Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Requip 2mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2mg ropinirole (as hydrochloride).

Excipients: Lactose Monohydrate

For full list of excipients see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Product imported from Greece:
Peach, pentagonal-shaped tablets with ‘4893’ on one side and ‘SB’ 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 L-dopa
- In combination with L-dopa, over the course of the disease, when the effect of L-dopa 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

Individual dose titration against efficacy and tolerability is recommended.

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

Treatment initiation
The initial dose should be 0.25 mg t.i.d for 1 week. Thereafter, the dose can be increased in 0.25 mg t.i.d increments, according to the following regimen.

	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 0.5 to 1 mg t.i.d (1.5 to 3 mg/day) may be given.

A therapeutic response may be seen between 3 and 9 mg/day. If sufficient symptomatic control is not achieved, or maintained, the dose of ropinirole may be increased up to 24 mg/day. Doses above 24 mg/day have not been studied.

When ropinirole is administered as adjunct therapy to l-dopa, the concurrent dose of l-dopa may be reduced gradually by around 20%.

When switching treatment from another dopamine agonist to ropinirole, the manufacturer'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.

Elderly
The clearance of ropinirole is decreased in patients over 65 years of age. The increase in dosage should be gradual and titrated against the symptomatic response

Renal Impairment
In parkinsonian 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 ropinirole and other excipients.
- In the absence of specific studies: severe renal impairment (creatinine clearance <30ml/min) and hepatic impairment.
- Pregnancy and lactation.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

Special Warnings
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. Furthermore, a reduction of dosage or termination of therapy may be considered.

Patients with psychiatric or psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks.

Pathological gambling, increases in libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson’s disease, including Requip.

Precautions for Use
Severe cardiovascular disease (in particular coronary insufficiency). Blood pressure monitoring is recommended, particularly at the start of treatment (due to the risk of postural hypotension).

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic interaction has been seen between ropinirole and L-dopa or domperidone which would necessitate dosage adjustment of either drug.

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 CYP 1A2. A pharmacokinetic study (with a ropinirole dose of 2mg, three times a day) in Parkinson patients revealed that ciprofloxacine increased the Cmax 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 drugs known to inhibit CYP 1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study in Parkinson patients between ropinirole (at a dose of 2mg, three times a day) and theophylline, a substrate of CYP 1A2, revealed no change in the pharmacokinetics of either ropinirole or theophylline.

4.6 Pregnancy and lactation

Pregnancy
In animal studies, 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. There was no teratogenic effect in the rat at 120 mg/kg and no indication of an effect on development in the rabbit. There have been no studies of ropinirole in human pregnancy. In consequence, ropinirole is contraindicated during pregnancy. If pregnancy is discovered during ropinirole treatment, specialised advice should be sought.

Lactation
Ropinirole may inhibit lactation; treatment with ropinirole during lactation is contraindicated.

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 also Section 4.4).*

4.8 Undesirable effects

a)
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. Common and uncommon events were generally determined from pooled safety data from clinical trial populations and are quoted as excess incidence over placebo. Rare and very rare events were generally determined from post-marketing data and refer to reporting rate rather than true frequency.

b)
Psychiatric disorders
Use in monotherapy studies:
Common: hallucinations.

Use in adjunct therapy studies:
Common: confusion, hallucinations.

Patients treated with dopamine agonists for treatment of Parkinson’s disease, including Requip, especially at high doses have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

Nervous system disorders
Uncommon: excessive daytime somnolence*, sudden onset of sleep*

Use in monotherapy studies:
Very common: somnolence, syncope.

Use in adjunct therapy studies:
Very common: dyskinesia, somnolence

Vascular disorders
Uncommon: hypotension, postural hypotension*.

Gastrointestinal disorders
Use in monotherapy studies:
Very common: nausea.
Common: abdominal pain, vomiting, heartburn.

Use in adjunct therapy studies:
Very common: nausea.
Common: heartburn.

Hepatobiliary disorders
Very rare: hepatic reactions, increased liver enzymes*.

General disorders and administrative site conditions
Use in monotherapy studies:
Common: leg oedema.
* See section c) below.

c)

Nervous system disorders
Ropinirole is associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes.

Vascular disorders
Following ropinirole therapy, hypotension or postural hypotension have been reported, rarely severe.

Hepatobiliary disorders
Very rare cases of hepatic reactions, mainly increase of liver enzymes, have been reported.

4.9 Overdose

There have been no incidences of intentional overdose with ropinirole in clinical trials. It is anticipated that the symptoms of ropinirole overdose will be 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 dopamine against.

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

5.2 Pharmacokinetic properties

Oral absorption of ropinirole is rapid. Bioavailability of ropinirole is approximately 50 % (36 to 57 %) and average peak concentrations of the drug are achieved at a median time of 1.5 hours post-dose. Wide inter-individual variability in the pharmacokinetic parameters has been and the increase in systemic exposure (Cmax and AUC) to the drug with an increase in dose over the therapeutic dose range is proportional after single administration. Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (mean value 6.7 L/kg, range 3.4 - 19.5 L/kg) and is cleared from the systemic circulation with an average elimination half-life of approximately 6 hours (range 3.4 - 10.2 h) and an apparent oral clearance of 58.7 L/h (range 18.5 - 132 L/h). Plasma protein binding of the drug is low (10 - 40 %). The cytochrome P450 isoenzyme CYP1A2 is primarily responsible for the oxidative metabolism of ropinirole. Ropinirole is mainly excreted in the urine as metabolites. The major metabolite is at least 100 times less potent than ropinirole in animal models of dopaminergic function.

5.3 Preclinical safety data

Toxicology: The toxicology profile is principally determined by the pharmacological activity of the drug: 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 a high dose (50mg/kg), 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 there was no evidence of any carcinogenic effect in the mouse. In the rat, the only drug-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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:
Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate.

Film Coat:
Hypromellose
Macrogol
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.
Keep the bottle tightly closed.

6.5 Nature and contents of container

Bottle of 84 with aluminium foil induction seal and polypropylene cap

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing Ltd.
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 0465/174/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 March 2006.

10 DATE OF REVISION OF THE TEXT

October 2008