip-Modutab prolonged-release tablets. If they occur, the dose of levodopa should be decreased.

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

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

Switching from Requip film-coated (immediate-release) tablets to Requip-Modutab prolonged-release tablets
Patients may be switched overnight from Requip film-coated (immediate-release) tablets to Requip-Modutab prolonged-release tablets. The dose of Requip-Modutab prolonged-release tablets should be based on the total daily dose of Requip film-coated (immediate-release) tablets that the patient was taking. The table below shows the recommended dose of Requip-Modutab prolonged-release tablets for patients switching from Requip film-coated (immediate-release) tablets:

Switching from Requip film-coated (immediate-release) tablets to Requip-Modutab prolonged-release tablets

Requip film-coated (immediate-release) Tablets Total daily dose (mg)	TRADE NAME prolonged-release Tablets Total daily dose (mg)
0.75 - 2.25	2
3 - 4.5	4
6	6
7.5 - 9	8
12	12
15 - 18	16
21	20
24	24

After switching to Requip-Modutab prolonged-release tablets, the dose may be adjusted depending on the therapeutic response (see "Initial titration" and "Therapeutic regimen" above).

Children and adolescents

Requip-Modutab prolonged-release tablets are 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 in patients over 65 years of age. Any increase in dosage should be gradual and titrated against the symptomatic response. For the very elderly, slower titration during treatment initiation may be considered.

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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Severe renal impairment (creatinine clearance <30 ml/min).
- Hepatic impairment.

4.4 Special warnings and precautions for use

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.

Patients with major psychiatric or psychotic disorders, or a history of these disorders, should not be treated with dopamine agonists unless the potential benefits outweigh the risks.

Impulse control disorders including pathological gambling and hypersexuality, and increased libido, have been reported in patients treated with dopamine agonists, including ropinirole, principally for Parkinson's disease. Those disorders were reported especially at high doses and were generally reversible upon reduction of the dose or treatment discontinuation. Risk factors such as a history of compulsive behaviours were present in some cases ([see section 4.8](#)).

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).

This medicinal product also contains lactose.

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

Requip-Modutab 3 mg prolonged-release tablets, contain the azo colouring agent sunset yellow FCF (E110), which may cause allergic reactions.

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 film-coated (immediate-release) tablet dose of 2 mg, three times a day) in Parkinson's disease patients, 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 (with a ropinirole film-coated (immediate-release) tablet 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.

4.6 Pregnancy and lactation

There are no adequate data from the use of ropinirole in pregnant women.

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.

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

4.7 Effects on ability to drive and use machines

Patients being treated with ropinirole and presenting with 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.

Adverse drug reactions reported in Parkinson's disease clinical trials with Requip-Modutab prolonged-release tablets at doses up to 24 mg/day

	In monotherapy	In adjunct therapy
<i>Psychiatric disorders</i>		
Common	Hallucinations	Hallucinations

<i>Nervous system disorders</i>		
Very common	Somnolence	Dyskinesia
Common	Dizziness (including vertigo)	Somnolence, dizziness (including vertigo)
<i>Vascular disorders</i>		
Common		Postural hypotension, hypotension
Uncommon	Postural hypotension, hypotension	
<i>Gastrointestinal disorders</i>		
Very common	Nausea	
Common	Constipation	Nausea, constipation
<i>General disorders and administrative site conditions</i>		
Common	Oedema peripheral	Oedema peripheral

In addition to the above adverse drug reactions, the following events have been reported with Requip film-coated (immediate-release) tablets in patients with Parkinson's disease during clinical trials (at doses up to 24 mg/day) and/or from post-marketing reports.

	<u>In monotherapy</u>	<u>In adjunct therapy</u>
<i>Immune system disorders</i>		
Not known	<i>Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus).</i>	
<i>Psychiatric disorders</i>		
Common		Confusion
Uncommon	Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia.	Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia.
Not known	Impulse control disorders including pathological gambling and hypersexuality and increased libido, have been reported in post marketing reports (see section 4.4)	
<i>Nervous system disorders</i>		
Very common	Syncope	Somnolence
Uncommon	Sudden onset of sleep, excessive daytime somnolence	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.	
<i>Vascular disorders</i>		
Uncommon	Postural hypotension or hypotension is rarely severe	
<i>Gastrointestinal disorders</i>		
Very common		Nausea
Common	Vomiting, heartburn, abdominal pain	Heartburn
<i>Hepatobiliary disorders</i>		
Not known	Hepatic reactions, mainly increased liver enzymes	

<i>General disorders and administrative site conditions</i>		
Common	Leg oedema	

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: DOPAMINE AGONIST, ATC code: N04BC04.

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

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

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

Clinical efficacy

A 36-week, double-blind, three-period crossover study, in monotherapy, conducted in 161 patients with early phase Parkinson's disease demonstrated that Requip-Modutab prolonged-release tablets were non-inferior to Requip film-coated (immediate-release) tablets on the primary endpoint, the treatment difference in change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score (a 3-point non-inferiority margin on the UPDRS motor score was defined). The adjusted mean difference between Requip-Modutab prolonged-release tablets and Requip film-coated (immediate-release) tablets at study endpoint was -0.7 points (95% CI: [-1.51, 0.10], p=0.0842).

Following the overnight switch to a similar dose of the alternative tablet formulation, there was no difference in the adverse event profile and less than 3% of patients required a dose adjustment (all dose adjustments were increases by one dose level. No patients required a dose decrease).

A 24-week, double-blind, placebo-controlled, parallel group study of Requip-Modutab prolonged-release tablets in patients with Parkinson's disease who were not optimally controlled on levodopa demonstrated a clinically relevant and statistically significant superiority over placebo on the primary endpoint, change from baseline in awake time "off" (adjusted mean treatment difference -1.7 hours (95% CI: [-2.34, -1.09], p<0.0001). This was supported by secondary efficacy parameters of change from baseline in total awake time "on" (+1.7 hours (95% CI: [1.06, 2.33], p<0.0001) and total awake time "on" without troublesome dyskinesias (+1.5 hours (95% CI: [0.85, 2.13], p<0.0001). Importantly, there was no indication of an increase from baseline in awake time "on" with troublesome dyskinesias, either from diary card data or from the UPDRS items.

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%). Following oral administration, of ropinirole prolonged-release tablets plasma concentrations increase slowly, with a median time to C_{\max} generally achieved between 6 and 10 hours.

In a steady-state study in 25 Parkinson's disease patients receiving 12 mg of ropinirole prolonged release tablets once daily, a high fat meal increased the systemic exposure to ropinirole as shown by an average 20% increase in AUC and an average 44% increase in C_{\max} . T_{\max} was delayed by 3.0 hours. However, these changes are unlikely to be clinically relevant (eg. increased incidence of adverse events).

The systemic exposure to ropinirole is comparable for ropinirole prolonged-release tablets and ropinirole film-coated (immediate-release) tablets based on the same daily dose.

Distribution

Plasma protein binding of ropinirole is low (10–40%). Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approx. 7L/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. Wide inter-individual variability in the pharmacokinetic parameters has been observed. Following steady-state administration of ropinirole prolonged-release tablets, the inter-individual variability for C_{\max} was between 30% and 55% and for AUC was between 40% and 70%.

5.3 Preclinical safety data

Reproductive Toxicity

Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg/day (approximately twice the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg/day (approximately 3 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg/day (approximately 5 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 4 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

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 IC₅₀ is 5-fold higher than the expected maximum plasma concentration in patients treated at the highest recommended dose (24 mg/day), see section 5.1.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Prolonged-release tablet cores: Hypromellose, hydrogenated castor oil, carmellose sodium, povidone (K29-32), maltodextrin, magnesium stearate, lactose monohydrate, anhydrous colloidal silica, mannitol (E421), iron oxide yellow (E172), glycerol dibehenate.

Film coating: OPADRY purple 03B20024 (hypromellose, titanium dioxide (E171), macrogol 400, carmine (E120), indigo carmine aluminium lake (E132), sunset yellow FCF aluminium lake (E110)).

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

Packs of 28 or 84 prolonged-release tablets in blisters (PVC/PCTFE/Aluminium)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Ltd.
Stonemasons Way
Rathfarnham
Dublin 16
Ireland

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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