



Agence française de sécurité sanitaire  
des produits de santé

**Direction de l'Évaluation  
des Médicaments et des Produits Biologiques**

## **PUBLIC ASSESSMENT REPORT Scientific Discussion**

**REQUIP LP 2 mg, 3 mg, 4 mg, 8 mg prolonged-release  
tablets**

**ROPINIROLE PAUCOURT LP 2 mg, 3 mg, 4 mg, 8 mg  
prolonged-release tablets**

**FR/H/111/06-09/MR**

**FR/H/255/06-09/MR**

**(Ropinirole)**

**Applicant:  
GLAXOSMITHKLINE**

<b>Date of the PAR: January 2008</b>
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## Information about the initial procedure:

Application/Legal Basis	Line extension
Active substance	Ropinirole
Pharmaceutical form	Prolonged-release tablets
Strength	2 mg, 3 mg, 4 mg, 8 mg
Applicant	GlaxoSmithKline
EU-Procedure number	FR/H/111/06-09 – FR/H/255/06-09
End of procedure	27/11/2007

### 1. INTRODUCTION

Based on review of the quality, safety and efficacy data, the Afssaps has granted a marketing authorisation (MA) for REQUIP LP/ROPINIROLE PAUCOURT LP 2 mg, 3 mg, 4 mg, 8 mg, prolonged-release tablets from GlaxoSmithKline on March 28<sup>th</sup> 2007. The marketing authorisation, REQUIP LP/ROPINIROLE PAUCOURT LP, was granted as a line extension to the marketing authorisation for REQUIP/ROPINIROLE PAUCOURT.

Ropinirole prolonged-release tablets present a simplified dosing regimen by allowing once-daily dosing. The once-a-day dosing could improve compliance, which may lead to improved efficacy. Ropinirole prolonged-release tablets are also referred to as Ropinirole controlled release (CR) tablets in this assessment report.

This is a **mutual recognition procedure**, with France acting as reference Member State. Austria, Belgium, Denmark, Finland, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden and Cyprus, Malta, Lithuania and Poland are involved as CMS respectively for REQUIP LP/ROPINIROLE PAUCOURT LP procedures.

The indication approved is: “*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).*

### 2. QUALITY ASPECTS

#### 2.1 Introduction

REQUIP LP/ROPINIROLE PAUCOURT LP is presented as prolonged-release tablets containing respectively 2 mg, 3 mg, 4 mg and 8 mg of ropinirole as hydrochloride.

Tablet cores:

Hypromellose 2208, hydrogenated castor oil, carmellose sodium, povidone K 29-32, maltodextrin, magnesium stearate, lactose monohydrate, anhydrous colloidal silica, mannitol (E421), iron oxide yellow (E172), glycerol dibehenate.

Film coating:

2 mg: OPADRY pink OY-S-24900 (hypromellose 2910, iron oxide yellow (E172), titanium dioxide (E171), macrogol 400, iron oxide red (E172)).

3 mg: OPADRY purple 03B20024 (hypromellose 2910, titanium dioxide (E171), macrogol 400, carmine (E120), indigo carmine aluminium lake (E132), sunset yellow FCF aluminium lake (E110)).

4 mg: OPADRY light brown OY-27207 (hypromellose 2910, titanium dioxide (E171), macrogol 400, sunset yellow FCF aluminium lake (E110), indigo carmine aluminium lake (E132)).

8 mg: OPADRY red 03B25227 (hypromellose 2910, iron oxide yellow (E172), titanium dioxide (E171), iron oxide black (E172), macrogol 400, iron oxide red (E172)).

Tablets are packed in PVC/PCTFE/Aluminium blister.

## 2.2 Drug substance

The drug substance, Ropinirole Hydrochloride, or 4-[2-(dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one, mono-hydro-chloride under its chemical name and is identical to that used for ReQuip film-coated (Immediate Release(IR)) Tablets. Therefore there is no change in Section 3.2.S. as regards the updated dossier submitted and approved for ReQuip IR. All variations submitted for ReQuip IR Tablets and approved by all CMS have been integrated in this new Marketing Application.

Ropinirole hydrochloride is a crystalline solid, with a high aqueous solubility. No evidence of polymorphism was observed during the development of the manufacturing process of the active substance where three synthetic routes were used. To-day Ropinirole Hydrochloride is currently manufactured by a five stage synthesis.

We note in recent manufactured batches of Ropinirole Hydrochloride, that impurity levels of the drug substance are significantly improved. Thus, only two specified related substances have been observed each at >0.05%. All other specified and unspecified impurities have been present at less than or equal to 0.05% and total impurity levels have been at up to 0.3%. Inorganic impurities are present at very low levels, heavy metals less than 10ppm and sulphated ash levels were less than 0.1% w/w. Residual solvents detected in recently manufactured batches have had levels of up to 0.06% w/w for a class 3 solvent, while the levels of class 2 solvents have been less than 0.01% w/w and any other solvent has been at a maximum of 0.01% w/w. Total levels of residual solvents have not been greater than 0.1% w/w.

## 2.3 Drug Product

The formulation is based on a 'Geomatrix®' technology licensed from SkyePharma. This technology consists of a 3 layer core in which the central, active-containing, slow-release layer is sandwiched between hydrophobic inactive barrier layers.

All tablet strengths are based on a common formulation system, with the quantity of the filler lactose monohydrate adjusted to accommodate the different drug contents. Hypromellose USP type 2208 has been chosen as the agent that controls release.

The pharmaceutical development is particularly well documented and all the process manufacturing parameters have been described and justified.

The manufacturing process involves the following steps: manufacture of the barrier compression mix, manufacture of the active mix, compression and film coating.

Data for four batches of ropinirole prolonged release tablets (one each of 2, 3, 4 and 8 mg tablet strengths) manufactured at the full commercial scale, at the proposed commercial site, using the proposed commercial equipment are presented. The process is validated at commercial scale.

The film coated tablets are formulated with well-known excipients. Colorants have been controlled both qualitatively & quantitatively to agreed specifications through appropriate Quality systems. Manufacture of the film coating suspension to current GMP ensures use of the correct film coat for various strengths of tablets.

Acceptable ropinirole content test has been evaluated with validated method and adequate distribution of active material throughout each batch of product is confirmed by the application of the Ph Eur test (2.9.40).

Levels for drug-related impurities in ropinirole prolonged release tablets are determined by a gradient HPLC method which resolves the specified impurities/degradation products from each others, from the formulation excipients and from ropinirole.

All the analytical methods used for control are suitably validated.

The limit for total drug-related impurities is supported by the presented real long-term stability studies.

An overview on stability data supports the proposed three-year shelf-life for ropinirole prolonged release tablets, 2mg, 3mg, 4mg and 8mg when tablets are stored into PVC / PCTFE /Alu blister packs.

Tablets should be stored in their original package at a temperature that does not exceed 25°C.

### **3. NON-CLINICAL ASPECTS**

#### **3.1 Discussion on the non-clinical aspects**

The present application concerns a prolonged release formulation of ropinirole tablets. The immediate (IR) release tablet formulation was first approved in Europe in 1996 (FR/H/111/01-05). Therefore, the applicant mainly refers to studies submitted and evaluated at that time. New pharmacology and toxicology non clinical studies were performed to complete the non clinical dossier for the current application of REQUIP LP.

Three new pharmacology studies have been presented.

The first was a primary pharmacodynamics study comparing the effect of continuous infusion of ropinirole by osmotic minipump with twice daily oral dosing in marmosets with MPTP-induced Parkinsonian-like deficits. This study showed that continuous release of ropinirole via osmotic minipump could significantly improve locomotor activity and reduce disability and the incidence of dyskinesia in an animal model of Parkinson's disease (MPTP marmosets). These results support the rationale of development of a prolonged release tablet formulation of ropinirole in the treatment of Parkinson's disease.

The second was a secondary pharmacodynamics study which examined the effect of ropinirole in a rat model of spinal sensitization. In this study, the intrathecal administration of ropinirole (60 µg) to rats did not inhibit capsaicin induced secondary hyperalgesia. Therefore, it was concluded that ropinirole was ineffective in this experimental model.

The third, which measured blockade of the hERG/IKr channel *in vitro* confirmed that ropinirole has the potential to prolong cardiac repolarisation. The expected C<sub>max</sub> in patients receiving the prolonged release tablet formulation is 13-fold lower than the concentration required to block hERG-mediated currents *in vitro*. Furthermore, a review of the available clinical trial and post-marketing data, considered in the context of overall patient exposure to ropinirole (>739,000 patient years, estimate to March 2005) does not suggest an increase in treatment-related risk for adverse events possibly linked to QTc prolongation at therapeutic dosages.

No new non clinical pharmacokinetic and toxicology studies were performed with ropinirole, which is acceptable for the present application. The applicant adequately justified that the end-of-shelf-life specification limit of impurity SB-270341 (hydroxymethyl-ropinirole), reduced to the ICH qualification threshold of 0.5%, is acceptable.

In spite of a PEC value above the limit of 0.01 µg/L, the applicant did not perform any Phase II assessment. The rationale is based on one hand on previous assessments which did not suggest any adverse effect towards the environment. On the other hand, the present application concerns a line extension of the IR formulation, so that the market share for this drug in this indication is not expected to increase significantly. Finally, the applicant provided comprehensive figures to show that the penetration factor used in the Phase I PEC calculation, and consequently the PEC, is likely to have been overestimated.

### **Conclusion:**

The present nonclinical dossier filed to support the marketing authorization of REQUIP LP, prolonged release tablets is acceptable. However, results of *in vitro* studies related to cardiac safety pharmacology should be summarized in section 5.3 of the SmPC. The MAH will submit a type II variation in order to modify the SPC wording for all products containing ropinirole.

## **4. CLINICAL ASPECTS**

### **4.1 Introduction**

Ropinirole is a potent and highly selective non-ergot dopamine agonist at the D<sub>2</sub>- and D<sub>3</sub>-dopamine receptor subtypes and is active both centrally and peripherally.

Ropinirole has been shown clinically to be an effective treatment for Parkinson's disease, which is characterized by a marked dopamine deficiency in the nigrostriatal system. As a selective D<sub>2</sub> / D<sub>3</sub>-dopamine agonist, ropinirole acts to alleviate the dopamine deficiency by stimulating striatal dopamine receptors.

Considering the relatively short elimination half-life of ropinirole (about 6 hours), the film coated (immediate release (IR)) tablets are to be taken three times daily. A low starting dose (0.75 mg/day) and a slow initial titration regimen of 0.75 mg weekly over the first four weeks are recommended.

With the prolonged release tablets a once daily administration, a higher starting dose (2 mg/day versus 0.75 mg/day) and a larger up-titration increment (2 mg versus 0.75 mg weekly) are claimed. Thus, a simplification of the dosing regimen and potentially an improvement of the treatment compliance could be obtained through the use of the prolonged release tablets. The simplification of the dosage regimen is of valuable importance as ropinirole is indicated for long term use in Parkinson's disease.

Subjects who are already receiving ropinirole IR tablets can switch overnight to the nearest equivalent dose of ropinirole prolonged release tablets and can take ropinirole prolonged release tablets with or without food. The once-a-day dosing could improve compliance, which may lead to improved efficacy.

REQUIP LP/ROPINIROLE PAUCOURT LP are available as 2 mg, 3mg, 4 mg and 8 mg prolonged release tablets. In this assessment report ropinirole prolonged release tablets are also referred to as Ropinirole controlled release (CR) tablets. The available dose range for both ropinirole IR and ropinirole prolonged release tablets allows for potential up-titration as the disease progresses.

#### **4.2 Pharmacokinetics**

The pharmacokinetics behaviour of ropinirole has been extensively investigated by oral and IV routes and the related data had been submitted in the initial file of the IR tablets formulation. Thus formal complete pharmacokinetic file is not required here as the drug under consideration is already approved and the application under consideration relates to the development of a prolonged release tablet with reference to the IR tablets formulations.

The applicant has performed an extensive clinical pharmacology program. Pharmacokinetics investigations have been undertaken in 6 phase I studies. Four studies have been conducted in healthy volunteers and two in Parkinson's disease patients. A total of 110 healthy volunteers and 51 Parkinson's disease patients have been investigated.

These studies aimed to:

- Select the most appropriate release profile among three CR tablet prototypes (study 161),
- Assess the relative bioavailability of the CR tablets comparatively to the IR tablets (studies 162 and study 161),
- Investigate the pharmacokinetics of ropinirole CR formulations after single and repeated dose administration (study 163).
- Test the food-intake effect on the bioavailability of the CR tablets (study 164 and 161).
- Assess the dose proportionality of the CR ropinirole tablets (study 165 and study 162).
- Check the dosage strength equivalence of ropinirole CR tablets (study 219).

## Pharmacokinetics studies conducted with the ropinirole CR tablets

Study No	Phase	Study title	Objective	Dose	Subjects treated		
					Ropinirole		Placebo
					CR	IR	
<b>Healthy volunteers</b>							
161	I	Single dose study to compare the pharmacokinetics of ropinirole CR (test formulations) with IR (reference formulation) and assess the influence of food and domperidone	Formulation selection / food effect	IR 0.25 mg tid CR 0.75 mg od in three formulations (Tablet A, B or C) Tablet C + high fat food Tablet C + domperidone 2x10 mg tid	14	14	-
162	I	Four-way crossover, placebo- and IR-controlled study to compare single dose pharmacokinetics of ropinirole CR and IR formulation	Dose proportionality	IR 0.25 mg tid CR 0.75 mg od & 3 mg od Domperidone 2x10 mg tid	34	-	-
163	I	Double-blind, two-way crossover, placebo-controlled single and repeat dose study to assess the pharmacokinetics of ropinirole CR	Repeat dose	CR 1.0 mg od Domperidone 2x10 mg tid	28	-	27
219	I	Open-label, randomised, five-way crossover single dose pharmacokinetic study to assess dosage strength equivalence of ropinirole CR	Dose strength equivalence	CR 1x1 mg, 2x1 mg, 1x2 mg, 3x1 mg, 1x3 mg Domperidone 2x10 mg tid	34	-	-
Total healthy volunteers					110	14	27
<b>Subjects with Parkinson's disease</b>							
164	I	Open-label, randomised, two part study to assess the relative bioavailability of ropinirole CR and IR formulations, and the effect of food on the pharmacokinetics of ropinirole CR formulation in subjects with early stage PD	Food effect / relative bioavailability	Slow up titration: 2, 3, 4, 6, 8 mg CR or adjustment to 8 mg CR IR 2.5 mg tid/CR 8 mg od CR 8 mg od fed vs. fasted	23	20	-
165	I	Open-label, up titration study to assess dose proportionality of ropinirole CR and to demonstrate the dose strength equivalence of ropinirole CR (1x8 mg vs 4x2 mg) in PD subjects	Dose proportionality / dose strength	Up titration: 2, 4, 6, 8 mg CR CR 1x8 mg; 4x2 mg	28	-	-

### Absolute Bioavailability

The absolute bioavailability of ropinirole via oral administration was investigated in the initial file of Requip IR tablets. No absolute bioavailability studies with the CR tablets have been conducted with the CR tablets.

From the initial file documentation, the absolute bioavailability of ropinirole was estimated to be about 50 % (36-57 %).

### Relative Bioavailability (ropinirole CR tablets versus IR tablets).

The systemic exposure to ropinirole after CR tablets administration compare to the current IR tablets has been investigated in two distinct studies: Study 162 (in healthy volunteers) and study 164 (in Parkinson's disease patients).

In Study 162, healthy subjects were randomised to receive either single doses of ropinirole CR 0.75 mg, ropinirole CR 3.0 mg or placebo, or three, 8-hourly doses of open-label ropinirole IR 0.25 mg, in each of four study periods. The treatment periods were separated by a wash-out period of 7 days. The subjects crossed over to each different treatment regimen and received concomitant domperidone (20 mg tid) with each regimen.

Dose-normalised AUC(0-∞) and C<sub>min</sub> values were similar for the ropinirole IR and ropinirole CR. However, dose-normalised C<sub>max</sub> for ropinirole CR was, on average, 31% lower than for ropinirole IR. The degree of fluctuation in plasma concentrations for ropinirole CR was approximately half that of ropinirole IR. T<sub>max</sub> for ropinirole IR was generally attained prior to 4 h post dose, whereas for ropinirole CR, t<sub>max</sub> was generally achieved between 8 and 10 h post-dose.

Study 164 was a randomized, open label, two period, *cross-over* study conducted in two parts. In Part A, the relative bioavailability of the CR formulation was compared to that of the IR formulation. Part B focused on the investigation of the food-effect (this part of the study is detailed below in the food-effect paragraph).

In Part A, patients were randomised to one of two treatment sequences, each comprising two periods. In Period 1 of treatment sequence 1, patients received 8 mg od ropinirole CR for 4 to 7 days. In Period 2, patients received ropinirole 7.5 mg IR (2.5 mg tid) for 4 to 7 days. In Period 1 of treatment sequence 2, patients received ropinirole 7.5 mg IR (2.5 mg tid) for 4 to 7 days. In Period 2, patients received 8 mg od ropinirole CR for 4 to 7 days.

A total 20 patients completed Part A of the study and were included in the pharmacokinetic analysis.

The ratios of dose-normalised AUC<sub>(0-24)</sub> and C<sub>min</sub>, for 8 mg od ropinirole CR relative to 2.5 mg tid ropinirole IR, were similar, being close to unity and with 90% CIs within the limits associated with bioequivalence (0.80 to 1.25). The dose-normalised C<sub>max</sub> for the CR formulation was, on average, 12% lower than for the IR formulation. The upper end of the 90% CI was less than unity, indicating that the lower C<sub>max</sub> observed for the CR formulation, compared to the IR formulation, was statistically significant.

It clearly appears that the administration of once a day 8 mg CR tablet leads successfully to a comparable systemic exposure to ropinirole as that obtained with the IR tablets administered following the current tid scheme (2.5mg x 3/day). These pharmacokinetics findings support strongly, that similar safety/efficacy profile might be obtained with Requip LP as compared to the current Requip IR tablets.

Bioequivalence: (dosage strength equivalence).

Two bioequivalence studies (study 165 and 219) have been conducted in order to test the bioequivalence of different dosage strengths:

Study 165 was an open-label, multicentre study. Patients received ropinirole CR od, starting at a dose of 2 mg/day with a weekly dose escalation of 2 mg (2, 4, 6, 8 mg).

In treatment sequence 1, patients received ropinirole CR 1 x 8 mg od in the first week, followed by ropinirole CR 4 x 2 mg od in the second week. In treatment sequence 2, patients received ropinirole CR 4 x 2 mg od in the first week, followed by ropinirole CR 1 x 8 mg od in the second week.

A total of 28 patients were included in the study among them 22 completed the study. 5 patients were withdrawn due to adverse events and one for personal reasons.

**Summary of Steady-State Ropinirole Pharmacokinetic Parameters (geometric mean (CVb%)) following Administration of 1 x 8.0 mg CR Tablet or 4 x 2.0 mg CR Tablets**

Dose of ropinirole CR	n	AUC(0-24) (ng.h/mL)	C <sub>max</sub> (ng/mL)	C <sub>min</sub> (ng/mL)	t <sub>max</sub> (h) <sup>a</sup>
1 x 8.0 mg	22	168 (69.1)	9.30 (67.2)	4.74 (88.0)	6.00 (2.00 - 20.0)
4 x 2.0 mg	22	152 (56.8)	8.50 (49.2)	4.49 (66.1)	10.0 (2.00 - 20.0)

a. median (range)

Bioequivalence was demonstrated for ropinirole CR 1 x 8.0 mg and ropinirole CR 4 x 2.0 mg in patients with Parkinson's disease.

In Study 219, the dosage strength equivalence of 2 x 1.0 mg tablets versus 1 x 2.0 mg tablet, and 3 x 1.0 mg tablets versus 1 x 3.0 mg tablet were investigated. The study was a five-way cross-over, single-dose study conducted in healthy male and female subjects. Subjects were randomised to receive one of the following dosage regimens of ropinirole CR at each treatment period: 1.0 mg tablet, 2 x 1.0 mg tablets, 2.0 mg tablet, 3 x 1.0 mg tablets and 3.0 mg tablet.

**Summary of Ropinirole Pharmacokinetic Parameters (geometric mean (CVb%))**

	2 x 1.0 mg (n = 33)	1 x 2.0 mg (n = 33)	3 x 1.0 mg (n = 33)	1 x 3.0 mg (n = 31)
AUC(0-∞) <sup>a</sup> (ng.h/mL)	18.4 (40.4%)	20.0 (38.3%)	28.1 (46.0%)	27.5 (46.4%)
AUC(0-t) (ng.h/mL)	18.3 (37.4%)	19.3 (36.3%)	27.2 (44.0%)	26.9 (44.2%)
C <sub>max</sub> (ng/mL)	1.00 (32.9%)	1.07 (31.2%)	1.49 (33.4%)	1.58 (33.8%)
t <sub>max</sub> <sup>b</sup> (h)	10.0 (3.00-18.0)	10.0 (3.00-24.0)	10.0 (4.00-18.0)	12.0 (3.00-26.0)
t <sub>1/2</sub> <sup>a</sup> (h)	4.74 (19.5%)	4.69 (20.3%)	4.67 (20.7%)	4.71 (16.7%)

a. 2 x 1.0 mg, n = 27; 1 x 2.0 mg, n = 30; 3 x 1.0 mg, n = 31; 1 x 3.0 mg, n = 29

b. t<sub>max</sub> data presented as median (range)

The 90% CIs for AUC(0-∞), AUC(0-t) and Cmax for the comparisons multiple tablets : single tablet were completely contained within the equivalence range (0.80, 1.25). Therefore, dosage strength equivalence was demonstrated for ropinirole CR 2 x 1.0 mg compared with CR 1 x 2.0 mg, and ropinirole CR 3 x 1.0 mg compared with CR 1 x 3.0 mg.

#### Influence of food

Food-intake effect on the bioavailability of the CR tablets was tested in patients at steady-state (study 164) as well as in healthy volunteers after single dose administration (study 161).

In Study 164 (Part B), patients received a single steady-state dose of ropinirole 8.0 mg CR in either the fed or fasted state, and then crossed over to the other state. Fasted state patients received a single dose of ropinirole CR after an overnight fast of at least 10 h and then continued fasting for another 4 h. The fed patients received a single dose of ropinirole CR immediately after a high-fat breakfast which they started to eat 30 min prior to dosing time. After ropinirole CR administration, no food was allowed for 4 h. There was a minimum of 3 days between treatment periods.

#### **Summary (Geometric Mean (CVb%)) of Ropinirole Pharmacokinetic Parameters in Patients with Parkinson's Disease**

<b>Parameter (unit)</b>	<b>Fasting (n = 20)</b>	<b>Fed (n = 20)</b>
<b>AUC(0-24) (ng.h/mL)</b>	139 (60.3%)	147 (57.2%)
<b>Cmax (ng/mL)</b>	7.59 (54.8%) <sup>a</sup>	8.73 (48.5%) <sup>a</sup>
<b>Cmin (ng/mL)</b>	3.94 (62.2%) <sup>a</sup>	3.77 (82.5%) <sup>a</sup>
<b>tmax (hours)<sup>b</sup></b>	6.00 (2.00 - 14.00) <sup>a</sup>	10.00 (4.00 - 14.00) <sup>a</sup>

a. n = 21

b. Median(range)

AUC(0-24) and Cmin were similar in the fed and fasted states, based on the ratios being close to unity and the 90% CIs being within the limits associated with bioequivalence (0.80 to 1.25). Cmax was slightly higher (15%) and tmax was slightly delayed by, on average, 2 h in the fed state compared with the fasted state. This small increase in Cmax and delay to Tmax is unlikely to be clinically relevant due to the relatively flat concentration-time profile of ropinirole following administration of ropinirole CR, suggesting flexibility, with respect to food intake, in the conditions of dosing for the CR formulation.

There was no evidence to suggest that the controlled release characteristics of ropinirole CR were lost when ropinirole CR was co-administrated with food (i.e. no evidence of dose dumping).

In Study 161 (Part II), the effect of food intake on the extent and rate of absorption of a single oral dose of ropinirole CR 0.75 mg was investigated in healthy subjects. Subjects were given a single dose of ropinirole CR 0.75 mg in the fasted condition and in the fed state (30 min after the start of a high-fat breakfast).

**Effect of Food - Summary of Statistical Analysis for Ropinirole Pharmacokinetic Parameters following a single dose in Healthy Subjects**

Parameter	Geometric mean (CVb%)		Ratio Fed:Fasted	95% CI
	Fasted (n = 14)	Fed (n=13)		
<b>AUC(0-∞) (ng.h/mL)</b>	5.95 (46.7%)	7.86 (47.0%)	1.30	(1.06, 1.60)
<b>Cmax (ng/mL)</b>	0.280 (50.7%)	0.414 (49.8%)	1.44	(1.24, 1.68)

Administration of ropinirole CR after a high-fat breakfast led to higher Cmax (44%) and AUC(0-∞) (30%) values compared to the fasted condition. There was no occurrence of dose dumping in any subject.

Distribution

No formal studies have been conducted with the claimed CR formulations. Plasma protein binding of the drug is low (10–40%). Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approx. 7L/kg).

Metabolism/excretion

No formal studies have been conducted with the claimed CR formulations. 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. Ropinirole is cleared from the systemic circulation with an average elimination half-life of about 6 hours. The increase in systemic exposure (C<sub>max</sub> 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.

Dose proportionality

Dose proportionality of plasma concentration profile has been extensively investigated with the CR formulations in healthy volunteers (study 162 and study 219) as well as in patients (study 165).

The design of Study 165 is detailed above (dosage strength equivalence). From this study information regarding the dose proportionality could be drawn for the 2 mg up to 8 mg dose range.

**Summary of Selected Plasma Ropinirole Pharmacokinetic Parameters  
(geometric mean (CVb%))**

Parameter	2 mg (n=22)	4 mg (n=22)	8 mg (n=22)
<b>AUC(0-24) (ng.h/mL)</b>	37.9 (56.7%)	76.3 (54.7%)	168 (69.1%)
<b>Cmax (ng/mL)</b>	2.16 (50.6%)	4.19 (50.7%)	9.30 (67.2%)
<b>Cmin (ng/mL)</b>	1.13 (76.5%)	2.36 (65.8%)	4.74 (88.0%)
<b>tmax (h)<sup>a</sup></b>	7.00 (1.00-20.0)	6.00 (4.00-24.0)	6.00 (2.00-20.0)

a. median (range)

This study results shows that almost linear pharmacokinetic behaviour was observed with the CR tablets when administered as repeated 2 mg, 4 mg and 8 mg daily dose.

In Study 162, the dose proportionality of single doses of ropinirole CR was investigated over the dose range 0.75 to 3.0 mg in healthy subjects.

T<sub>max</sub> and t<sub>1/2</sub> values were similar for both the 0.75 mg and 3.0 mg doses of ropinirole CR.

In Study 219, the dosage proportionality of ropinirole CR was investigated over the dose range 1.0 to 3.0 mg in healthy subjects. The design of this study is detailed in section “*dosage strength equivalence*”

**Summary of Ropinirole Pharmacokinetic Parameters  
(Geometric Mean (CVb%))**

Parameter (unit)	CR 1.0 mg (n = 32)	CR 2.0 mg (n = 33)	CR 3.0 mg (n = 31)
AUC(0-∞) <sup>a</sup> (ng.h/mL)	8.50 (44.2%)	20.0 (30.0%)	27.5 (46.4%)
AUC(0-t) (ng.h/mL)	8.34 (44.8%)	19.3 (36.3%)	26.9 (44.2%)
C <sub>max</sub> (ng/mL)	0.493 (32.7%)	1.07 (31.2%)	1.58 (33.8%)
t <sub>max</sub> <sup>b</sup> (h)	10.0 (3.00-16.0)	10.0 (3.00-24.0)	12.0 (3.00-26.0)
t <sub>1/2</sub> <sup>a</sup> (h)	4.93 (22.1%)	4.69 (20.3%)	4.71 (16.7%)

a. n for 1.0 mg = 31, 2.0 mg = 30, 3.0 mg = 29

b. t<sub>max</sub> data are presented as median (range)

Studies 162 and 219 outcome gives confirmation of the linear pharmacokinetics behaviour of ropinirole CR tablets at the lowest 0.75 up to 3 mg daily doses.

Time dependency

Complete plasma concentration profiles from single and repeated-dose were assessed in Study 163. This was a double-blind, two-way crossover, placebo-controlled, randomised single and repeat dose study in healthy volunteers.

Eligible subjects were randomised to receive 1.0 mg ropinirole CR (Geomatrix) tablets or placebo, at 24 hour (h) intervals (in the morning) over nine days, without dosing on Day 2, i.e. between the single dose (SD) and the multiple dose (MD) phases of the two treatment periods. The single dose and multiple dose phases of a treatment period were therefore separated by a wash-out period of one day, and the two treatment periods were separated by a wash-out period of seven days.

**Summary of Single and Repeat Dose Ropinirole Pharmacokinetic Parameters  
(geometric mean CVb%)**

Parameter	Single Dose (n = 28)	Repeat Dose (n = 27)
C <sub>max</sub> (ng/mL)	0.512 (48.3%)	0.633 (44.4%)
t <sub>max</sub> (h) <sup>a</sup>	10.0 (2.00 - 22.0)	6.00 (2.00 – 18.0)
AUC(0-24) (ng.h/mL)	7.64 (51.2%)	9.82 (51.7%)
AUC(0-∞) (ng.h/mL)	8.80 (56.1%)	Not Determined
t <sub>1/2</sub> (h) <sup>b</sup>	4.73 (22.6%)	Not Determined
C <sub>min</sub> (ng/mL)	0.138 (110%)	0.170 (98.6%)
Degree of fluctuation (DF) <sup>c</sup>	0.865 (75.0%)	1.02 (44.4%)

a) t<sub>max</sub> is reported as median (range)

b) t<sub>1/2</sub> reported as arithmetic mean (CVb%)

c) DF= (C<sub>max</sub>-C<sub>min</sub>)/C<sub>avg</sub>,

AUC(0-24) increased on average by 26% upon repeated administration of ropinirole CR and C<sub>max</sub> increased by an average of 24%.

Based on trough concentrations of ropinirole (collected on Days 4 -9), steady-state concentrations appeared to have been achieved within 4 days of dosing with ropinirole CR 1.0 mg od.

#### Intra- and inter-individual variability

The inter-subject variability as assessed by the coefficient of variation (CV) for the systemic exposure parameters (AUC<sub>τ</sub> and C<sub>max</sub>) was generally of the same magnitude with the CR formulations (CV of 50-75 %) as compared to the IR formulation (CV of 42-68 %).

There is no reliable estimation of the intra-subject variability.

#### Pharmacokinetics in target population

The pharmacokinetics of ropinirole was extensively investigated in healthy volunteers as well as in Parkinson's disease patients. No significant differences were evidenced regarding systemic exposure to ropinirole and its main metabolites in patients as compared to healthy volunteers.

#### Special populations

No formal study was conducted in subjects with renal impairment, or impaired hepatic function.

No specific study has investigated the effect of gender on the pharmacokinetics of ropinirole and most pharmacokinetic studies were conducted in male and female subjects. No gender effect has been evidenced.

No specific study has been conducted in order to compare the pharmacokinetics of CR formulations in elderly subjects comparatively to young subjects. However the PK-population analysis performed with the sparse data from pivotal Phase III clinical studies (studies 168 and study 169) evidenced age as an influential covariate on clearance. The population mean estimate for apparent clearance (CL/F) in subjects <65 years was 54.7 L/h and in subjects >65 years of age was 47.7 L/h. The magnitude of this small difference of 13% in CL/F is similar to that observed in the original population pharmacokinetic analysis for ropinirole IR tablets (15%) and is unlikely to be of any clinical relevance.

As well as with the IR formulations no pharmacokinetic investigation has been conducted with the CR formulation in subjects below 18 years of age.

#### Conclusions

- The administration of once a day CR tablet leads to a comparable systemic exposure to ropinirole as that obtained with the IR tablets administered at the approximately same daily dose. These pharmacokinetic findings support strongly, that similar safety/efficacy profile might be obtained with Requip LP as compared to the current Requip tablets administered at the same daily dose.
- No significant food-effect on the bioavailability of ropinirole when administered as CR formulation. Dose dumping by food-intake could be excluded.
- Ropinirole CR tablets show linear pharmacokinetic behaviour with doses ranging from 0.75 up to 8 mg daily.
- The different CR tablets strengths shows similar bio-pharmaceutical performances (when administered at the same dose).

- Plasma concentration profiles of ropinirole remain almost steady after repeated administration. No unexpected accumulation occurs and no metabolism shift is observed after repeated use.
- There is no significant higher inter subject variability with the CR formulations as compared to the IR formulations.

#### **4.3 Discussion on the clinical aspects**

##### **4.3.1. Dose finding studies**

Two phase II studies (Study 166 and 167) were conducted to determine the optimal starting dose and titration.

In Study 166 three starting doses (1, 2, and 3 mg) of ropinirole CR tablets administered were compared to 0.75 mg of ropinirole IR (0.25 mg t.i.d). The results from this study supported the use of starting doses of ropinirole CR tablets of up to 3 mg once daily in future clinical studies, since the three different doses of ropinirole CR were well tolerated.

However, a dose of 2 mg was chosen as the starting dose for up-titration for clinical trials since this dose yields a simple titration regimen. From a kinetic point of view, the 2 mg starting dose of ropinirole CR lead to almost 3 times the 0.75 mg starting dose of ropinirole IR, however, its tolerability was as good as 0.75 mg and thus considered acceptable.

The ropinirole CR titration regimen was evaluated in Study 167. The primary objective of this study was to compare the safety and tolerability profile of two initial titration regimens of ropinirole CR tablets (Regimen A: 2, 3, 4, 6 mg, Regimen B: 2, 4, 6, 8 mg), using the registered titration regimen of ropinirole IR tablets as a reference (i.e., 0.75, 1.5, 2.25, 3.0 mg over a four week period).

The data indicated that all three ropinirole titration regimens were well tolerated. Both ropinirole CR titration regimen A and B have the same tolerability. Based on these data, regimen B (2, 4, 6, 8 mg) which was well tolerated was chosen to take forward to the Phase III studies as it allows patients to more rapidly achieve a therapeutic dose. The maintenance dose of up to 24 mg once daily was chosen based on experience with ropinirole IR tablets.

##### **4.3.2 Efficacy**

Efficacy of ropinirole CR tablets in early and advanced PD has been demonstrated in 2 multicentre, controlled Phase III clinical studies: Study 168 and Study 169 over 36 and 24 weeks respectively.

The inclusion and exclusion criteria applied to the clinical studies ensured recruitment of consistent population representative of early and advanced PD patients. Age at diagnosis and the sex-ratio is considered representative of typical patients presenting PD at different evolution stage.

Study 168 was a randomised, double-blind, three periods, two treatment crossover study. It was designed to demonstrate the non-inferiority of the ropinirole CR tablet to the currently marketed ropinirole IR tablet as monotherapy in subjects with early stage PD. The primary efficacy variable for this study was the difference between ropinirole IR and CR in the change

from period baseline in the UPDRS total motor score as recorded at the end of each flexible dose maintenance period.

For the primary endpoint, the non-inferiority of ropinirole CR to ropinirole IR was assessed by comparing the confidence interval for the treatment difference with a non-inferiority margin of 3 points. Based on data from a previous ropinirole IR study (study 056) where ropinirole IR was compared to L-dopa, a difference of 3-point non-inferiority margin on the UPDRS motor score between ropinirole CR and ropinirole IR was viewed as not clinically significant.

During the initial 12-week up-titration period, there was an improvement in the UPDRS total motor score for both formulations. The magnitude of this improvement was greater for subjects receiving ropinirole CR compared to ropinirole IR; at the end of the up-titration period (Week 12 OC) the mean UPDRS total motor score had improved by 10.4 points for subjects receiving ropinirole CR and by 8.9 points for subjects receiving ropinirole IR.

The adjusted mean difference between ropinirole CR and ropinirole IR at study endpoints was -0.7 points (95% CI [-1.51, 0.10]). As the upper limit of the 95% CI was less than the pre-defined threshold of 3 points, ropinirole CR was demonstrated to be non-inferior to ropinirole IR.

The dose progression of the up-titration scheme for ropinirole CR was more than twice as fast as ropinirole IR. This difference explains the higher final dose in the Requip CR group and this is due to the disparities of the two titration schemes and the protocol design.

At the end of maintenance period 3 despite very dissimilar mean daily doses in the 4 sequences (ranging from 9.8mg/day to 18.8mg/day), the mean UPDRS motor scores were comparable (ranging from 10.2 to 12.8), indicating that the higher doses reached by ropinirole CR did not provide additional clinical benefit on average, and are likely to be supra-therapeutic in the majority of patients. The nature of the flat exposure-response curve also suggests that patients have a good response at lower doses of ropinirole CR.

Patients that began the study receiving Requip CR, have received higher doses than those that began by Requip IR. Data show no difference between the two formulations independently of randomization sequences and this is in favour of equivalence of the two treatments despite the doses differences if patients have begun either the CR or IR form. Nevertheless, in order to confirm the non-inferiority, a re-analysis taking into account only the patients included in the sequences starting with the immediate release form (IR-PR-PR and IR-IR-PR), that is to say, only the patients who received the "therapeutic doses" was requested.

Results of this post-hoc analysis on the primary criteria on the PP demonstrated the non-inferiority of ropinirole CR versus ropinirole IR. This result supports those obtained from the original analysis that included data from all four treatments sequences.

There were no statistically significant differences between ropinirole CR and IR tablets for any of the secondary variables. Both tablet formulations were efficacious.

Study 169 was a randomised, double-blind, placebo-controlled, parallel group study designed to compare ropinirole CR tablets with placebo as adjunct therapy to L-dopa in advanced stage PD subjects who had demonstrated a lack of control with L-dopa therapy (e.g. end of dose akinesia or simple "on/off" fluctuations). The primary efficacy variable was mean change

from baseline in awake time ‘off’ at Week 24 last observation carried forward (LOCF), and was analysed in terms of absolute change from baseline.

At week 24 LOCF, in the ropinirole CR group, total awake time spent “off” had decreased, on average, by approximately 2 hours and on average, by approximately half an hour in the placebo group. The adjusted mean difference in total awake time spent “off” between ropinirole CR and placebo was -1.7 hours (95% CI: [-2.34, -1.09]) indicating a statistically significant benefit of ropinirole CR over placebo.

The odds of a ropinirole CR recipient achieving a 20% reduction in awake time spent “off” and a 20% reduction in L-dopa dose was more than 4 times that of a placebo recipient.

From Week 2 onwards, the proportion of responders on the CGI-I scale was greater for subjects receiving ropinirole CR than for subjects receiving placebo. At Week 24 LOCF, 42% of subjects in the ropinirole CR group compared to 14% of subjects in the placebo group were responders.

There was a statistically significant benefit of ropinirole CR over placebo for time to reinstatement of L-dopa following a reduction in dose. At any time point, subjects who received placebo were approximately 5 times more likely to require reinstatement with L-dopa than subjects who received ropinirole CR.

Analysis of the primary variable was supported by clinically meaningful and statistically significant superiority over placebo for the secondary efficacy parameters except for change from baseline in the Epworth Sleepiness Scale (ESS) total score, the change from baseline in the social support, cognitive impairment and bodily discomfort domains of the Parkinson’s disease Quality of Life Questionnaires (PDQ-39).

Long term efficacy and safety was assessed in [Study 196](#), an open-label, extension study for subjects with PD who required dopaminergic therapy and had previously taken part in ropinirole CR Studies 167 or 164.

For this open study, there was no protocol defined primary efficacy variable. However, the efficacy profile of ropinirole CR was monitored during the study using Clinical Global Impression (CGI) and UPDRS assessments.

Long-term treatment of subjects with PD with ropinirole CR resulted in small improvements from screening in both the mean total UPDRS motor score and the mean total UPDRS ADL scores over the course of 21 months treatment. The proportion of subjects assessed as ‘mildly ill’ and better on the CGI severity of illness scale was higher at all visits during the long-term treatment phase than at screening.

The results of this study support the extended use of ropinirole CR.

### **4.3.3 Safety profile**

The safety profile of ropinirole CR tablets has been established based on data from 560 PD subjects, 151 of whom received the maximum allowable dose (24mg/day).

No new safety concern emerged regarding this new formulation of ropinirole, from the results of the clinical studies, included ongoing long-term exposure studies.

The safety profile of ropinirole CR appears to be similar to the well known safety profile of ropinirole immediate release. Indeed, the AE profile of ropinirole CR tablet was as expected, with the most frequently reported AEs being dopaminergic in nature.

A higher incidence of dyskinesia was observed in patients with advanced stage PD treated with ropinirole CR in combination with L-dopa. During the assessment of the French marketing authorisation application, Section 4.2 “Posology and method of administration” of the SmPC was revised to advise prescribers of this observation.

Interim long-term data from extension studies have not revealed any new safety concerns regarding the long-term use of ropinirole CR tablets.

## **5. OVERALL DISCUSSION , BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

The benefit/risk of REQUIP LP/ROPINIROLE PAUCOURT LP 2 mg, 3 mg, 4 mg and 8 mg is considered positive.

The administration of once a day CR tablet leads to a comparable systemic exposure to ropinirole as that obtained with the IR tablets administered at the approximately same daily dose.

The SPC, Patient Information Leaflet (PIL) and packaging are in the agreed template.

The Member States mutually recognised the French evaluation of the marketing authorisation.

### *Commitments made during the procedure*

#### **1. Submission of Updated eCTD Modules**

GSK commits to provide updated eCTD modules to those Member States managing this procedure in eCTD (Belgium, Luxembourg, The Netherlands and Spain) for the sections that have been amended during the Mutual Recognition Procedure for Ropinirole prolonged release tablets.

#### **2. Submission of Type II Variations for Cardiac Safety Pharmacology Wording in SmPC Section 5.3**

The non clinical assessment report for ropinirole prolonged release tablets issued by AFSSAPS in August 2007 requested results of in vitro studies related to cardiac safety pharmacology be summarised in Section 5.3 of the SmPC. So that wording in section 5.3 of the SmPC can be agreed for all of the ropinirole containing products, GSK has committed to submit type II variation applications to all of the ropinirole-containing products that GSK holds marketing authorisations for through the mutual recognition procedure in the European Union.

#### **3. Agreement on PSUR Periodicity with AFSSAPS**

GSK has committed to agree the PSUR periodicity for ropinirole prolonged-release tablets with AFSSAPS.

#### **4. Submission of Updated Detailed Description of the Pharmacovigilance System**

GSK has committed to provide the Reference Member State and all the Concerned Member States with an updated Detailed Description of the Pharmacovigilance System (DDPS) shortly

after the conclusion of the mutual recognition procedure for ropinirole prolonged-release tablets.

#### **5. Validation of a Suitable Method for the Determination of Nitromethane**

GSK commits to validating a suitable method for the determination of Nitromethane in ropinirole hydrochloride and to testing three consecutive industrial scale batches by this method within three months of completion of this Mutual Recognition Procedure.