

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006, as
amended**

**ADARTREL
(Ropinirole)**

FR/W/014/pdWS/001

**Marketing Authorisation Holder:
GlaxoSmithKline Laboratoires**

Rapporteur	France
Finalisation procedure (day 120)	10 September 2010
Date of finalisation of PAR	November 2010

ADMINISTRATIVE INFORMATION

Invented name of the pharmaceutical product in the originating Member State	ADARTREL
INN of the active substances	Ropinirole hydrochloride
MAH	GlaxoSmithKline Laboratoires
Currently approved Indication (s)	Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.
Pharmacotherapeutic classification	N 04BCO4 - Dopamine Agonists
Pharmaceutical form(s)	Film-coated-tablets
Strength(s)	0.25 mg, 0.5 mg, 1 mg, 2 mg

1. EXECUTIVE SUMMARY AND RECOMMENDATION

In accordance with Article 46 of Regulation (EC) No 1901/2006, GlaxoSmithKline submitted the study report of a clinical study (open-label, dose-rising, multi-centre study) in adolescent RLS patients to assess the single dose pharmacokinetics and tolerability of ropinirole.

SmPC changes are proposed in sections 4.2 and 5.2

After the circulation of the assessment reports and comments received from the CMS, a variation is proposed in order to include pharmacokinetics data in children in section 5.2 of the SPC (with a cross reference in section 4.2 Children and adolescents) according to article 46 of the paediatric regulation.

The proposed wording is the following:

Paediatric population

Limited pharmacokinetic data obtained in adolescents (12-17 years, n=9) showed that the systemic exposure following single doses of 0.125 mg and 0.25 mg was similar to that observed in adults (see also section 4.2; subparagraph "Children and adolescents).

2. INTRODUCTION

Adartrel (ropinirole) have been approved for the *treatment of moderate to severe idiopathic/primary restless legs syndrome (RLS).*

In accordance with Article 46 of Regulation (EC) No 1901/2006, GlaxoSmithKline submitted information about paediatric studies.

Following the approval of ropinirole IR to treat adult patients with RLS and during the development of the CR-RLS tablet formulation for adult patients, a clinical development programme was compiled to investigate the effects of ropinirole in adolescent RLS patients.

Although there are no systematic prevalence studies or estimates of the prevalence of RLS in the paediatric population, several reports and studies in the literature confirm that RLS symptoms may be observed in children and most frequently in adolescents. Ropinirole administration in the adolescent population is supported by the existing pre-clinical safety assessment and toxicology data conducted to support adult administration. No toxicity has been found and there is no class effect which would be of specific concern in the paediatric population.

The first objective of the programme was to identify the optimal starting dose of ropinirole IR in adolescent patients. A single dose pharmacokinetic (PK) study (SK&F101468/253) was conducted to assess the tolerability and pharmacokinetics of ropinirole IR in adolescent patients with RLS.

The MAH stated that the submitted paediatric study does not influence the benefit risk for ADARTREL and thus, no changes to the SmPC, PIL or Labelling are proposed.

3. SCIENTIFIC DISCUSSION

3.1 Information on the pharmaceutical formulation used in the study

Ropinirole IR tablets were used in Study SK&F101468/253. The starting dose was selected as 0.125 mg instead of the 0.25 mg starting dose used in adults. This was because it was expected that the ropinirole exposure in a 12 year old at a dose of 0.125 mg would not exceed the mean exposures seen for ropinirole in adults at a starting dose of 0.25 mg.

During Study SK&F101468/253 the CR-RLS formulation development was completed in adults and it was intended to use this tablet formulation in subsequent adolescent RLS studies. To obtain adolescent PK data on the new formulation it was proposed that this formulation should be incorporated into the ongoing adolescent pharmacokinetic study. In a period of 3 years, seven sites only managed to recruit 8 of the planned 14 subjects for this study. An interim analysis showed that data from these subjects was sufficient to characterise the pharmacokinetics of ropinirole IR in adolescents. The protocol was therefore amended to include the CL-RLS tablet formulation for the remaining 6 subjects to be recruited and to no longer investigate the 0.125mg IR dose.

Shortly after the implementation of this amendment and following consultation with the FDA, a decision was made to withdraw the NDA for ropinirole CR-RLS. GSK therefore took the decision to terminate Study SK&F101468/253. At this time only one subject had been enrolled under the amended protocol.

3.2 Clinical aspects

➤ Description

Study SK&F101468/253 was an open-label, dose-rising, multi-centre study in adolescent RLS patients to assess the single dose pharmacokinetics and tolerability of ropinirole.

➤ Methods

Objectives

Primary

- To assess the single dose pharmacokinetics of ropinirole in adolescent RLS patients.

Secondary

- To assess the tolerability of a single dose of ropinirole in adolescent RLS patients.

Endpoints

Primary

- $AUC_{(0-\infty)}$: the area under the plasma concentration-time curve from the time of dosing to infinity for ropinirole calculated using the trapezoidal rule.
- C_{max} : the maximum observed plasma concentration for ropinirole.

Secondary

- t_{max} : time to reach the maximum observed plasma concentration for ropinirole.
- $t_{1/2}$: half life for ropinirole.
- For SKF-89124 and SKF-104557, ratio of AUC metabolite: AUC ropinirole.

Safety Endpoints

- Safety: adverse events, vital signs, ECG data, clinical laboratory parameters
- At each dose level and dose level by study part (i.e., pre and post amendment 05):
- Change from pre-dose baseline in blood pressure and heart rate measurements for supine and standing.
- Change from pre-dose baseline in orthostatic (supine to standing) blood pressure and heart rate measurements.
- Incidence of adverse events, in particular nausea, vomiting and symptomatic orthostatic hypotension.

Inclusion Criteria

A subject was eligible for inclusion in this study only if all of the following criteria applied:

1. Male and female adolescents subjects diagnosed with probable or definite RLS aged between 12 and 17 years old inclusive.
2. Body weight \geq 35 kg.
3. A female was eligible to enter and participate in this study if she was of:
 - non-childbearing potential; or,
 - child-bearing potential, had a negative pregnancy test (urine) at screening, and agreed to use an effective contraception
4. Subjects should preferably have been non-smokers for the previous 3 months. However, if a subject did smoke, their smoking habits must have remained constant from 7 days prior to dosing with study medication until completion of the study.
5. The parent/guardian must have given written informed consent for the child to participate in this investigation. Adolescents who were intellectually able to understand the concepts and procedures of the protocol also signed the informed consent.

A child diagnosed with ADHD could participate if they were not currently taking psychostimulant medication. Participants with a history of stimulant treatment were considered for participation under certain circumstances, e.g. if they did not receive a clinically important benefit in view of the treating physician, or if they were on a planned extended "drug holiday" from their psychostimulant medication.

Exclusion Criteria

A subject was not eligible for inclusion in this study if any of the following criteria applied:

Subjects suffering from RLS symptoms which required treatment during the daytime (daytime defined as 10.00 until 18.00), subjects who suffered from a primary sleep disorder other than RLS that may significantly affected the symptoms of RLS (e.g. narcolepsy, sleep terror disorder, sleep walking disorder and breathing related sleep disorder), signs of secondary RLS (e.g. renal failure at end-stage renal disease).

Exclusion criteria were also related to clinical diagnoses, medical history and prior or concomitant medication which would have prevented the patient from taking part in the study.

Treatments Administered

All subjects were scheduled to participate in two study periods (Period 1 and Period 2), separated by a 7 – 14 day washout period. For each study period, subjects attended the clinic on the dosing day to receive their study medication at approximately 09:00 hr or 17:00 hr and remained in the clinic for approximately 10-16 hrs. Subjects were asked to return the following morning for a 24 hour PK blood sample and safety assessments.

Treatment A: Ropinirole 0.125 mg IR

Treatment B: Ropinirole 0.25 mg IR

Treatment C: Ropinirole 0.5 mg CR-RLS

Eight subjects received a single dose of 0.125 mg ropinirole IR in Period 1 and six patients went on to receive a single dose of 0.25 mg ropinirole IR in Period 2, after a 7-14 day washout.

Preliminary PK assessments were conducted on the first 8 subjects enrolled in the protocol. Based on these analyses a protocol amendment was implemented to enrol additional subjects to receive a higher dose of 0.25 mg ropinirole IR in Period 1 and then 0.5 mg ropinirole CR-RLS in Period 2. However, only a single subject was subsequently enrolled and administered this dose.

Sample Size

A sufficient number of adolescent (aged 12-17) RLS patients (minimum of 6 males and 6 females plus a further 2 subjects of either gender), to ensure 14 evaluable subjects was planned.

Pharmacokinetic Data Analysis

Pharmacokinetic parameters were estimated by non-compartmental techniques, including the maximum plasma concentration (C_{max}), the time taken to achieve C_{max} (T_{max}) and the area under the plasma concentration-time curve. In addition, the ratio of AUC metabolite: AUC ropinirole was calculated in order to investigate if there are any metabolic differences in the clearance of ropinirole between adolescents and adults. Pharmacokinetic data was summarised using descriptive statistics PK.

➤ Results

Subject Disposition and Demographics

The study did not enrol the target number of subjects; however, there was a balance (5 females and 4 males).

Number of Subjects	
Number of subjects planned, N:	14
Number of subjects entered, N:	9
Number of subjects included population in All Subjects (safety) population, n (%):	9 (100)
Number of subjects included in PK population, n (%):	9 (100)
Number of subjects completed as planned, n (%):	7 (78)
Number of subjects withdrawn (any reason), n (%):	2 (22)
Number of subjects withdrawn for SAE, n (%):	0
Number of subjects withdrawn with AE, n (%):	1 (11)
Demographics	
Age in Years, Mean (Range)	14 (12-17)
Sex, n (%)	
Female:	5 (56)
Male:	4 (44)
BMI, (kg/m²) Mean (Range)	22.2 (15.6-29.7)
Height, (cm) Mean (Range)	165 (144-184)
Weight, (kg) Mean (Range)	61.3 (39.7-100.7)
Ethnicity, n (%)	
Hispanic or Latino:	0
Not Hispanic or Latino:	9 (100)
Race, n (%)	
White – White/Caucasian/European Heritage	9 (100)

PHARMACOKINETICS

Ropinirole PK parameters following single administration of ropinirole

Parameter	Statistic	Treatment N (n)		
		0.125 mg IR 8 (8)	0.25 mg IR 7 (7)	0.5 mg CR- RLS 1 (1)
AUC(0-t) (ng.h/mL)	Geo Mean (CVb%)	1.20 (72.0)	2.51 (70.0)	3.38
Cmax (ng/mL)	Geo Mean (CVb%)	0.238 (35.1)	0.444 (37.6)	0.608
tmax (h)	Median (range)	1.53 (1.00-4.08)	1.50 (1.02-4.00)	4.15
tlast (h)	Median (range)	10.00 (5.42-16.00)	11.93 (5.83-15.90)	9.95

Summary of SKF-104557 pharmacokinetic parameters following single administration of ropinirole

• Parameter	• Statistic	• Treatment • N (n)		
•		• 0.125 mg IR • 8 (8)	• 0.25 mg IR • 7 (7)	• 0.5 mg CR-RLS • 1 (1)
• AUC(0-t) (ng.h/mL)	• Geo Mean (CVb%) • Range	• 1.25 (49.7) ¹ • • 0.539-1.87	• 2.40 (48.4) • • 1.17-4.18	• 8.36
• Cmax (ng/mL)	• Geo Mean (CVb%) •	• 0.196 (33.0) •	• 0.359 (58.8) •	• 0.750
• tmax (h)	• Median (range)	• 1.80 (1.00- 4.08)	• 2.08 (1.05- 4.05)	• 4.15
• tlast (h)	• Median • (range)	• 10.00 • (1.17-16.00)	• 11.93 • (5.83-15.90)	• 23.93

Summary of SKF-89124 pharmacokinetic parameters following single administration of ropinirole

Parameter	Statistic	Treatment N (n)	
		0.25 mg IR 7 (3)	0.5 mg CR-RLS 1 (1)
AUC(0-t) (ng.h/mL)	Geo Mean (CVb%)	0.0319	NA
Cmax (ng/mL)	Geo Mean (CVb%)	0.0271 (11.5)	0.0361
tmax (h)	Median (range)	1.05 (0.55-1.50)	4.15
tlast (h)	Median (range)	1.05 (0.55-2.22)	4.15

SKF-89124 was generally non quantifiable for the 0.125 mg dose.

Following oral administration of ropinirole IR, ropinirole was absorbed quickly, with peak concentrations observed approximately 1.5 hours after dosing. Ropinirole t_{max} was similar for the two IR doses and was observed later (4 hours) for the one subject who received ropinirole CR.

Appearance of SKF-104557, the primary metabolite, into plasma was rapid (median t_{max} 2 hours) following administration of ropinirole IR. SKF-104557 t_{max} was similar for the two IR doses and was observed later (4 hours) following ropinirole CR.

Following IR ropinirole single dose, over the dose range 0.125 mg to 0.25 mg, ropinirole and SKF-104557 appeared linear with the PK parameters for 0.25 mg ropinirole IR being approximately 1.5 to 2-fold higher than the corresponding values for 0.125 mg ropinirole IR.

The extent of SKF-104557 exposure was comparable to that of ropinirole as assessed by both AUC(0-t) and C_{max}. Plasma concentration-time profiles for SKF-89124, a secondary metabolite, were limited, with quantifiable concentrations in only 6% of the samples analysed and none following the 0.125 mg ropinirole IR dose.

Thus PK parameters for this metabolite were considered too low to provide a meaningful assessment.

Comparison of Ropinirole Pharmacokinetics between Adolescents and Adults

Single dose C_{max} and AUC values of ropinirole following administration of ropinirole IR to adolescent subjects were compared with C_{max} and AUC values obtained following single doses of ropinirole IR in the adult population. Dose-for-dose comparisons in the PK of ropinirole were made for the 0.25 mg dose from the current study with those obtained in the group of healthy adults from Study 101468/201 who received 0.25mg ropinirole IR as a single dose. For practical purposes, blood samples were only collected up to 16 hours post-dose in this adolescent study, therefore AUC(0-t) values for ropinirole in the adolescent group were compared to AUC(0-16) values in the adult group.

	C _{max} (ng/mL)			AUC(0-t) (ng.h/mL)		AUC(0-16) (ng.h/mL)
	Adolescent		Adult	Adolescent		Adult
	0.125 mg	0.25 mg	0.25 mg	0.125 mg	0.25 mg	0.25 mg
N	8	7	24	8	7	24
Min	0.135	0.231	0.187	0.441	1.29	0.805
Max	0.364	0.728	1.26	2.48	5.69	7.04
Geo Mean	0.238	0.444	0.496	1.20	2.51	3.22
CVb%	35.1	37.5	43.0	72.0	70.0	52.1

On average, C_{max} for the 0.25 mg ropinirole IR dose in the adolescent subjects was comparable with C_{max} observed for a 0.25 mg ropinirole dose in the adult population. On average, AUC(0-t) in adolescents was approximately 22% lower than AUC(0-16) observed in the adult group. This is likely to be an artefact because the last quantifiable concentration was prior to 16 h in most adolescent subjects and hence an under-estimation of the true AUC(0-16).

The ropinirole concentration-time profiles observed in adolescent subjects were evenly distributed within the range of the concentration-time profiles observed in the adult population thus indicating a similar PK profile for ropinirole in adolescent and adult subjects.

Pharmacokinetic Conclusions

Ropinirole and SKF-104557 appeared rapidly in the plasma following ropinirole IR administration with median t_{max} ranging from 1 to 2 hours. Ropinirole and SKF-104557 exposures appeared to be approximately linear across the dose range 0.125 to 0.25 mg ropinirole IR. Systemic exposure to SKF-89124 was low following ropinirole IR and CR administration.

The pharmacokinetics of ropinirole in adolescents was similar to those observed in adults.

Safety

Adverse events were collected through pre-dose to follow-up.

Adverse events

Five subjects reported a total of 13 adverse events (AEs) on the IR tablet and 3 AEs were reported by the single subject receiving the 0.5 mg CR-RLS tablet. All AEs were described as mild in nature except a shoulder injury that was considered not to be related to the study drug. The only AEs reported more than once were headache and upper abdominal pain, reported by 3 and 2 subjects, respectively.

The majority of AEs were not considered related to study drug by the investigator. All the AEs with a probable or suspected relationship to the study drug were reported by one subject who experienced;

- orthostatic hypotension at 1 hour 42 minutes after the 0.125 mg dose
- headache at 2 hours 43 minutes after the 0.125 mg dose
- dizziness approximately 2 hours after the higher 0.25 mg dose.

Serious adverse events and withdrawals due to an adverse event

There were no serious adverse events or deaths reported during the study.

Laboratory data

There were no changes in laboratory parameters considered clinically important and reported as adverse events by the investigator.

ECGs

There were no changes in ECG measurements considered clinically important and reported as adverse events by the investigator.

Blood Pressure

The mean values of supine systolic pressure after the first dose of ropinirole (Period 1) were generally slightly higher after dosing than at pre-dose. The highest mean value was seen at 3 hours post dose. Similar changes were seen in diastolic pressure with the highest mean values seen at 0.5 and 1 hour post dose.

On standing, the mean values of systolic blood pressure were similar to those seen at pre-dose.

A similar pattern of changes to Period 1 was seen in Period 2 (second dose) for supine systolic blood pressure. The blood pressure response to standing also appeared similar in Period 2 to Period 1. Of note however, at the 1.5 hour post dose time point, unlike Period 1, a small increase rather than a decrease in standing systolic pressure was seen suggesting that the changes are a reflection of natural variability rather than a drug effect.

The mean heart rate (beats per minute) post dosing was relatively stable, with no evidence of a consistent change or dose effect.

There was no apparent association between those diastolic or systolic blood pressure measurements falling outside the pre-set limits and times of maximum plasma concentrations. Also there was no evident difference in the number of subjects with values outside the limits between the two treatment groups (dose effect). Thus there were no signals that the diastolic or systolic blood pressure measurements were related to administration of study drug. The pre-set flagging limits were derived from adult blood pressure data. The large number of supine diastolic blood pressure readings below 60 mmHg appears to be typical of an adolescent population and was seen after both doses and at pre-dose.

Orthostatic Blood Pressure

There were no major consistent differences in the mean orthostatic systolic or diastolic blood pressure readings or the associated change from baseline readings. In Period 1, the largest orthostatic value

observed for systolic blood pressure was 10 mmHg at 1.5 hours post dose, representative of a small decrease in systolic blood pressure on standing. In comparison during Period 2, a small increase in systolic blood pressure on standing of 3 mmHg was observed at 1.5 hours post dose, therefore suggestive of natural variation in the data rather than a drug effect. For diastolic blood pressure, very small increases were observed on standing at all time points for both study periods.

Similarly, the largest change from the baseline reading in Period 1 for systolic blood pressure was observed at 1.5 hours post dose; however, the changes at 1 and 2 hours were minimal. At the 1.5 hour post dose time point in Period 2 a small increase was seen, rather than the decrease which was seen in Period 1, supportive of normal variation rather than a drug effect.

Safety conclusions

There were few adverse events reported and all but one unrelated adverse event were of mild severity. These data indicated a good tolerability profile but only 9 subjects were enrolled in the study and they received single doses of ropinirole that were below and equal to the lowest doses recommended for adults as starting doses. Therefore no firm conclusions can be drawn from the safety data collected in the study.

4. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

The pharmacokinetics of ropinirole in adolescents was similar to those observed in adults. Single doses of 0.125 mg and 0.25 mg IR ropinirole were generally well-tolerated. Nevertheless, safety should be validated in further studies

The PK and safety data from this study supports the evaluation of ropinirole in adolescents. Nevertheless, the real incidence of Restless Legs Syndrome in this population should be defined.

PROPOSED CHANGES IN THE SPC

After the circulation of the assessment reports and comments of the CMS, a type IB variation is proposed in order to include pharmacokinetics data in children in section 5.2 of the SPC (with a cross reference in section 4.2 Children and adolescents) according to article 46 of the paediatric regulation.

The proposed wording is the following:

Paediatric population

Limited pharmacokinetic data obtained in adolescents (12-17 years, n=9) showed that the systemic exposure following single doses of 0.125 mg and 0.25 mg was similar to that observed in adults (see also section 4.2; subparagraph "Children and adolescents).