CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-658/S13

Trade Name: Requip

Generic Name: ropinirole hcl

Sponsor: Glaxosmithkline LLC

Approval Date: May 4, 2005

Indications: For the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-658/S13

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-658/S13

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA (Serial Number)	**20658 (SE1-013)**
Sponsor:	**Glaxo Smith Kline**
Drug:	**Requip**
Proposed Indication:	**Restless Leg Syndrome**
Material Submitted:	**Response to Approvable**
Correspondence Date:	**3/3/05**
Date Review Completed	**4/27/05**
Reviewer:	**Norman Hershkowitz MD, PhD**

1. Introduction

Previous response to approvable resulted in a second approvable action as a result of the following issues:

- An analysis of QTc suggested the possibility of potential QT prolongation at doses that would be recommended for the treatment of RLS. These data were however were based upon a preliminary small study. Because a definitive QT investigation was underway the division requested an analysis of such data prior to an approval action.
- Additional information, most notably CRFs for patients who discontinued treatment secondary to adverse events was requested, for the ophthalmologic study # 125 that examined potential alterations in retinal function.
- The division requested that the Sponsor produce a PPI that combines use information for both Requip indications, as opposed to 2 separate PPIs.
- The division recommended that a (b) (4)
- The division requested a change in to the Requip sample package language so as to more clearly identify that the medication is for the treatment of moderate to severe primary restless leg syndrome and to direct the patient to the PPI.

This review will briefly address these issues below.

2. QT changes

Dr. Sally Yasuda of OCPB has reviewed the definitive QT study and has concluded that there is no evidence to indicate that QT changes occur at doses of up to 4 mg QD. The questions remain whether this division should request an additional QT study examining higher doses approved for Parkinson's disease (up to 8 mg TID versus 4 mg QD). Previous review of post marketing cases revealed 3 post-

marketing cases of Torsade's; one suspicious, one with insufficient information and one where there was an obvious cause other then ropinirole.

Additional information on the single suspicious case has been obtained since the previous review. In this case, Torsade's resolved and QT shortened when two medications were discontinued, one of which was ropinirole. The additional new information that has been identified is in regard to one of the medications that this patient was receiving (budipine), which was not discontinued. It has been found that there is data to indicate this medication produces QT prolongation. The lack of a sufficient number of strong reports of Torsade's despite its long term marketing, the borderline results on HERG analysis (albeit low borderline), and now the lack of a distinct signal in the present low dose well controlled studies suggests that additional high Parkinson's dose QT studies are unnecessary.

3. Ophthalmologic Changes

Dr. Wiley Chambers has examined additional data submitted by the Sponsor and concluded that the labeled language should be revised to more clearly represent the study that was performed; i.e. the Sponsor principally examined ERGs and did not perform routine ophthalmologic exams (e.g. visual acuity) nor did the routinely examine visual field (if ERGs were normal). He recommends the following language:

> ***Human:*** In order to evaluate the effect of REQUIP in humans, ocular electroretinograms (ERG) assessments were conducted during a 2-year, double-blind, multicenter, flexible dose, L-dopa controlled clinical study of REQUIP in patients with Parkinson's disease. A total of 156 patients (78 on ropinirole, mean dose 11.9 mg/day and 78 on L-dopa, mean dose 555.2 mg/day) were evaluated
> for evidence of retinal dysfunction through electroretinograms. There was no clinically meaningful difference between the treatment groups in retinal function over the duration of the study.

4. PPI

The Sponsor has referred this division to a study comparing the division to comprehensibility of the PPI in different formats. This division has provided DSRCS with this study and is abiding with DSRCS's decision that allows the use of two separate PPIs (reverse sides of the page). The PPI has been edited by this reviewer and Dr. Feeney and will be included in the final letter.

5. (b) (4)

The Sponsor has agreed to (b) (4).

6. Requip Sample Package Language

The Sponsor has altered the language of the sample package so as to more clearly identify that the medication is for the treatment of moderate to severe primary restless leg syndrome and to direct the patient to the PPI.

DMETS has additional recommendations that includes: 1) change in the color of the indication under drug name to increase contrast for readability, 2) Change labeling over tablet to better identify each tablet to day, dose and tablet identification (Requip/ropinirole). This reviewer agrees except that it is probably not necessary to repeat the tablet name if there is insufficient space.

7. Labeling

Final recommended labeling (including PPI) has been made in consultation between this reviewer, Dr. Feeney (team leader) and Dr Katz (DNDP Director). The final labeling will be found in the action letter.

8. Conclusions

This reviewer believes that the present submission is adequate and that an approval may be granted.

N. Hershkowitz MD,PhD
Medical Reviewer
J. Feeney, M.D. _____

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/s/

Norman Hershkowitz
5/3/05 03:22:44 PM
MEDICAL OFFICER

John Feeney
5/23/05 03:32:48 PM
MEDICAL OFFICER
Concur

MEMORANDUM

DATE: May 2, 2005

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-658/S-013

SUBJECT: Action Memo for NDA 20-658/S-013, for the use of Requip (ropinerole hydrochloride) as a treatment for Restless Legs Syndrome (RLS)

NDA 20-658/S-013, for the use of Requip (ropinerole hydrochloride) as a treatment for Restless Legs Syndrome (RLS), was submitted by SmithKline Beecham Corp. on 7/3/03. The application has been the subject of two Approvable letters, dated 12/24/03 and 2/24/05. In the latter letter, the division asked the sponsor to address the following issues:

1) Analyses of data from a single study (Study 249) suggested a dose dependent increase in the QTc interval. Although we acknowledged that the analyses were not definitive (due to the design of the study), we asked the sponsor to provide the results of a then on-going study designed to adequately characterize the effect of ropinerole on the QTc interval up to a maximum dose of 4 mg (the maximum recommended dose for patients with RLS). In addition to the possible increase in QTc interval, there had been several post-marketing reports of torsades de pointes.
2) We had additional questions about the data in a study designed to examine potential ophthalmologic toxicity (a concern raised by animal findings)
3) We asked the sponsor to produce a single patient package insert (PPI) that incorporated information for patients with either RLS or PD (they had proposed a single PPI with RLS-specific information on one side and PD-specific information on the other side of a single sheet).
4) The sponsor had proposed (b) (4) .
5) We had some comments about the language to be placed on the 2 week sample kit.

The sponsor responded to the Approvable letter in a submission dated 3/3/05. This submission has been reviewed by Dr. Norman Hershkowitz, medical officer, Dr. Sally Yasuda, Office of Clinical Pharmacology and Biopharmaceutics, Drs. Toni Piazza-Hepp and Ellen Tabak, Division of Surveillance, Research, and Communication Support, Dr. Wiley Chambers, supervisory medical officer,

ophthalmology, and Dr. John Feeney, neurologic drugs team leader. The review team has concluded that the application should be approved.

Specifically, Dr. Yasuda has reviewed the results of Study 902, a placebo controlled study in which intensive EKG monitoring was conducted after 4 daily doses of 1-4 mg of ropinerole (approximately 70-80 subjects/treatment condition). In addition, the positive control moxifloxacin was included. Dr. Yasuda describes the results and study design in detail. In brief, the maximum mean change in QTcF was less than 5 msec for ropinerole 1, 3, and 4 mg; the maximum mean change for ropinerole 2 mg was 5.32 msec. As can be seen from the second table on page 14 of Dr. Yasuda's review, larger changes were seen for the corresponding placebo treatments. Further, the assay was validated because a 10.85 msec maximum mean change for moxifloxacin, the positive control, was detected. This study demonstrates that, up to doses of 4 mg, there is no evidence for a clinically important effect of ropinerole on the QTc interval. Further, as Dr. Hershkowitz describes, in the one patient in whom there was the greatest suspicion that the torsades could have been related to ropinerole, it has been learned that the patient was receiving budipine, a drug known to be associated with QT prolongation. However, the patient's QTc prolongation and torsades reversed with the discontinuation of ropinerole (and another drug), and the budipine was continued without a recurrence of the event. Although this case is difficult to interpret (I do not believe that the contribution of ropinerole can in any definitive sense be considered to have been ruled out), it is the only case of torsades of which we are aware in which the contribution of ropinerole can even be reasonably considered, and given the absolute lack of evidence that ropinerole increases the QTc interval (at least up to single daily doses of 4 mg), I do not believe that any additional evaluation is necessary at this time.

Regarding the additional data we requested related to the ophthalmology study, Dr. Wiley has concluded that the sponsor has adequately answered our questions, and language describing the (lack of findings) has been drafted for labeling.

As noted above, we asked the sponsor to produce a single PPI that incorporated language for patients who had either RLS or PD (we believed that the vast majority of the relevant information for patients with either condition was the same, and it would have been less confusing for patients to just read one comprehensive sheet). In support of their proposal to have a two-sided sheet (one side for each indication), the sponsor submitted the results of a study that they performed in which they "assigned" a diagnosis of either RLS or PD to volunteers and gave them each two PPIs: one that was comprehensive (according to the division's preference), and one that was two-sided, with disease specific information on each side (according to the sponsor's preference). The sponsor then measured comprehension, and further catergorized the subjects into high and low reading comprehension strata. According to the sponsor, the results demonstrate that there was a greater disparity in comprehension between

the high and low comprehension strata for the combined PPI as compared to that for the two-sided PPI. In the sponsor's estimation, this provides evidence that the two-sided PPI is easier to understand. Drs. Piazza-Hepp and Tabak have reviewed this study, and agree with the sponsor's interpretation and proposal for a two-sided PPI.

However, as Dr. Feeney points out, it appears that the sponsor has focused on the wrong comparison. In our view, the correct comparison should be **between** the two proposed PPIs **within** a particular comprehension stratum. That is, we believe the comparison of interest is how the low-comprehension stratum differs in their comprehension of both the two-sided and the comprehensive PPI, and similarly for the high-comprehension stratum. An examination of these comparisons makes clear that, within a given comprehension stratum, there were no material differences in comprehension of either PPI proposal. Although we had proposed a single comprehensive PPI, and we disagree with the sponsor's interpretation of their study, given the results of this study, and the absence of any other evidence that our original proposal would be, in fact, less confusing, we have concluded that the sponsor's proposal of a two-sided, disease-specific, PPI is acceptable.

The sponsor has agreed to (b) (4) .

Finally, while this application has been under review, Dr. Lisa Jones, of the division's Safety Team, has been reviewing data relevant to the possibility that Parkinson's Disease and/or its treatments is associated with an increased risk of melanoma. This review has been conducted in the context of an NDA for rasagiline, a proposed treatment for PD. Based on her review of a study performed by the sponsor of this latter application, in which the prevalence of melanoma in a cohort of PD patients was compared to the prevalence of melanoma in an age and sex matched control group taken from the American Academy of Dermatology screening program, she has concluded that there is an approximately five-fold increase in the observed to expected ratio for melanoma (invasive plus in situ tumors) in the PD population; again, the study could not distinguish between the effects of the disease, or the drugs used to treat these patients. Further, there are published articles of epidemiologic studies that also suggest an increased risk of melanoma in this population (see, for example, Moller H, et al. Atypical cancer pattern in patients with Parkinson's Disease. *British Journal of Cancer* (2005) **92**, 201-205.), which documents an approximately two fold increase in the risk for melanoma). Because we cannot distinguish between the contribution to this risk of PD or its treatments, and because ropinerole is an established treatment for PD to be given chronically to patients with RLS, we are requiring that a statement be placed in the Precautions section of labeling describing this risk, and recommending that patients be examined periodically for the emergence of melanoma.

We have negotiated labeling with the sponsor, and therefore I will issue the attached Approval letter.

Russell Katz, M.D.

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/s/

Russell Katz
5/4/05 02:48:03 PM
MEDICAL OFFICER

Medical Officer's Consultation Review of NDA 20-658/S-013
Ophthalmology Consult

NDA # 20-658/S-13		Submission date:	3/03/05
Ophthalmology		Review date:	4/28/05

Drug name: Ropinirole

Sponsor: SmithKline Beecham

Indication: Parkinson's disease

.

Submitted: Amendment to supplement (including study evaluating retinal safety from Study 125).

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on Approvability

From an ophthalmology prospective, there are no objections to the approval of this supplement with the labeling modifications recommended in this review.

B. Recommendation on Phase 4 Studies and Risk Management Steps

No Phase 4 studies are recommended from an ophthalmologic prospective.

II. Summary of Clinical Findings

Although there are numerical differences favoring L-dopa in comparison to ropinirole, the differences are not statistically or clinically significant.

III. LABELING (limited to areas of ophthalmologic concern)

The proposed labeling listed below is not acceptable.

(b) (4)

It is recommended that the second paragraph be revised to reflect that only the electroretinograms were adequately evaluated. The recommended revised section is:

Retinal Pathology: Albino Rats: Retinal degeneration was observed in albino rats in the 2-year carcinogenicity study at all doses tested (equivalent to 0.6 to 20 times the maximum recommended human dose on a mg/m^2 basis), but was statistically significant at the highest dose (50 mg/kg/day). Additional studies to further evaluate the specific pathology (e.g., loss of photoreceptor cells) have not been performed. Similar changes were not observed in a 2-year carcinogenicity study in albino mice or in rats or monkeys treated for 1 year. The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (e.g., disk shedding) may be involved.

Human: In order to evaluate the effect of REQUIP in humans, ocular electroretinograms (ERG) assessments were conducted during a 2-year, double-blind, multicenter, flexible dose, L-dopa controlled clinical study of REQUIP in patients with Parkinson's disease. A total of 156 patients (78 on ropinirole, mean dose 11.9 mg/day and 78 on L-dopa, mean dose 555.2 mg/day) were evaluated for evidence of retinal dysfunction through electroretinograms. There was no clinically meaningful difference between the treatment groups in retinal function over the duration of the study.

STUDY 125

Comments in this review are limited to areas of ophthalmologic concern.

STUDY DESIGN

This was a 2-year double-blind, double-dummy, multicenter, parallel group, flexible dose study in patients with early-onset Parkinson's disease (PD). Male and female out-patients, 30 to 75 years of age with idiopathic PD (Hoehn and Yahr stage I-II.5) of less than 2 years duration, who required dopaminergic therapy and who satisfied all other entrance criteria were eligible for the study.

Both double-blind medications (ropinirole and l-dopa), were provided in a double-dummy presentation and therefore all patients received both tablets and capsules.

Following a 1 to 2 week placebo run-in period, eligible patients were randomly assigned (1:1) to ropinirole or l-dopa. All randomized patients initiated therapy at dose level 1 (0.75 mg/day ropinirole or 50 mg/day l-dopa). Mandatory up titration occurred during the first 4 weeks of the study up to either 3 mg/day Ropinirole or 200 mg/day l-dopa. At the week 4 visit, patients received dose level 5 (4 mg/day ropinirole or 300 mg/day l-dopa). Thereafter the dose was flexible with the potential to be titrated up in increments to a maximum of 24 mg/day (ropinirole) or 1,000 mg/day (l-dopa) (dose level 12), according to the judgment of the investigator based on the efficacy and tolerability of the study medication. Titration to the maximum tolerated dose was encouraged. However, if patient symptoms were inadequately controlled, supplementary open-label l-dopa medication in either group was permitted and the patients were allowed to continue in the study.

Patients who completed the study or who withdrew after at least 12 months were given the option to enter a voluntary 1 week down-titration and then unmedicated washout phase lasting up to 2 weeks, with assessments at the end of each week. At the investigators discretion, patients were allowed to continue on double-blind medication until the study was unblinded.

Reviewer's Comments: *While the basic design of the study is acceptable from an ophthalmologic prospective, specific elements of the study limit the amount of information available from the study. Specifically, visual acuity was not measured and visual fields were performed only if the ERG was abnormal.*

Efficacy Parameters
The primary efficacy parameter was the percentage decrease in putamen 18Fdopa influx constant (Ki) using 18F-dopa 3D PET scanning techniques. These images were analyzed by a central region of interest (ROI) analysis on spatially transformed data by a single investigator.
The PET scan data were also analyzed using statistical parametric mapping (SPM) on spatially transformed data and by each individual centre on nonspatially transformed data (i.e., local ROI analysis).

The secondary efficacy parameters were:
• Unified Parkinson's Disease Rating Scale (UPDRS) total motor score.
• Requirement for supplementary L-dopa medication.
• Increases in "offs" duration.
• Time to withdrawal.
• Clinical Global Impression (CGI) improvement scale.

Safety Parameters
The primary safety parameter was the incidence of retinal dysfunction as assessed by ERG.

The secondary safety parameter was dyskinesia (assessed from AEs and the UPDRS Part IV score).

Safety was also assessed by AE monitoring, vital signs and laboratory data.

Reviewer's Comments: *Ophthalmic data is limited to ERG findings.*

ERG RESULTS

	Left Eye			Right Eye		
	L-dopa	**Ropinirole**	**L-dopa – Ropinirole (p)**	**L-dopa**	**Ropinirole**	**L-dopa – Ropinirole (p)**
Scotopic Rod ERG						
b-wave amplitude (µV)	71	68		73	71	
[F1.1.3]	174.0	160.1		175.1	170.1	
	(91.5)	(83.3)		(91.1)	(91.8)	
	-3.6	+0.9	+5.5	-3.8	-2.9	+2.6
	(76.1)	(47.1)	(0.55)	(63.8)	(51.1)	(0.74)
b-wave latency (msec)	71	68		73	71	
[F1.2.3]	96.7	91.8		94.7	90.7	
	(21.2)	(23.3)		(21.1)	(23.6)	
	-3.2	-1.2	-1.1	-0.9	-2.0	+0.4
	(15.8)	(9.2)	(0.45)	(13.2)	(11.0)	(0.76)
Standard Flash (DA)						
b-wave amplitude (µV)	72	69		74	72	
[F2.1.3]	386.6	344.5		383.6	347.8	
	(169.2)	(144.3)		(171.0)	(145.6)	
	-8.8	-6.6	+11.7	-9.6	-13.4	+15.2
	(82.4)	(74.7)	(0.33)	(78.3)	(74.9)	(0.19)
b-wave latency (msec)	72	69		74	72	
	(7.6)	(7.7)		(7.1)	(8.1)	
	+0.5	+1.1	-1.3	+0.9	+1.0	-0.7
	(4.5)	(5.9)	(0.12)	(4.4)	(6.6)	(0.37)
a-wave amplitude (µV)	72	69		74	72	
[F2.3.3]	225.1	192.2		227.5	190.6	
	(120.5)	(103.2)		(119.9)	(106.0)	
	-4.8	+1.2	+9.9	-15.0	-1.4	+3.6
	(55.3)	(59.8)	(0.23)	(49.7)	(60.7)	(0.64)
a-wave latency (msec)	72	69		74	72	
[F2.4.3]	21.3	21.3		21.2	21.2	
	(8.2)	(8.1)		(8.3)	(8.1)	
	+0.1	+0.1	-0.2	+0.1	+0.1	-0.2
	(3.4)	(3.7)	(0.69)	(3.7)	(3.8)	(0.72)

	Left Eye			Right Eye		
	L-dopa	**Ropinirole**	**L-dopa – Ropinirole (p)**	**L-dopa**	**Ropinirole**	**L-dopa – Ropinirole (p)**
30Hz Cone Flicker						
Implicit time (msec)	66	64		67	66	
[F4.7.3]	26.7	26.0		26.7	26.3	
	(6.9)	(5.8)		(6.5)	(5.8)	
	-1.0	+0.5	-0.8	-0.8	-0.3	-0.4
	(7.2)	(5.1)	(0.35)	(5.8)	(3.8)	(0.50)
Amplitude (µV)	72	69		74	72	
[F4.8.3]	94.4	86.8		94.6	85.7	
	-3.3	-6.3	+6.4	-2.2	-4.0	+5.6
	(27.3)	(25.0)	(0.085)	(26.0)	(22.8)	(0.11)
Photopic ERG						
b-wave amplitude (µV)	72	69		74	72	
[F5.1.3]	127.6	121.2		125.4	123.4	
	(62.3)	(59.6)		(60.8)	(62.2)	
	-12.1	-15.9	+4.9	-10.0	-18.6	+7.7
	(31.3)	(28.7)	(0.27)	(33.6)	(28.7)	(0.088)
b-wave latency (msec)	72	69		74	72	
[F5.2.3]	34.3	34.9		34.1	35.0	
	(6.6)	(7.6)		(6.2)	(7.0)	
	+1.8	+1.8	-0.8	+1.9	+2.1	-1.1
	(5.2)	(5.1)	(0.14)	(5.7)	(5.6)	(0.045)
a-wave amplitude (µV)	72	69		74	72	
[F5.3.3]	43.4	41.3		45.0	41.4	
	(20.3)	(20.8)		(18.7)	(23.8)	
	-0.3	-1.6	+1.8	-1.1	-2.6	+3.0
	(14.6)	(16.3)	(0.41)	(15.5)	(19.6)	(0.20)
a-wave latency (msec)	72	69		74	72	
[F5.4.3]	17.0	17.8		17.1	17.9	
	(5.2)	(5.8)		(5.3)	(6.9)	
	(3.2)	(3.2)	(0.82)	(3.9)	(3.7)	(0.65)
Colour Contrast Thresholds						
Protan (%)	18	10		18	10	
[F6.9.3]	7.9	19.2		7.3	17.9	
	(3.1)	(22.3)		(2.9)	(22.1)	
	-0.8	-1.5	-3.4	-0.6	-3.9	-1.1

	Left Eye			Right Eye		
	L-dopa	**Ropinirole**	**L-dopa – Ropinirole (p)**	**L-dopa**	**Ropinirole**	**L-dopa – Ropinirole (p)**
	(2.8)	(11.8)	(0.22)	(1.9)	(10.3)	(0.61)
Deutan (%)	18	10		18	10	
[F6.10.3]	9.1	19.1		9.7	19.5	
	(4.1)	(21.2)		(5.8)	(23.8)	
	-0.9	-5.8	-1.2	-1.8	-1.5	-3.5
	(3.0)	(11.2)	(0.40)	(1.9)	(10.3)	(0.37)
Tritan (%)	18	10		18	10	
[F6.11.3]	12.9	13.7		12.2	13.3	
	(9.1)	(3.1)		(5.3)	(3.0)	
	-0.1	-2.7	+2.8	-1.6	-1.2	-0.8
	(3.1)	(3.2)	(0.031)	(5.1)	(3.0)	(0.53)
Electro-oculogram						
Dark trough (µV)	18	10		18	10	
[F7.12.3]	200.8	162.5		199.4	169.6	
	-17.2	+11.7	+0.8	-28.3	-0.5	-2.1
	(75.6)	(66.1)	(0.97)	(76.2)	(47.9)	(0.92)
Light peak (µV)	18	10		18	10	
[F7.13.3]	493.1	370.4		500.3	368.2	
	(160.8)	(143.0)		(175.0)	(368.2)	
	-1.1	+8.0	+76.2	-48.6	-0.5	+16.6.
	(158.1)	(157.6)	(0.20)	(149.6)	(101.1)	(0.75)
Arden ratio (%)	18	10		18	10	
[F7.14.3]	262.2	226.4		264.7	219.3	
	(64.4)	(37.9)		(54.3)	(35.1)	
	+13.3	-4.5	+31.6	+13.3	+4.0	+26.3
	(56.0)	(61.2)	(0.15)	(59.7)	(68.6)	(0.31)
Pattern Electroretinography						
P50 amplitude (µV)	18	10		18	10	
[F8.15.3]	2.4	2.1		2.3	2.2	
	(0.9)	(0.8)		(0.8)	(0.5)	
	0.0	-0.2	+0.3	+0.1	-0.1	+0.3
	(0.6)	(0.2)	(0.10)	(0.7)	(0.3)	(0.20)
N95 amplitude (µV)	18	10		18	10	
[F8.16.3]	3.6	3.0		3.4	3.3	
	+0.2	-0.2	+0.6	+0.4	+0.2	+0.4

	Left Eye			Right Eye		
	L-dopa	**Ropinirole**	**L-dopa – Ropinirole (p)**	**L-dopa**	**Ropinirole**	**L-dopa – Ropinirole (p)**
	(0.9)	(0.6)	(0.060)	(0.9)	(0.8)	(0.22)
P50 latency (msec)	18	10		18	10	
[F8.17.3]	50.1	50.3		49.8	51.1	
	(3.6)	(2.5)		(3.5)	(2.6)	
	+1.2	+1.6	-0.6	+0.7	+0.5	-0.7
	(3.8)	(3.7)	(0.70)	(3.4)	(2.9)	(0.53)

Reviewer's Comments: *The vast majority of values show mild differences clinically in favor of L-dopa for most values measured (i.e., positive amplitudes and negative latencies). The values are not statistically or clinically significant.*

Evidence of Retinal Dysfunction

Analysis Group	N to Y	Same	Y to N	Total
L-dopa	2	64	1	67
Ropinirole	1	58	2	61

Reviewer's Comments: *There is no significant difference between groups.*

VISUAL FIELD TEST

L-Dopa			**Final**		
Baseline		**N**	**X**	**Y**	**Total**
N	10	11	7	0	28
X	0	14	34	1	49
Y	0	0	0	1	1

Ropinirole			**Final**		
Baseline		**N**	**X**	**Y**	**Total**
N	7	15	6	0	28
X	10	6	29	2	47
Y	0	0	0	3	3

Reviewer's Comments: *After inquiry, it was determined that visual fields were not performed unless the ERG performed at that visit was abnormal. This led to an incomplete data set which is unusable.*

ADVERSE EVENTS

Reviewer's Comments: *There were no recognizable clinically significant adverse events that were not present at baseline or not likely to be directly related to Parkinsonism.*

The printed comments in Appendix H, pages 1834-1859 were incomplete in the original submission. The full comments have been provided with the amendment. No significant abnormalities, except those directly related to the underlying disease or those that were pre-existing before the study have been identified.

RECOMMENDATIONS:

From an ophthalmology prospective, there are no objections to the approval of this supplement with the labeling modifications recommended in this review.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wiley Chambers
4/29/05 08:59:46 AM
MEDICAL OFFICER

CLINICAL REVIEW: RESPONSE TO APPROVABLE

Application Type	NDA 20658
Submission Number	013
Submission Code	SE (AZ and BZ)
Letter Date	8/23/04 and 9/30/04
PDUFA Goal Date	2/24/05
Reviewer Name	Norman Hershkowitz and Janeth Rouzer
Review Completion Date	1/24/05
Established Name	Ropinirole
(Proposed) Trade Name	Requip
Therapeutic Class	Dopamine Agonist
Applicant	GSK
Priority Designation	S
Dosing Regimen	0.25 to 4 mg 1-3 hours
Indication	(b) (4) Restless Leg Syndrome
Intended Population	Patients with this Disorder

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1 EXECUTIVE SUMMARY

The present submission constitutes a response to approvable for an efficacy supplement for the use of ropinirole (Requip) in restless leg syndrome (RLS), a dopamine agonist that is presently labeled for use in Parkinson's disease, Previous reviews indicated four specifically identified clinical issues that the Sponsor was requested to address prior to consideration of approval:

- While three pivotal trials indicated efficacy, post-hoc analysis of a small sub-sample of North American participants in one of the pivotal trials along and an analysis of restless leg syndrome as a secondary endpoint in a small, US non-pivotal trial suggested that efficacy may not apply to this population. The decision to approve was therefore made dependent on the outcome of a large pivital placebo-controlled, double-blind, US study (study 249).
- An unexpected case of pulmonary fibrosis was observed in the RLS clinical trials data base. Because of the unexpected and serious nature of this report the Sponsor was requested to provide more information about the single case of pulmonary fibrosis. The Sponsor was also requested to examine their safety databases across all indications (Parkinson's disease, RLS, etc.) for any cases of fibrotic complications associated with the use of Requip.
- This division expressed concern about the absence of ECG data timed to dose escalation, particularly considering the expected expansion of use of Requip that will result from this new indication. It was suggested that the Sponsor obtain and submit additional ECG data in patients with RLS at multiple time points following dosing. The division was particularly interested in examining "QTc, at Tmax of parent drug and any active metabolites." It was advised that the Sponsor may be able to accomplish this by incorporating the ongoing efficacy trial, 249, and that the total number of patients should include an adequate sample of patients at the highest daily dose examined (4 mg/kg).
- Additional analysis of data on hypotension and orthostatic hypotension was requested in studies that used a "forced titration" paradigm with a schedule similar to that used in pivital trials so as to better characterize this potential adverse event.

Study 249 was a multi-center (USA), randomized double-blind placebo-controlled, parallel group, flexible dose (1.25 to 4 mg) trial that compared Requip to placebo in 380 patients (187 Requip and 193 placebo) diagnosed with moderate to severe RLS. The primary endpoint was the mean change from baseline in the International Restless Leg Syndrome Rating Scale (IRLS scale) at week 12 or the last observation carried forward (LOCF). Secondary Endpoints in a primary inferential set were analyzed in a hierarchical fashion with the 12 week or LOCF Clinical Global Impression of Improvement (CGI-I) as the first to be analyzed if the primary endpoint was found to be significant. Both these endpoints were found to be statistically significantly improved in the drug as compared to the placebo group. The fact that the present study examined such a large population of patients and demonstrated a high degree of statistical significance suggests that the negative results in the previous studies, which were smaller (n=114 and n=65), may have been a result from a sampling error. The fact that mean ropinirole

beneficial effects measured by IRLS were numerically greater in the present US study then prior pivotal studies is reassuring. There is no obvious reason to believe that the European population is different from an American population, most of who are of European ancestry.

The Sponsor responded to questions regarding pulmonary fibrosis by providing the following: 1) a discussion of published reports, 2) additional information on the index case, 3) examination of the Sponsor's post-marketing safety data base (OCEANS)[1] and clinical trials database, 4) A Bayesian analysis comparing ergot and non-ergot dopamine agonist AERS reporting rates for fibrosis, 5) an examination of relative 5-HT receptor activity for dopamine agonists. Published reports failed to identify additional cases of frank fibrosis related to ropinirole. The additional information on the index case from the RLS clinical study database suggested other more likely causes to explain the observed finding and resolution of the signs and symtpoms despite continued treatment. A number of patients derived from the Sponsors database (OCEANS and clinical trials) were described with potential pulmonary fibrosis, or its associated signs and . This reviewer believes that the best evidence for pulmonary fibrosis comes from 3 cases described as pulmonary fibrosis and 1 potential case that described associated events but no fibrosis. Two of these fibrosis cases are complicated by other factors. One of these cases is complicated by the uncertain diagnosis of fibrosis versus atelectasis. Nonetheless, if you compare an incidence based upon 3 cases, the calculated incidence, using the Sponsor's exposure data, is 0.52/100,00 patient-years which is in the lower range (0.7/ 100,000 patient years) of what may be expected in the general population but substantially lower for that expected in aged population. Thus, a study from New Mexico demonstrated that the incidence of pulmonary fibrosis in males and females between ages 65- 74 years were 22 and 12 per 100,000 per year, respectively. The incidences in patients older then 75 was 102 in males and 57 in females per 100,000. Examination of the Sponsors database for retropertineal fibrosis failed to identify cases. Some cases associated with potential cardiac fibrosis where observed but most were confounded. The Sponsor performed a Bayesian analysis of disproportionality using the AERs database, i.e. the Multi-item Gamma Poisson Shrinker (MGPS) analysis. This analysis revealed a nearly insignificant signal for ropinirole when compared to the ergot-based dopamine agonists. The Sponsor also argued that one of the presumed mechanisms of fibrosis is related to the actions of agents on 5HT receptors and that while ergot-derivatives displayed diverse agonist and antagonist properties at multiple receptor sub-types, pramipexole and ropinirole showed a >100-fold affinity for the D2/D3 receptors versus the 5-HT sub-types. This reviewer agrees that there does not appear to be an obvious signal for fibrosis syndromes associated with the use of ropinerol at the present time. This adverse event should not prevent the approval of this new indication, but continued vigilance is necessary. Information in the labeling, however, should be expanded so as to indicate that more then one case has been identified.

1 OCEANS (Operating Companies Event Accession and Notification System) is GSK's worldwide safety database. Data mining analyses of OCEANS data use only spontaneous adverse event reports for clinical marketed non-vaccine products; clinical trials reports are not included.

The Sponsor adapted an ongoing double blind placebo control trial (study 249)l to address the divisions concern regarding the lack of good EKG studies. The Sponsor added a new phase in an amendment during which patients were to return to the clinic 1 to 2 days following the administration of the last study dose on week 12 or after early withdrawal for EKG monitoring. This should be sufficient time to clear the parent drug (Tmax = 6 hours). At this time, pre-dose baseline EKGs and one and two hour posts dose EKGs were examined. Patients were administered a single dose of Requip that was previously observed to be optimally therapeutic. A latter EKG was evaluated at a follow-up visit 7 ± 3 days following the ECG Visit. All of EKGs, during the cardiac phase and follow-up visit, were obtained in triplicate. EKG recording was controlled for activity and time after a meal. Examination of pre-dose versus post dose QTcF and QTcB demonstrated only small to borderline mean prolongations in interval (≤4). However, when the follow-up period was used as a baseline mean QTc intervals changes appeared rather significant (10 msec). This may indicate the potential effect of a metabolite that was not sufficiently cleared. Examination of old mass balance studies indicated some potential slowly cleared metabolites. Outlier examination confirmed this observation. Examination of dose QTc response data also indicated a preponderance of QTc prolongation in dosages of 4 mg daily. A review of the AERs database by this reviwer identified 3 cases of Torsades de pointe with ropinirole but none with other oral dopamine agonists (pergolide, pramipexole and bromocriptine). The Sponsor is presently performing a well controlled QTc study to examine for a potential ropinirole effect at RLS dosages. The signal for potential QTc prolongation is strong enough that this reviwer feels that an approvable action should be made until the results from the more definitive study are available. This reviwer also, however feels that a second QTc study should be initiated that examines doses used in Parkinson's disease.

Examination of the new forced titration blood pressure results indicted a larger signal for hypotensive AEs then that observed in the pivotal trials. Thus, the two studies in patients with RLS that used a forced-titration regimen and orthostatic challenges with intensive blood pressure monitoring, 14 of 55 patients (25%) receiving ropinirole experienced an adverse event associated with a reduction in blood pressure. Eleven of these patients had a documented orthostatic change in blood pressure whereas 3 had other reductions in blood pressure. One additional patient was noted to have an episode of vasovagal syncope (although no blood pressure recording was documented). None of the 26 patients receiving placebo had a similar adverse event. In these studies, 20% of ropinirole-treated patients and 12% of placebo-treated patients experienced an orthostatic blood pressure decrease of at least 40 mm Hg systolic and/or at least 20 mm Hg diastolic; not all of these changes were associated with clinical symptoms. Except for its forced nature these studies used a similar titration schedule as those in the phase 3 efficacy trials. This should be described in the labeling.

In summary the NDA supplement is approvable pending completion and FDA review of the controlled EKG interval study. A number of additional recommendations are made with regard labeling changes for fibrosis and blood pressure alterations.

2 INTRODUCTION AND BACKGROUND

Ropinirole (Requio) is a dopamine agonists that is presently labeled for use in the symptomatic treatment of Parkinson's disease at a dose up to 8 mg TID. The Sponsor had previously submitted an efficacy supplement (7/3/03) for its approval in the use of Restless Leg Syndrome (RLS) at a lower dose (up to 4 mg qD). The Sponsor was informed on 12/24/03 that the application was considered approvable and required additional clarification. The clinical issues that the Sponsor was required to address prior to approval were reviewed by this reviwer (Dr. Hershkowitz) in this document and include the following:

- The original submission included 2 pivotal 12 week, flexible dosing, placebo control double blind study (study 190 and 194) that used co-primary endpoints the IRLS scale (International Restless Leg Rating scale) and CGI to determine effectiveness and a pivotal 36 week randomized withdrawal study for drug responders (study 188) that used a single endpoint (IRLS scale). There was also a small supplementary 12 week double blind placebo control study examining PLMS using a polysomnography (study 191). IRLS scale and CGI were secondary endpoint in the latter study. Overall Requip was found effective in the treatment of patients with moderate to severe RLS in the all pivotal trials. However, when North American patients (USA and Canada) were partitioned out of the only pivotal trial (194) that included this group the effect trended in the wrong direction with placebo winning over drug. Examination of the secondary endpoints of IRLS scale and CGI in the non-pivotal trial 191, a US study that was principally designed to examine PLMS, also failed to demonstrate a difference between IRLIS and CGI. This led this division to defer its decision of effectiveness till the completion of a large US study (249). This study is included in the present submission.
- An unexpected case of pulmonary fibrosis, which is usually associated with the class of ergot based dopamine agonist (bromocriptine and pergolide) and not the present drug or other non-ergot based dopamine agonists (pramipexole), was observed in the RLS clinical trials data base. There was also a report of another suspicious case reported in the present label. Because of the unexpected and serious nature of this report the Sponsor was requested to provide more information about the single case of pulmonary fibrosis. The Sponsor was also requested to examine their safety databases across all indications (Parkinson's disease, RLS, etc.) for any cases of fibrotic complications associated with the use of Requip.
- In the approvable letter this division expressed concern about the absence of ECG data timed to dose escalation, particularly considering the expected expansion of use of Requip that will result from this new indication. It was suggested that the Sponsor obtain and submit additional "ECG data in patients with RLS at multiple time points after dosing…" The division was particularly interested in examining "QTc, at Tmax of parent drug and any active metabolites." It was advised that the Sponsor may be able to accomplish this by incorporating the ongoing efficacy trial, 249, and that the total number of patients should include an adequate sample of patients at the highest daily dose examined (4 mg/kg).

- As ropinirole is vaso-active it may lead to orthostatic blood pressure changes. It has been suggested that a relatively healthy population, such as RLS patients, may be at a greater risk in developing orthostatic changes then those with Parkinson's disease. The pivotal trials, which used a titration to optimal effect design, failed to reveal a strong orthostatic signal. Interpretation of these studies, however, may be obfuscated by the fact that titration was truncated as a result adjustment of doses because of competing adverse events. Blood pressure was monitored in two forced titration studies in an RLS population using a similar schedule as that used in the pivotal efficacy trials. It was argued these trials may better represent the orthostatic adverse event profile. The Sponsor was asked to perform a more through analysis of this data.

Other issues addressed by the Sponsor, reviewed by Dr. Rouzer (A DNDP medical Officer) and included in this review are as follows:

- A final safety update.
- An update of the clinical literature.
- The foreign regulatory history.

Previous studies have indicated that another dopamine agonist (pramipexole) produces morhpometric changes in pigmented rat retinas. This division requested that a similar study be performed for the present drug as part of a phase 4 commitment. In negotiations with this division it was agreed that human retinal studies performed as a part of a long term clinical trial (study 125), if found adequate, may act in lieu of the requested information. These data are presented in the present submission and reviewed by the FDA's expert Dr. Wiley Chambers in a separate document.

Other issues regarding problems in the Carton and Container Labeling-Patient Sample Kit can be found in a review by DMETS.

6 INTEGRATED REVIEW OF EFFICACY- STUDY 249 (REVIEW BY DR. HERSHKOWITZ)

Requip is presently approved for the treatment of Parkinson's disease. The objective of the original submission, for which this is a response to approvable, was to demonstrate the potential effectiveness of this agent in the treatment of Restless Leg Syndrome. The original submission included 2 pivotal 12 week, flexible dosing, placebo control double blind study (study 190 and

194) that used co-primary endpoints the IRLS scale (International Restless Leg Rating scale) and CGI to determine effectiveness and a pivotal 36 week randomized withdrawal study for drug responders (study 188) that used a single endpoint (IRLS scale). There was also a small supplementary 12 week double blind placebo control study examining PLMS using a polysomnography (study 191). IRLS scale and CGI were secondary endpoint in the latter study. Overall Requip was found effective in the treatment of patients with moderate to severe RLS in the all pivotal trials. However, when North American patients (USA and Canada) were partitioned out of the only pivotal trial (194) that included this group the effect trended in the wrong direction with placebo winning over drug. Examination of the secondary endpoints of IRLS scale and CGI in the non-pivotal trial 191, a US study that was principally designed to examine PLMS, also failed to demonstrate a difference between IRLIS and CGI. This led this division to defer its decision of effectiveness till the completion of a large US study (249). This study is presented and discussed in this section.

6.1 Indication

The Sponsors wishes to develop Requip for patients with RLS.

6.1.2 General Discussion of Endpoints

The method of analysis of endpoints in the present study is similar to that used in previous pivotal trial. This was performed by first testing a primary endpoint and subsequently testing selected secondary endpoints "in the secondary inferential set" in a hierarchical fashion (see below).

6.1.2.1 Primary Endpoint

This endpoint was the mean change from baseline in the International Restless Leg Syndrome Rating Scale (IRLS scale) at the week 12 or the last observation carried forward (LOCF). This was identical to one of the co-primary endpoints used in the previous pivotal trials.

The IRLS scale was developed and validated by the International RLS Study group (IRLSSG). The scale has been used in a number of treatment studies and has been found to correlate to the CGI. In the prior 2 pivotal trials this division required that an analysis of efficacy be determined by this endpoint along with the CGI because of its novelty in the regulatory milieu. The IRLS is a 10 question scale. Each question is rated 0 to 4 with the higher score representing increased morbidity. Questions measures particular domains of RLS in terms of symptoms, severity, frequency, sleep disturbance mood and on overall effect on life.

6.1.2.2 Secondary Endpoints in the Primary Inferential Set

The following secondary endpoints were examined:

- The 12 week or LOCF Clinical Global Impression of Improvement (CGI-I) as measured by the proportion of patients with scores of much improved or very much improved. This endpoint was used as the second co-primary endpoint in the prior pivotal trials. It is a 7 point scale with 1 as very much improved and 7 as very much worse.
- The change in the IRLS scores from baseline at week 1.
- The CGI-I score at 1 week.

6.1.2.3 Secondary Endpoints

- CGI-I analysis at day 3 and the time to response in the CGI (defined as much improved or very much improved).
- Change from baseline in the Periodic Limb Movement (PLM) Index (PLM/hr) and change from baseline in the number of PLMs as measured by actigagraphy. The actigraph is used at home and measures the intensity and time of leg kicks. It is noteworthy that it is routine practice to measure PLMS using EMGs as a part of polysomnography. The actigraph allows home measurement. Actigraph records correlate well with those from polysomnography if sleep is not disturbed. The records correlate less in disturbed sleep.2
- Change from baseline in Sleep Disturbance, Sleep Quantity, and Somnolence domains of the MOS Sleep scale at week 12 or LOCF.
- Change from baseline in the IRLS Scale total score at Day 3.
- Change from baseline in the CGI Severity of Illness scale at Week 12 LOCF.
- Change from baseline in the Profile of Mood State (POMS) scale at Week 12 LOCF.
- Proportion of patients satisfied with their treatment at Week 12 LOCF.
- The clinical Global Impression of Severity (CGI-S) at different visits throughout the study.
- The RLS Quality of life questioner difference between baseline and week 12 or LOCF.

2 Ancoli-Israel, S, Actigraphy, In Principles and Practice of Sleep Medicine, ed Kryger, Roth and Dement Saunders, Philidelphia, 2000.

- The Medical Outcomes Study (MOS) Sleep Scale at baseline and week 12 or LOCF. This is a battery that measures various aspects of sleep (sleep initiation, maintenance, perceived adequacy, somnolence, respiratory impairments and regularity).

- The Hospital Anxiety and Depression Scale (HADS) is a questionnaire that was administered at baseline and week 12 or LOCF.

- The Profile of Mood State (POMS) Scale is a questionnaire for "mood states" that was administered at baseline and week 12 or LOCF.

- A patient satisfaction questionnaire for the drug was administered on week 12 or last visit.

6.1.3 Study Design

6.1.3.1 General Design Features

The study was a multi-center (USA), randomized double-blind placebo-controlled, parallel group, flexible dose trial that compared Requip to placebo in patients diagnosed with moderate to severe RLS. The study was of 14 weeks in duration and divided into three phases:

- **One week screening and washout phase**: Patients who met inclusion criteria with a diagnosis of RLS, according to the IRLSSG diagnostic criteria, where admitted into the study. If presently medicated for RLS, this medication was discontinued for 5 half-lives or 7 days, whichever was longer before a baseline evaluation, in the next phase, was obtained.
- **!2-week treatment phase:** Patient were randomized to either drug or placebo in a 1:1 ratio. Patient started on requip at doses of 0.25 and flexably titrated to 4 mg/day (see "Drug Dosage" for titration schedule). Patient were evaluated at baseline, day 3 and 1, 2,3,5,6,8,10 and 12 weeks following drug/placebo initiation. Some patients had an additional visit performed 1 to 2 days after week 12 for an optional EKG evaluation phase that was added as an emendment to the study (see section on EKG in Safety).
- **Follow up visit 7± 3 days after the last dose:** This would occur after the last dose which was either after the 12 week visit, the final EKG visit or after early withdrawal.

6.1.3.2 Number of Patients

It was planned that 360 patients would be screened and randomized (180 per treatment arm. However, 380 patients (187 Requip and 193 placebo) were randomized and included in the ITT analysis. Eight-six patients were included for EKG analysis.

6.1.3.3 Principal Inclusion Criteria

- Patients 18 to 79 years of age with a diagnosis of RLS based upon a diagnostic clinical interview and the international RLS study group (IRLSSG) diagnostic criteria.
- Patient had RLS symptoms with a history of a minimum of 15 nights of RLS symptoms during the previous month. In the case of a patient currently receiving RLS medication this criteria may be waived.
- Patient had documented RLS symptoms for at least 4 of the 7 nights during the Screening/Washout phase (between Screening Visit and Baseline Visit

6.1.3.3 Principal Exclusion Criteria

- Patients who suffered from RLS symptoms as part of their usual RLS symptom pattern during the daytime (daytime defined as 10:00 until 18:00).
- Patients who suffered from a primary sleep disorder other than RLS that may significantly affect the symptoms of RLS.
- Patients with signs of secondary RLS (i.e. renal failure, iron deficiency anemia or pregnancy at baseline).
- Patients who suffered from other movement disorders (i.e. Parkinson's disease, dyskinesias, and dystonias).
- Patients who had medical conditions which could affect assessments of efficacy (i.e. diabetes, peripheral neuropathy, rheumatoid arthritis, or fibromyalgia syndrome) or render the patient "unsuitable for study" ((e.g., symptomatic orthostatic hypotension, severe cardiovascular disease, hepatic or renal failure, etc.).
- Patients with augmentation or end of dose rebound at baseline.
- Patients who took any medication known to affect RLS or sleep that had not been discontinued prior to the Baseline Visit (e.g. antidepressants, lithium, anticonvulsants, opoids, hypnotics dopamine active agents, ands sedating antihistamines.) Rare exceptions were allowed if it was thought that the medications were not influencing the symptoms of RLS. In this case the drug dose was required not to change during the study.
- Patients who had a diastolic BP $\geq$110mmHg or $\leq$ 50mmHg OR systolic BP
- $\geq$ 180mmHg or $\leq$ 90mmHg at screening or baseline.

6.1.3.4 Drug Dose

Drug and identical matched placebo doses where evaluated and titrated according to an established protocol in steps and at predetermined times based upon tolerability and therapeutic response. Dosing started at 0.25 mg. Dose was administered 3 to 1 hours prior to sleep. The decision to raise dose was based upon the investigators clinical judgment but also guided by the CGI. Thus, if the CGI was rated "very much worse" to "minimally improved" the investigator was to increase to the next dose level. If however the CGI was observed to be "much improved" to "very much improved" the dose was maintained. These changes were permitted only if they were clinically tolerated. The table below presents timed schedule of dosing steps under ideal circumstances. Doses need not increase in this manner if conditions where not ideal, but may be increased at the next schedule time. Dosing changes were allowed up to and including the 10th week visit allowing two weeks on stable dosing at the time of endpoint evaluation. Dosage reduction because of AEs to previous dosage was permitted along with latter increases on AE abatement. If patient participated in the EKG study, the dose was administered during the clinic visit. Patient compliance was encouraged and monitored. This dosing regimen was nearly identical to that used in the other two pivotal trials except for the fact that dosing increases were limited to the 8th week in prior studies whereas they were permitted up to and including the 10th week in the present study.

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Dosage Level	Dosage of Ropinirole or Matching Placebo	Clinic Visit[2]	Duration (Days)
1	0.25 mg (0.25 mg + placebo)	Day 0	3 days
2	0.5mg (0.25mg + 0.25mg)	Day 3	4 days
3	1.0mg (0.5mg + 0.5mg)	Week 1 (Day 7)	7 days
4	1.5mg (1.0mg + 0.5mg)	Week 2	7 days
5	2.0mg (1.0mg + 1.0mg)	Week 3	7 days
6	2.5mg (2.0mg + 0.5mg)	Week 4	7 days
7	3.0mg (2.0mg + 1.0mg)	Week 5	7 days
8	4.0mg (2.0mg + 2.0mg)	Week 6	

1. This table is for illustrative purposes only, and represents the situation if the investigator decided to increase the dose at each of the scheduled clinic visits up to and including Week 6 clinic visit
2. Decision to change dosage level was made at the scheduled clinic visits from Day 3 onwards.

6.1.3.5 Protocol Schedule

A schedule of events for his protocol is contained in the following two continuous Tables.

Assessments	Screening	Base-line	Double-Blind Treatment Phase											Early Withdrawal	Follow Up[1]
		Day 0	Day 3	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 8	Wk 10	Wk 12	ECG Visit		7±3 days
Written informed consent	X														
RLS Diagnostic Clinical Interview	X														
IRLSSG Diagnostic Criteria	X														
Inclusion/exclusion criteria	X	X													
Patient demography	X														
RLS history	X														
RLS Symptoms Documentation	X	X													
Sitting blood pressure and pulse	X	X													
Orthostatic blood pressure & pulse	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Pre/Post dose Orthostatic blood pressure and pulse rate[2]		X[2]							X[2]						
Weight	X											X		X	
Height	X														
ECG, 12 Lead	X[3]												X[7,8]	X[7]	X[7]
Medical/surgical history	X														
Physical examination	X[3]														
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory evaluation	X[3]											X		X	X[4]
Pregnancy test	X											X		X	X
IRLS Rating Scale		X	X	X	X	X	X	X	X	X	X	X		X	X
RLS Quality of Life Questionnaire		X										X		X	
MOS Sleep Scale		X										X		X	
CGI Scales (Improv. & Severity)		X[5]	X	X	X	X	X	X	X	X	X	X		X	
POMS scale		X										X		X	
HADS scale		X										X		X	
Patient Satisfaction Question												X		X	

Analysis:

Assessments	Screening	Base-line	Double-Blind Treatment Phase											Early Withdrawal	Follow Up[1]
		Day 0	Day 3	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 8	Wk 10	Wk 12	ECG Visit		7±3 days
Actigraphy (3 nights prior to visit)[6]		X							X						
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical procedures		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient randomization		X													
Study conclusion form												X[9]	X	X[9]	

1. Scheduled from ECG Visit; IRLS Rating Scale = International Restless Legs Syndrome Rating Scale; MOS = Medical Outcomes Study; CGI = Clinical Global Impression.
2. Orthostatic blood pressure/pulse rate assessments conducted at the Baseline Visit and Week 6 Visit (pre-dose and 2 hours post-dose).
3. If clinically significant abnormal laboratory, ECG, or physical examination findings were noted at the screening evaluation, repeat assessments are to be performed during the Washout/ Screening phase. Patients who have clinically significant abnormal findings that have not resolved by the time of the baseline examinations will be excluded from the study.
4. Laboratory evaluations performed at follow-up only if clinically significant abnormalities were noted at Week 12 or Early Withdrawal.
5. CGI "Global Improvement" was not assessed at baseline.
6. Actigraphy measurements performed at home for 3 consecutive nights prior to Baseline Visit (days -3, -2, and -1) and three consecutive nights at home immediately prior to Week 6 Visit while on study medication.
7. Triplicate 12-Lead ECG, if possible.
8. Pre-dose, 1-hour Post dose and 2-hour Post dose.
9. Complete at Week 12 Visit or Early Withdrawal Visit if no ECG Visit was scheduled, otherwise form was completed at ECG Visit.

6.1.3.5 Data Analysis

Patient numbers were selected to detect a difference of 3 in the IRLS scale at a 90% power. This is more sensitive then prior pivotal trials. The number of patient selected was also sufficient to detect a difference of 60 VS 40 percent responder rate on the CGI-I, a secondary endpoint in the present study. All analyses were performed with a predetermined alpha of 0.05.

The principal analysis included the ITT population that consisted of any patient receiving a dose of drug/placebo and with a post baseline efficacy assessment. Per protocol analysis was also carried out which consisted of patients in the ITT population but without major protocol violations or a break of 3 or more consecutive days in study medication immediately before week 12 or LOCF analysis. If there were incomplete response to the IRLS at 12 week or last visit the last complete response was carried forward and used for the primary analysis.

The analysis was planned so that if the primary endpoint was found positive the secondary endpoints in the primary inferential set would be compared in a hierarchical fashion. The first analysis to be performed in this hierarchy was the CGI-I scale at the Week 12 or LOCF. If this was found positive the IRLS score at week I would be compared, and if this was positive the CGI-I at one week would be compared. All confidence intervals and hypothesis testing was considered positive at a p value of 0.05 and 95% confidence interval. All testing was two sided.

As part of a determination of an effect of the interaction of center effect and the center by treatment any center that recruited less then 8 patients was grouped together. There was no subgroup analysis.

Change from baseline was simply calculated by subtracting baseline from the post-treatment value.

For IRLS score imputation techniques, based upon the response to other questions, were used to provide a full score. This was only done if there were no more then 1 out of 10 questions missing[3]. Similar imputation techniques, but with more liberal criteria, where used for secondary endpoints of MOS RLS quality of life questionnaire, and POMS. For all other testing a single missing item would be interpreted as the complete score missing.

If two or more responses were given on the ORLS or CGI-I the worst response was used.

6.1.4 Efficacy Findings

6.1.4.1 Patient disposition

A table summarizing the disposition of patients who were randomized is presented in the table below. Approximately 12 to 14% of patients in either group did not complete the study. Similar numbers of patients were noted to be discontinued in placebo and drug treatment groups. While the number of patients was generally comparable across treatment groups for the different subcategories a far greater number of patients discontinued because of a loss to follow-up in the drug group (6 Vs 1). A somewhat greater number of patients discontinued because of protocol deviation and insufficient therapeutic effect in the placebo group.

3 This was done in the following fashion:

(b) (4)

	Ropinirole N=187		Placebo N=193		Total N=380	
	n	(%)	n	(%)	n	(%)
Completion Status						
Completed	164	(87.7)	167	(86.5)	331	(87.1)
Prematurely Discontinued	23	(12.3)	26	(13.5)	49	(12.9)
Primary Reason for Premature Discontinuation						
Adverse Event[1]	7	(3.7)	9	(4.7)	16	(4.2)
Insufficient Therapeutic Effect	2	(1.1)	5	(2.6)	7	(1.8)
Lost to Follow-Up	6	(3.2)	1	(0.5)	7	(1.8)
Protocol Deviation (Including non-compliance)	4	(2.1)	9	(4.7)	13	(3.4)
Other Reason	4	(2.1)	2	(0.1)	6	(1.6)

Data Source: Section 11, Table 11.1.2.

1. One ropinirole patient (Patient 249.023.00997) and one placebo patient (Patient 249.024.00224) were reported discontinued in the follow-up phase because of fatal SAEs (see Section 8.3) and one ropinirole patient (Patient 249.024.00222) was discontinued because of a pre-treatment AE (see Section 6.4.3). All other AEs leading to discontinuation occurred during the treatment phase.

The table below presents information on protocol violations that led to exclusion from the per protocol analysis. Except the fact that a much greater number of patients in the placebo group where in the "missed medication" groups the treatment groups were comparable. Many more patients appeared to miss medication in the placebo group, perhaps because of the perceived lack of efficacy.

All patients randomized to ropinirole were included in the ITT population and all but one randomized to the placebo group were included in the ITT population.

	Ropinirole N=187		Placebo N=193		Total N=380	
	n	(%)	n	(%)	n	(%)
Patients with at Least One Protocol Violation Leading to Exclusion[1]	**21**	**(11.2)**	**30**	**(15.5)**	**51**	**(13.4)**
Does Not Have Total Score ≥15 on the IRLS Scale at Baseline	0		2[2]	(1.0)	2[2]	(0.5)
Suffered from Primary Sleep Disorder Other Than RLS	0		1	(0.5)	1	(0.3)
Medical Conditions Affecting Assessment of Efficacy	5	(2.7)	4	(2.1)	9	(2.4)
Taking Medication Known to Induce Drowsiness, Affect RLS or Sleep (Including Inadequate Washout)	6	(3.2)	4	(2.1)	10	(2.6)
Withdrawal, Introduction or Change in Dose of HRT and/or Any Drug Known to Inhibit CYP1A2	1	(0.5)	0		1	(0.3)
Study Medication Non-Compliance	4	(2.1)	5	(2.6)	9	(2.4)
Missed Study Medication for 3 or More Consecutive Days Immediately Prior to Final Assessment	5[3]	(2.7)	16	(8.3)	21	(5.5)
Prohibited Concomitant Medication	3	(1.6)	5	(2.6)	8	(2.1)

Data Source: Section 11, Table 11.2.1.

1. Patients may have had more than one protocol violation leading to exclusion.
2. These patients had a score of 14 on the IRLS Scale at baseline.
3. One additional ropinirole patient (Patient 249.047.00588) was reported as missing study medication for 3 or more consecutive days prior to the final on-treatment visit but was not coded as having met this protocol violation criterion. This patient was, however, coded as 'study medication non-compliance' and therefore excluded from

No patient in the ropinirole group had a protocol deviation. One patient in the placebo group had three protocol deviations.

6.1.4.2 Demographics and Baseline Features

The demographics for the ITT analysis of the experimental groups are presented in the table below. Both groups had a similar breakdown on the examined categories. As a whole, more females then male where examined and very few non-white groups were included.

	Ropinirole N=187		Placebo N=193		Total N=380	
Age (years)						
Mean (SD)	52.2 (12.79)		52.4 (13.15)		52.3 (12.96)	
Range	18-79		19-78		18-79	
Sex, n (%)						
Male	78	(41.7)	70	(36.3)	148	(38.9)
Female	109	(58.3)	123	(63.7)	232	(61.1)
Race, n (%)						
White	181	(96.8)	191	(99.0)	372	(97.9)
Black	3	(1.6)	1	(0.5)	4	(1.1)
Oriental	0		0		0	
Other	3	(1.6)	1	(0.5)	4	(1.1)

Data Source: Section 11, Table 11.3.2

Baseline features for patients in both experimental groups are presented in the table below. Most of the reported features where similar between the two groups except for a slight preponderance of "night time only" RLS and PLMS[4] in the control group.

4 This is incontrast to the fact that PLM Index on actigraphy for placebo at basleine was lower (22.2 for the placebo group Vs 27.5 for drug group).

	Ropinirole N=187	Placebo N=193	Total N=380
Age at Onset of RLS (years)[1]			
Mean (SD)	32.6 (16.44)	34.4 (17.78)	33.5 (17.13)
Median (Range)	33.0 (4 – 70)	35.0 (2 – 71)	34.0 (2 – 71)
New Medication Near Time of Onset			
Yes, n (%)	0	5 (2.6)	5 (1.3)
Duration of Disease (years)[1]			
Mean (SD)	19.6 (14.72)	18.0 (14.40)	18.8 (14.56)
Median (Range)	15.0 (0 – 62)	14.0 (0 – 65)	15.0 (0 – 65)
History of or Current PLMS			
Yes, n (%)	74 (39.6)	89 (46.1)	163 (42.9)
Current Alcohol Use			
Yes, n (%)	95 (50.8)	101 (52.3)	196 (51.6)
Alcohol Consumption (Units/Week)[2]			
n	94	101	195
Mean (SD)	4.2 (4.55)	4.2 (3.91)	4.2 (4.22)
Median (Range)	3.0 (0–24)	3.0 (0 – 18)	3.0 (0 – 24)
Current Caffeine Use			
Yes, n (%)	144 (77.0)	155 (80.3)	299 (78.7)
Caffeine Consumption (Cups/Day)[2]			
Mean (SD)	2.7 (1.94)	2.7 (2.11)	2.7 (2.03)
Median (Range)	2.0 (0 – 12)	2.0 (0 – 12)	2.0 (0 – 12)
Current Sleep Disorder			
Yes, n (%)	2 (1.1)	2 (1.0)	4 (1.1)
First Degree Relative with RLS/PLMS			
Yes, n (%)	80 (42.8)	79 (40.9)	159 (41.8)
Time Symptoms Mainly Present			
Night-time Only, n (%)	63 (33.7)	82 (42.5)	145 (38.2)
Evening & Night-time, n (%)	120 (64.2)	107 (55.4)	227 (59.7)
Daytime, Evening & Night-time, n (%)	4 (2.1)	4 (2.1)	8 (2.1)

Data Source: Section 11, Table 11.7.1.

1. For these characteristics, the denominators for the ropinirole, placebo and total groups were 187, 192 and 379, respectively.
2. Summary statistics for alcohol or caffeine consumption were calculated only for those patients who reported use of alcohol or caffeine.

Concomitant medications were received by 171 patients (91.4%) in the ropinirole group and 166 patients (86.0%) in the placebo group. The most frequently used classes of concomitant medication were analgesics. Analgesics were used by 75 patients (40.1%) in the ropinirole group and 71 patients (36.8%) in the placebo group.

A similar proportion of patients in each treatment group met the definition for overall compliance (ropinirole: 177 patients or 94.7%; placebo: 173 patients or 89.6%).

6.1.4.3 Dose Titration

The median dose for the ropinirole achived at week 12 was at 2.0 mg (range 0.25 to 4.0 mg), a lower then maximal permitted dose (4 mg).

6.1.4.4 Efficacy Results

6.1.4.4.1 Primary endpoint

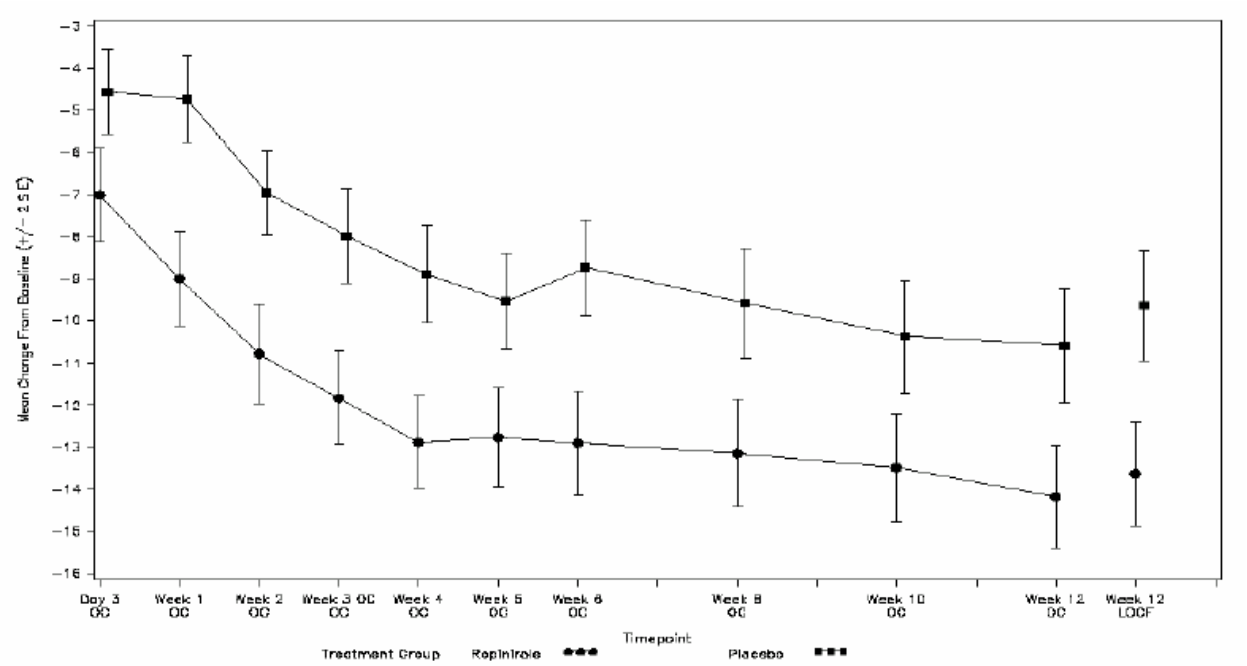
The primary endpoint consisted of the mean change form baseline in the IRLS Scale at week 12 of LOCF. Results of the analysis for the ITT population are presented in the table below. It should be remembered that the total IRLS score can vary from 0 to 40. Higher scores are associated with greater morbidity. A statistically significant ($p<0.0001$), but modest, reduction in morbidity is apparent in the IRLS score is appreciated. Thus there was a difference of 4 (and 3.7 adjusted for center) in the mean scores of the IRLS between drug and placebo. This however was not very different, and even somewhat greater, from the effect observed for similarly designed prior pivotal trials, 190 and 194, where a change of 2.8 and 1.9, respectively, was observed. A similar and statistically significant change ($p<0.0001$) and difference (-4.1 adjusted) was also observed in the PP analysis.

IRLS Scale Total Score	Ropinirole N=187	Placebo N=193
Score at Baseline, n	187	192
Mean (SD)	22.0 (4.99)	21.6 (4.79)
Score at Week 12 LOCF[1], n	186	191
Mean (SD)	8.4 (7.32)	11.9 (9.20)
Change from Baseline to Week 12 LOCF[2], n	186	190
Mean (SD)	-13.6 (8.42)	-9.6 (8.97)

Data Source: Section 12, Table 12.1.1 and Table 12.1.2.

1. Note that the Day 3 IRLS Scale total score was not used to derive this endpoint at Week 12 LOCF (as the recall period for this scale was one week).
2. Change from baseline was calculated for patients who had both a baseline score and a Week 12 LOCF total

The trend in the mean change from baseline in the IRLS scores in the two groups at various measured time are presented in the figure below. What is apparent is that an effect (difference between placebo and drug groups) may have been observed at one week following treatment and appeared to be maintained at about the same magnitude throughout the 12 week experimental period. This effect was not statistically analyzed.



6.1.4.4.2 Secondary endpoints in the primary inferential sets

The first in the hierarchical evaluation for this group of endpoints were those patients with CGI-C of "much improved" or "very much improved" scores at week 12 or LOCF. The results of this analysis for both the ITT and PP population is presented in the Table below. The data includes the adjusted odds ration (and its confidence interval) and p value. The adjusted odds ratio indicates the likelihood of having the class of improved response of drug over placebo. The confidence interval and p value indicates statistical significance for a greater response of drug over placebo in the ITT as well as the PP population.

Population	Ropinirole Responders % (n/N)	Placebo Responders % (n/N)	Adjusted[1] Odds Ratio	95% CI for Odds Ratio	P-Value
ITT Week 12 LOCF	73.3 (137/187)	56.5 (109/193)	2.1	1.4, 3.3	0.0006
PP Week 12 LOCF	75.9 (126/166)	58.3(95/163)	2.4	1.5, 3.9	0.0005

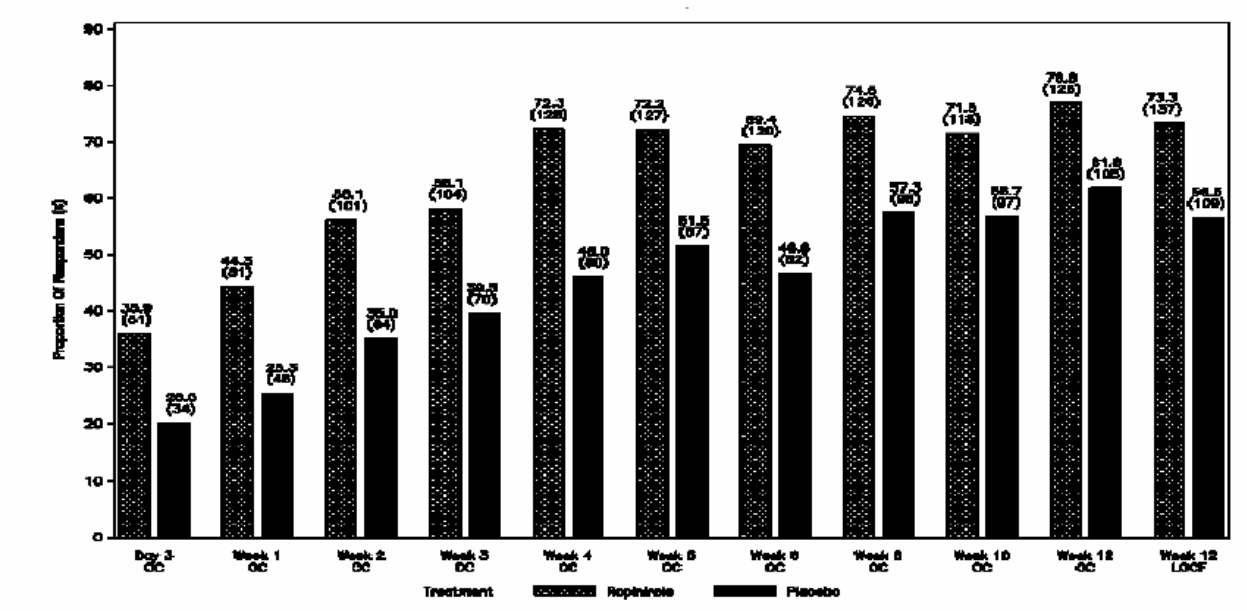
Data Source: Section 12, Table 12.2.2 and Table 12.2.3; Attachment 1, Table 14 and Table 16

1. Adjusted for center group

This effect is similar in magnitude to the effects observed in the previous two pivotal trials (190 and 194), both of which demonstrated a significant therapeutic drug effect. The magnitude of this effect for the ITT population is presented in the table below.

	Percent of Patients with "much improved" or very much improved score on the CGI-C	
	Ropinirole	Placebo
Protocol 190	53%	41%
Protocol 194	59%	40%

The trend in changes over time is presented in the figure below. It is apparent that an effect may have been observed as early as 3 days and was maintained throughout the study. This was not statistically analyzed.



The second (change in IRLS at week 1) and third (change CGI-I at week 1) secondary endpoints were examined in the primary inferential set, in order, in the ITT population. Both were found to be statistically significant. The magnitude of effect, as measured by the difference with placebo, was similar when these endpoints were examined at week or LOCF. This was also true for PP populations. The following two tables present these data.

IRLS Scale Total Score	Ropinirole N=187	Placebo N=193
Score at Baseline Mean (SD)	n=187 22.0 (4.99)	n=192 21.6 (4.79)
Score at Week 1 OC Mean (SD)	n=183 12.9 (7.81)	n=182 16.8 (7.21)
Change from Baseline to Week 1 OC[1] Mean (SD)	n=183 -9.0 (7.65)	n=181 -4.7 (6.91)

Data Source: Section 12, Table 12.1.1 and Table 12.1.2.

1. Change from baseline was calculated for patients who had both a baseline score and a Week 1 OC total score.

CGI-I Score at Week 1 LOCF	Ropinirole N=187		Placebo N=193	
	(n/N)	(%)	(n/N)	(%)
Very much improved or Much improved	81/187	43.3	48/193	24.9

Data Source: Section 12, Table 12.2.1.

6.1.4.4.3 Secondary endpoints

There was a statistically significant improvement in favor of ropinirole: for the proportion of patients with a score of "very much improved" or "much improved on the CGI-I scale" at Day 3, the mean change from baseline in PLMs and PLMI (PLMs/hour) as measured by actigraphy at Week 6, the mean change from baseline in the Sleep Disturbance, Sleep Quantity, and Sleep Adequacy of the MOS Sleep scale at Week 12 LOCF (the change in Somnolence was greater for ropinirole than placebo but not statistically significant), the mean change from baseline in the overall life impact score on the RLS Quality of Life Questionnaire, and the mean change from baseline in the anxiety domains of the Hospital Anxiety and Depression Scales (the change in the depression domain was greater for ropinirole than placebo, but not statistically significant).

6.1.4.4.4 Statistics Reviewer's Conclusion

The statistics reviewer (Dr. Kun He) concluded that the present study is consistent with "evidence that ropinirole is effective in patients in USA." They note that there was a statistically significant difference in favor of ropinirole in the ITT analysis of the IRLS and the CGI-C. Effects were similar across different genders and age.

6.1.6 Reviewer's Efficacy Conclusions

The present study has provided the necessary information to conclude, based upon previous decisions as to what constitutes an acceptable therapeutic effect, that ropinirole is indeed efficacious in a US population of patients. Results of this study was requested before an action was taken because of the suggestion that effects in a North American population may differ from that observed in the pivotal trials as a whole. Thus, a previous subpopulation analysis in North American centers of IRLS in the pivotal study 194 was not positive for a therapeutic effect and indeed demonstrated a slight non-statistically significant superiority of placebo over ropinirole[5]. Moreover, the IRLS as a secondary endpoint in the small study (191) that examined PLMS was also not found to be statistically significant. The fact that the present study examined such a large population of patients (n=380) and demonstrated a high degree of statistical significance suggests that the negative results in the previous studies, which were smaller (n=114 for study 194 and 65 for study 191), may have been a result from a sampling error. The fact that mean ropinirole beneficial effects measured by IRLS were numerically greater in the present US study then prior pivotal studies is reassuring. There is no obvious reason to believe that the European population is different from an American population, most of who are of European ancestry.

7 SAFETY FOR ADDED STUDY (249) AND FINAL SAFETY UPDATE (REVIEW BY DR. ROUZER)

7. 1 REVIEW OF SAFETY FROM STUDY 249

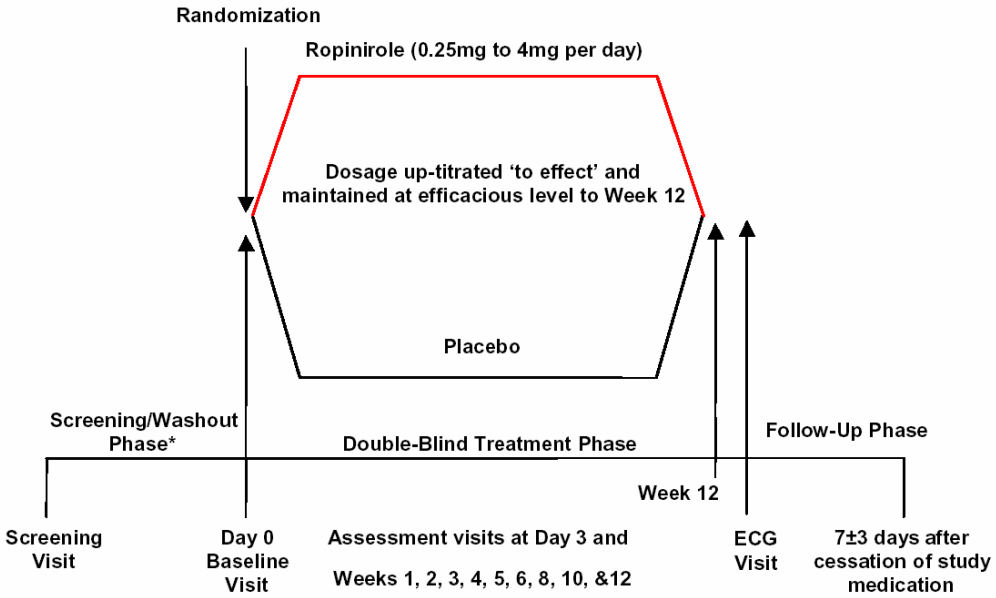
7.1.1 Methods and Findings

The safety population consisted of all randomized patients who received at least one dose of study medication. A total of 380 patients received study medication (ropinirole 187, placebo 193).

Study Schematic Design

5 Although not statistically significant the CGI trended to favor ropinirole as having a more beneficial effect.

14.2. Appendix 2: Study Schematic Diagram



*Patients must discontinue any previous medication known to affect RLS or sleep for a minimum of 7 day prior to the baseline visit. Actigraphy will be performed three consecutive nights immediately prido baseline and Week 6 visits.

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SK&F101468 - Protocol: 249
Table 11.1.1
Patient Disposition
All Patients

Study Stage / Population	Ropinirole		Placebo		Total	
Randomised	187	(100.0%)	194	(100.0%)	381	(100.0%)
Completed	164	(87.7%)	167	(86.1%)	331	(86.9%)
Withdrawn	23	(12.3%)	27	(13.9%)	50	(13.1%)
Safety Population	187	(100.0%)	193	(99.5%)	380	(99.7%)
Intention to Treat Population	187	(100.0%)	193	(99.5%)	380	(99.7%)
Per Protocol Population	166	(88.8%)	163	(84.0%)	329	(86.4%)
ECG Population	41	(21.9%)	45	(23.2%)	86	(22.6%)
Actigraphy Population	110	(58.8%)	113	(58.2%)	223	(58.5%)
HADS Population - Anxiety	68	(36.4%)	68	(35.1%)	136	(35.7%)
HADS Population - Depression	24	(12.8%)	27	(13.9%)	51	(13.4%)

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The overall duration of exposure to study medication for the Safety population is summarized in Sponsor's Table 39.

Table 39 Overall Duration of Exposure to Study Medication (Safety Population in Protocol SKF-101468/249)

	Ropinirole N=187		Placebo N=193	
Days	n	(%)	n	(%)
1-2	1	(0.5)	1	(0.5)
>3-7	0		3	(1.6)
>7-14	1	(0.5)	6	(3.1)
>14-21	0		4	(2.1)
>21-28	5	(2.7)	2	(1.0)
>28-35	4	(2.1)	0	
>35-42	5	(2.7)	2	(1.0)
>42-49	1	(0.5)	2	(1.0)
>49-56	1	(0.5)	1	(0.5)
>56-63	4	(2.1)	1	(0.5)
>63-70	0		0	
>70-77	0		2	(1.0)
>77-84	74	(39.6)	73	(37.8)
>84-91	88	(47.1)	90	(46.6)
>91-98	3	(1.6)	6	(3.1)
>98	0		0	

Data Source: Section 11, Table 11.8.

Summary statistics for the number of days at each dose are shown in Sponsor's Table 40 for the Safety population:

Table 40 Summary Statistics for Number of Days at Each Dose (Safety Population in Protocol SKF-101468/249)

Dose[1]	Days	Ropinirole N= 187	Placebo[2] N= 193
0.25mg/day	n[3]	187	193
	Mean (SD)	7.0 (12.39)	4.8 (5.37)
	Median (Range)	3.0 (2 – 85)	3.0 (1 – 44)
0.5mg/day	n[3]	183	188
	Mean (SD)	12.0 (16.46)	7.9 (11.35)
	Median (Range)	5.0 (1-83)	5.0 (1 – 79)
1.0mg/day	n[3]	173	181
	Mean (SD)	19.6 (20.82)	10.1 (10.0)
	Median (Range)	7.0 (1 – 80)	7.0 (1 – 74)
1.5mg/day	n	146	170
	Mean (SD)	16.0 (16.32)	12.0 (13.57)
	Median (Range)	7.5 (1-73)	7.0 (4 – 75)
2.0mg/day	n[3]	119	150
	Mean (SD)	14.7 (14.64)	12.1 (11.88)
	Median (Range)	7.0 (1– 62)	7.0 (5 – 65)
2.5mg/day	n	92	138
	Mean (SD)	15.8 (14.72)	11.9 (11.04)
	Median (Range)	8.0 (1 – 58)	7.0 (5 – 57)
3.0mg/day	n[3]	63	121
	Mean (SD)	16.7 (12.67)	12.1 (8.75)
	Median (Range)	14.0 (2 – 50)	8.0 (4 – 44)
4.0mg/day	n	45	106
	Mean (SD)	28.8 (13.45)	35.9 (10.42)
	Median (Range)	28.0 (1 – 46)	42.0 (1 – 47)

Data Source: Section 11, Table 11.4.6

1. The extent of exposure information includes those patients for whom a dose reduction to the specified dose occurred.
2. Patients in the placebo group received 0 mg of active study medication.
3. Patients with missing duration of dosing information, or whose visit information could not be slotted in accordance with the visit windows designated in Section 5.8.6.3 are not included in summary statistics of extent of exposure for the period when their dosing information was missing or visit information could not be slotted.

The median duration of exposure for the starting dose of ropinirole (0.25mg/day) or matching placebo was 3 days, reflecting the fact that for many patients the dosage level was increased at the first scheduled visit on Day 3; the dosage level could then be increased again on Day 7. The median duration of exposure for doses between 0.5-2.5mg/day of ropinirole or matching placebo was between 5-8 days, reflecting the fact that many patients remained on a dosage level for one week. No further increases in dose were allowed after Week 10.

In the ropinirole group, 45 patients (24.1%) received the highest dosage level of 4.0mg/day; median exposure at this dosage level was 28.0 days and mean exposure was 28.8 days. In the placebo group a higher proportion of patients received the highest dosage level of matched placebo (106 patients, 54.9%); median exposure at this level was 42 days; mean exposure was 35.9 days. At Week 12 LOCF, 19.8% or ropinirole and 53.6% of placebo patients were receiving 4 mg/day ropinirole or matching placebo, respectively.

Dose Adjustments

Dose reduction to the patients's previous dosage level was allowed, if necessary, due to an AE. Such a reduction was permitted twice prior to Week 10 and only after the patient had reached dosage level 2. Dosage reductions were more prevalent in the ropinirole group, with 51 patients (27.3%) having one dose reduction and 16 patients (8.6%) having 2 dose reductions, compared to 8 patients (4.1%) and 2 patients (1.0%), respectively, in the placebo group.

A summary of dose reductions, by dose, in the Safety population is shown in Sponsor's Table 42:

Table 42 Number (%) of Patients with Dose Reductions by Dose (Safety Population in Protocol SKF-101468/249)

	Ropinirole N=187		Placebo[1] N=193	
Dose Reduced From[2]:	n/N[3]	(%)	n/N[3]	(%)
0.5mg	2/183	(1.1)	0/188	0
1.0mg	18/173	(10.4)	1/181	(0.6)
1.5mg	21/146	(14.4)	1/170	(0.6)
2.0mg	15/119	(12.6)	1/150	(0.7)
2.5mg	11/92	(12.0)	3/138	(2.2)
3.0mg	7/63	(11.1)	3/121	(2.5)
4.0mg	9/45	(20.0)	3/106	(2.8)

Data Source: Section 11, Table 11.4.8.

1. Patients in the placebo group received 0 mg of active study medication.
2. Patients who had two dose reductions from different dose levels are included in the numerator at each of the two dose levels. Patients who had two dose reductions from the same dose level are counted only once in the numerator at that dose level.
3. n/N = number of reductions from specified dose / number of patients exposed to specified dose.

In the ropinirole group, dose reductions from the patient's previous level occurred at all dosage levels; however, dose reductions were most frequent at the 4 mg/day dose level. Nausea was the most common AE with an action of 'dose reduced' recorded in the CRF. On-treatment nausea was reported for 83 patients in the ropinirole group and 15 patients in the placebo group and was reported in association with a dosage reduction for 43 patients in the ropinirole group (25.7%) compared to no patient in the placebo group. Nausea led to interruption of therapy in 2 ropinirole patients (1.1%) and no placebo patients.

7.1.1.1 Deaths

There were two deaths occurring in the Study 249, one in each treatment group.

249.023.00997
Protocol ID: 101468 249
Investigator Number: 23
Patient Number: 997
Treatment Number: 1475
Case ID: A0506061A
Suspect Drug: Ropinirole
Serious Events: Abdominal pain, ill-defined disorder, death

This 57 yoF was enrolled in a blinded study for the treatment of RLS. Past medical history included hysterectomy and arterial grafts in abdomen and left arm. Medical conditions at the time of the event included hypercholesterolemia and hypertension. Concomitant meds included Premarin, traimterene, Coumadin, Lipitor, Centrum silver, vitamins and glucosamine chondroitin complex.

The patient received oral investigational product from February 10, 2004 starting at dose of 0.25mg daily. The dose was gradually uptirated to 2.5mg from March 15, 2004 until April 1, 2004.

On (b) (6) after the start of investigational product, (b) (6) after being titrated to dose level 6, and (b) (6) after the last dose, the patient developed abdominal pain and was hospitalized. Investigational drug was discontinued. Patient underwent abdominal surgery on (b) (6) and died in the hospital (b) (6). The family reported to the investigator that the patient had adhesions that caused intestinal perforations. It is not known if an autopsy was performed. The investigator reported the death due to adhesions causing intestinal perforations and the abdominal pain was probably unrelated to treatment with investigational product.

249.024.00224
Protocol Id: 101468 249
Investigator number: 024
Patient Number: 00224
Treatment Number: 01189
Case Id: A0430874A
Study Drug: Placebo
Event: Traffic accident, Death

This 43 yo M was a enrolled in a double-blind, placebo-controlled parallel group study for the treatment of RLS. The patient's medical history included hypertension, heartburn, occasional headaches and hypoglycemia in the past.

The past received study drug stating at a dose of 0.25mg daily from October 10 2003. The dose was uptitrated to 0.5mg daily from October 13 2003.

On (b) (6) after the first dose of investigational product, and (b) (6) after the drug was uptitrated, the patient was hit by a passing vehicle while riding a motorcycle, and subsequently died that day. An autopsy was performed but the results were unavailable. The investigator reported the motorcycle accident as unrelated to treatment with investigational drug.

7.1.1.2 Other Serious Adverse Events

None on rorinirole; 1 case each of chest pain and pneumonia on placebo for which study drug was not stopped.

7.1.1.3 Dropouts

Adverse events leading to discontinuation of individual ropinirole patients were palpitations, hyperacusis, dry mouth, back pain, nausea, and depression. On-treatment AEs leading to discontinuation in the placebo group were diarrhea, headache, migraine, RLS, confusional state, insomnia, nephrolithiasis and erectile dysfunction.

Table 64 Location of Narratives for Patients with Serious AEs, AEs Leading to Premature Discontinuation and AEs of Special Interest (Protocol SKF-101468/249)

	Serious Adverse Event	Adverse Event Leading to Discontinuation	Adverse Event of Special Interest
Ropinirole			
249.001.00392		Dry mouth	
249.001.00773			RLS (Augmentation)
249.005.00452			RLS (Augmentation)
249.005.00454			Orthostatic hypotension
249.008.00906			Hypotension[3]
249.013.00793		Hyperacusis	
249.014.00090		Palpitations	
249.019.00965		Nausea	
249.020.00174			RLS (Augmentation)
249.023.00997	Ill-defined disorder (fatal)[1]/ Abdominal pain[1]	Abdominal pain[1]	
249.024.00220		Depression	
249.024.00222		Back Pain[2]	
249.027.00261			Syncope
249.039.00749			Syncope[3]
249.044.00541			Hypotension
Placebo			
249.001.00389			RLS (Augmentation) [1]
249.003.00413	Chest pain		
249.012.00068		Mental confusion	
249.013.00074		Insomnia	
249.019.00963		Erectile dysfunction	
249.024.00224	Road traffic accident (fatal) [1]	Road Traffic Accident[1]	
249.024.00225	Pneumonia		Orthostatic hypotension[1]
249.040.00495		Diarrhea	
249.044.00543		RLS (worsening of RLS) [1]	
249.047.00857		Nephrolithiasis	
249.052.00648		Headache	
249.057.00700		Migraine	

1. Follow-up phase
2. Pre-treatment phase
3. ECG phase; post-dose

Selected cases are as follows:

249.14.90 Palpitations

This 43 yo WF was enrolled in a blinded study for the treatment of RLS. Patient's medical history was significant for cardiac murmur and mitral valve prolapse. Patient's baseline signs and symptoms included a UTI for which patient received amoxicillin.

On November 19, 2003, 16 days after starting drug, the patient reported palpitations. Ropinirole dose was 0.5mg/day at the time of onset. The event was moderate and occurred imtermittently

with a total of 45 episodes. It resolved on 11 December 2003 for a total duration of 23 days. Screening ECG on 03 October 2003 showed left anterior hemiblock. Baseline pulse on 03 November 2003 was 70. No corrective therapy was taken; study drug was stopped in response to this event. The investigator considered the event to be related to study drug. Patient's last dose of study drug was 07 December 2003.

249.13.74 Insomnia
This 60yo WM was enrolled in a blinded study for the treatment of RLS. At entry the patient's medical history was significant for chronic sinusitis and somnolence.

The patient received clarythromycin for chronic sinusitis and modafinil beginning 15 September 2003 for daytime hypersomnolence prior to and concurrent with study entry.

On October 5, 2003, 11 days after starting study drug, the patient reported insomnia. The patient was receiving placebo.

The remaining ADRS leading to discontinuation in ropinirole patients included 1 case each of hyperacusis, nausea, depression, back pain, dry mouth but were unremarkable upon examination.

7.1.1.4 Common Adverse Events

Overall, 155 patients (82.9%) in the ropinirole group and 129 patients (66.8%) in the placebo group reported at least one AE. AEs in the ropinirole group were most commonly gastrointestinal disorders (ropinirole: 55.1%; placebo: 19.2%) or nervous system disorders (ropinirole: 42.2%; placebo: 30.6%). The most common AEs by preferred term (i.e. those occurring in >=5% patients in either group) during the treatment phase are shown in Sponsor's Table 44:

Table 44 Number (%) of Patients with the Most Common Adverse Events (≥5% in either treatment group) During the On-Treatment Phase (12-Week On-Treatment Phase Plus the ECG Visit) (Safety Population in Protocol SKF-101468/249)

	Ropinirole N=187		Placebo N=193	
Preferred Term	n	(%)	n	(%)
Nausea	83	(44.4)	15	(7.8)
Headache	31	(16.6)	36	(18.7)
Somnolence	24	(12.8)	13	(6.7)
Nasopharyngitis	21	(11.2)	23	(11.9)
Dizziness	20	(10.7)	11	(5.7)
Vomiting	17	(9.1)	3	(1.6)
Restless Legs Syndrome	10	(5.3)	5	(2.6)

Data Source: Section 13, Table 13.6.1

Of the most common AEs during the 12-week treatment phase, nausea, somnolence, dizziness and vomiting occurred in a higher proportion of patients in the ropinirole group than the placebo

group and at the 3 and 4mg dose. The most common AEs in the ropinirole group had a mean duration of less than 16 days. The mean duration of the most common AE, nausea, was 11.0 (SD 13.74) days and 11.9 (SD 21.26) days in placebo patients. The mean duration of RLS was 7.9 days (8.13) in the ropinirole group and 12.8 days (15.2) in placebo. The differences in mean durations of somnolence, dizziness and vomiting were less than 5 days between treatment groups.

There were no reports of sudden onset of sleep, hallucination, or fibrotic complications in this study. The incidences of syncope, hypotension and orthostatic hypotension were low with 1-2 patients (0.5-1.1%) in the ropinirole group experiencing one of these events during treatment. Augmentation was reported for 3 ropinirole patients (1.6%) and 1 placebo patient (0.5%) during the treatment phase.

On-treatment serious AEs led to the premature discontinuation from the study in <5% of patients in either treatment group. No particular AE led to premature discontinuation of more than one patient in the ropinriole group.

Pregnancies
There were no reported pregnancies

7.1.1.5 Clinical Laboratory Evaluations

Clinical laboratory evaluations were conducted at screening (and repeated during the washout/screening phase if clinically indicated), at Week 12 or at the patient's withdrawal visit if discontinued prematurely. Specified ranges were used to identify clinical laboratory values that met pre-specified criteria for potential clinical concern. The proportion of patients with lab values that met pre-specified criteria for potential clinical concern was low (<2%) in both treatment groups.

A summary of the proportion of patients with laboratory values that met criteria for potential clinical concern at Week 12 is provided in Sponsor's Table 50:

Table 50 Number (%) of Patients with Laboratory Values that Met Pre-Specified Criteria for Potential Clinical Concern at Week 12 (Safety Population in Protocol SKF-101468/249)

Parameter	Week 12[1]	Ropinirole N= 187 n/N[2]	(%)	Placebo N= 193 n/N[2]	(%)
Hematology					
Hematocrit	High	0/163		0/165	
	Low	1/163	(0.6)	0/165	
Hemoglobin	High	0/163		0/165	
	Low	0/163		0/165	
RBC Count	High	0/163		0/165	
	Low	1/163	(0.6)	0/165	
WBC Count	High	0/162		1/164	(0.6)
	Low	1/162	(0.6)	1/164	(0.6)
Basophils[3]	High	0/162		0/164	
Eosinophils[3]	High	0/162		0/164	
Lymphocytes	High	0/162		0/164	
	Low	2/162	(1.2)	1/164	(0.6)
Monocytes[3]	High	0/162		0/164	
Neutrophils	High	0/162		0/164	
	Low	1/162	(0.6)	0/164	
Platelets	High	0/163		0/165	
	Low	1/163	(0.6)	0/165	
Liver Function					
ALT[3]	High	0/158		1/161	(0.6)
AST[3]	High	0/157		0/157	
Alkaline Phosphatase[3]	High	0/158		0/161	
Total Bilirubin[3]	High	0/159		0/161	
Renal Function					
Creatinine	High	0/158		1/161	(0.6)
	Low	0/158		0/161	
Potassium	High	1/156	(0.6)	0/157	
	Low	0/156		0/157	
Sodium	High	1/158	(0.6)	0/161	
	Low	0/158		0/161	
Blood Urea Nitrogen[3]	High	2/159	(1.3)	3/161	(1.9)

Data Source: Section 13, Table 13.4.

1. Patients with laboratory values that met pre-specified criteria for potential clinical concern at the time of premature withdrawal are tabulated in Section 13, Table 13.4.
2. n/N = number of patients with a value that met pre-specified criteria for potential clinical concern/ number of patients with a Week 12 assessment.

In summary, ropinirole up to 4mg/day had an acceptable safety profile in this 12 week dose escalation study in US patients. Nausea appears to be the dose-limiting common event.

7.2 Final Safety Update

The data cut-off date for this update is 15 April 2004 and includes the following information:

- Overall extent of exposure to ropinirole in the RLS clinical development program
- Status of the two ongoing studies (249 and SB-999910/188) including reports of pregnancies, SAEs, and deaths, and
- Post-marketing surveillance safety data including spontaneous report, published literature and regulatory reports received by the sponsor up to and including the cut-off date.

7.2.1 Adequacy of Patient Exposure and Safety Assessments

A total of 6 studies (the 12-week efficacy studies, the 36 week maintenance of effect study and the 7-week clinical pharmacology studies) were completed at the time of the supplemental application and safety data from these studies were reported at that time. The 52-week continuation studies (Studies 192 and 243) were ongoing and interim data were provided for these studies with both the supplemental application and the 120-day safety update.

A summary of the number of RLS patients by cumulative exposure to ropinirole as of 16 April 2004 is presented in Sponsor's Table 1.

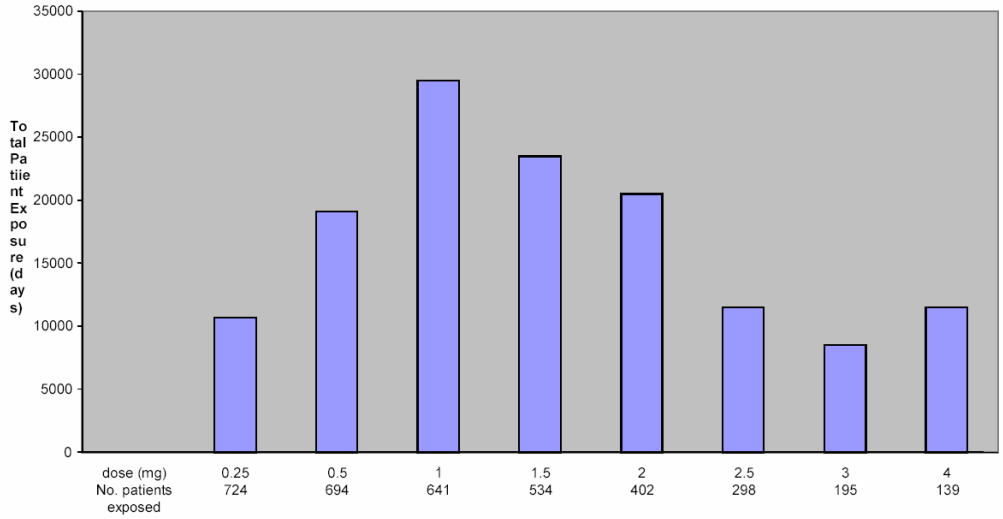
Table 1 Cumulative Exposure to Ropinirole as of 16 April 2004[1]

RLS Study	Number of RLS Patients by Duration of Cumulative Exposure to Ropinirole				
	< 3m (<81 days)	≥ 3m (≥81 days)	≥ 6m (≥ 161 days)	≥ 9m (≥245 days)	≥ 12m (≥ 350 days)
Placebo-controlled Study[2]	171	352	119	30	0
Open-label Continuation Study	20	370	347	332	321
Total	191	722	466	362	321

Data Source: Source Table 007 and 007A

1. Exposure data from Study 249 and Study SB-999910/188 are not included because these studies are ongoing and treatment is double-blinded.
2. Only includes ropinirole patients from completed placebo-controlled studies (Studies 207, 218, 190, 191, 194, and 188) who did not participate in an open-label continuation study (Study 192 or 243).

Figure 1 Total Cumulative Exposure to Ropinirole by Dose
Studies 207, 218, 188, 190, 191, 194, 192 and 243 (16 April 2004)



Across the ropinirole in RLS clinical trial program (completed placebo-controlled studies and open-label continuation studies) up to April 16, 2004, 466, 362, and 321 RLS patients have received ropinirole for at least 6, 9, and 12 months, respectively.

7.2.2 Study 249: A 12 Week, Double-Blind, Placebo-Controlled, Parallel group study to Assess The Efficacy and Safety of Ropinirole in Patients Suffering from RLS

The study consists of three phases: a one-week Screening/Washout Phase, a 12-week treatment phase, and a one-week follow-up phase. Eligible patients are randomized in a 1:1 fashion to receive either ropinirole (0.25mg to 4mg) or placebo and attend up to 13 clinic visits (14 for patients who consent to a follow-up ECG visit). Safety assessments include AE reporting, orthostatic BP and HR, clinical labs, and ECG.

380 patients received blinded study medication.

Deaths, Serious Adverse Events, and Pregnancies

As of the data cut-off date, there were no reports of pregnancy. Two nonfatal SAEs (pneumonia and chest pain) and 2 fatal SAEs were reported. The first patient with a fatal SAE report (road traffic accident) was hit by a passing vehicle while riding a motorcycle and died of injuries. The second fatal SAE occurred in a patient with a SAE of abdominal pain.

None of the reported SAEs was considered by the investigator to be related to study medication. Study med was discontinued due to the abdominal pain; study med was interrupted and subsequently restarted due to the chest pain. No action was taken with regard to study medication because of the pneumonia. The treatment blind was not broken for any of the patients with an SAE.

7.2.3 Study SB-999910/188: Effects of Dopaminergic Agonist Treatment on Spinal Cord Excitability in RLS (FLEXOR REFLEX STUDY)

This is a single center, randomized, double-blind, parallel group, placebo-controlled flexible dose titration study conducted in 20 RLS patients (10 ropinirole and 10 placebo) and 20 age and sex matched normal controls (10 ropinirole and 10 placebo) in the US. The primary objective is to evaluate the effects of stimulation of dopaminergic D2, D3 receptors on spinal cord excitability as measured by flexor reflex and on the severity of symptoms in patients with mild to moderately advanced RLS. The study will last for approximately 6 weeks for RLS patients and 1 week for controls. Subjects in each group (RLS patients and normal controls) will be randomized in a 1:1 fashion to receive up to 2mg ropinirole (RLS patients) or up to 0.5mg rorinirole (normal controls) once daily at night. Safety assessments include AE reporting, BP and HR assessments, ECGs and clinical labs.

Enrollment in this study is ongoing. Eighteen RLS patients and 7 normal controls were enrolled as of 15 April 2004.

Deaths, Serious Adverse Events, and Pregnancies
There have been no reports of deaths, SAEs, or pregnancy from this study as of the data cut-off date.

7.3 Post-Marketing Surveillance

7.3.1 Safety in Special Groups and Situations

There have been no reports of pregnancy from any study in the RLS clinical development program as of the data cut-off date for this report.

7.3.2 Overdose

GSK searched its clinical safety database on 15 April 2004 to identify any postmarketing clinical trial and spontaneous AE reports received for ropinirole in which patients had received an overdose with this medication, regardless of indication.

The Sponsor has proposed modifying the Overdose section of the Labeling of the Parlinson's disease clinical trial program. (b) (4) The largest overdose reported in Parkinson's disease was 435mg taken over a 7-day period (average 62.1 mg/day). Of patients who took a dose greater then 24 mg/day, reported symptoms included nausea, visual hallucinations, hyperhidrosis, claustrophobia, dizziness, chorea, palpitations, asthenia and nightmares. Additional symptoms reported where the dosage was either 24mg or less or unknown included vomiting, coughing, fatigue, syncope, vasovagal syncope, dyskinesia, agitation, chest pain, orthostatic hypotension, chorea, somnolence and confusional state. The labeling change is supported by the data.

Since the 120-day safety update, there has been one additional report of overdose, which occurred in a RLS patient. The patient's pharmacist in error dispensed ropinirole at dose 5.0 instead of 0.5mg. The patient took the 5.0mg dose each night for three weeks and experienced vomiting every evening, decreased body weight, refluxesophagitis, burning feeling in tongue and abnormal hot taste in mouth. The vomiting resolved when the 5.0 mg dose was discontinued. The other events remained unresolved at the time of reporting.

There has also been one report describing the wife of a patient taking ropinirole, who accidently took one 10mg tablet of her husband's ropinirole and experienced nausea and weakness.

A total of 13 post-marketing reports were previously reported (12 with the supplemental application and one new report in the 120-day update). No further information has been received for any of these cases up to 15 April 2004. As previously reported, 11 of the 13 patients were receiving ropinirole for Parkinson's disease, one for RLS, and unspecified for the remaining patient.

The single patient receiving ropinirole for treatment of RLS, a 33 yo F, was hospitalized with extrapyramidal effects, tremor and breathlessness after taking an overdose of ropinirole (exact dose unspecified) with alcohol. The overdose was taken approximately 5 months after ropinirole was started (0.25mg daily) and 3 months following a dose increase to 3 mg daily. The patient

had a history of depression, was on the following concomitant meds: prochlorperazine, propanolol and omeprazole. Ropinirole was discontinued, and the events resolved. The reporting nurse did not know whether the overdose was intentional or accidental.

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.

7.3.3 Drug Abuse

Ropinirole is not a controlled substance. Animal studies and human clinical trials with ropinirole did not reveal any potential for drug-seeking behavior or physical dependence, drug abuse or withdrawal. No AEs suggesting drug-seeking behavior were identified with the exception of 1 patient in the placebo group of the 2 week efficacy studies who reported "euphoria" as an AE.

7.3.4 Geriatrics

Exposure to study medication by age: Sponsor's 2.74 Table 66 summarizes patient exposure by age. The overall duration of exposure was assessed in age groups of 18-64 years, 65-74 years and >=75 years. The majority of patient exposure years in both treatment groups are in the 18-64 year age group (ropinirole: 51 exposure years and placebo: 48 exposure years).

2.7.4 Table 66 Summary of Patient Exposure (Years) to Ropinirole by Age (Safety Population: 12-Week Efficacy Studies 190, 194, 191, Combined)

	Ropinirole N=309 n (exposure yrs)	Placebo N=307 n (exposure yrs)
Age		
18-64 years	250 (51.40)	236 (48.02)
65-74 years	51 (10.05)	54 (11.09)
≥75 years	8 (1.66)	17 (3.13)

Source Data: Table 011

7.3.5 Serious ADRs

The GSK Clinical Safety database (OCEANS) containing AEs received from spontaneous, literature and regulatory reporting, post-marketing surveillance studies and clinical studies (SAE

reports only) was searched on April 15 2004 to identify all ropinirole post-marketing AE reports listing restless legs syndrome as the indication. The search retrieved a total of 80 reports summarized by source and seriousness in Sponsor's Table 2. These reports are cumulative and include all events previously reported in NDA 20-658/S013 and the 120-day update in addition to reports received since the data cut-off date for the 120-day update. No new information has been received on the previously

reported cases. A total of 22 reports met International Conference on Harmonization (ICH) criteria for a serious case (see Sponsor's Tables 3 and 4, following).

Table 2 Postmarketing Reports for Ropinirole in which Restless Legs Syndrome is a Treatment Indication or Clinical Condition

Source	Serious	Non-serious	Total
Spontaneous	18	46	64
Regulatory	2	2	4
Literature	2	10	12
Total	22	58	80

Sudden Onset of Sleep

Among the 22 reports that were considered to meet the criteria for a serious report, 6 documented the occurrence of sudden onset of sleep/sleep attacks or falling asleep while driving in patients receiving ropinirole for treatment of RLS or Parkinson's disease. These six cases were previously reported in NDA 20-658/S013 and the 120-day safety update. There were no new reports of April 15, 2004. The patients with Parkinson's disease had concurrent restless legs at the time of developing sudden onset of sleep. These 6 patients were in the age range of 37 to 79 years, and 4 patients were receiving ropinrole at doses exceeding 4 mg daily. The Sponsor argues that all 6 patients with reports of either sudden onset of sleep or falling asleep when driving presented with other underlying sleep problems, or were taking concomitant meds which may have contributed to the development of the event.

Table 3 A Summary of Serious Postmarketing Reports of Sudden Onset of Sleep in Patients With Restless Legs Syndrome Receiving Ropinirole

OCEANS Number	Age (years)	Sex	Total Daily Dose (mg)	Ropinirole Indication	Adverse Events (verbatim)	Comments
A0349982A (United States)	79	M	6	Restless Leg Syndrome	Sleepiness, constipation and headache.	The patient had a medical history of poor sleep. Approximately two to three weeks after initiation of ropinirole, the patient fell asleep briefly whilst driving. Treatment with ropinirole was maintained and the events resolved. The reporting physician felt that the sleepiness may have been related to the patient's medical history of poor sleep.
B0228688A (United Kingdom)	74	M	1.25	Restless Leg Syndrome	Sleep Attacks	Report received via a regulatory authority. No details of the patient's medical history were provided. Concomitant medications included allopurinol, dextropropoxyphene and metoclopramide. Other concomitant medications included capsaicin, ibuprofen, ipratropium, loratadine, pergolide and cod liver oil. In the same month as starting treatment with ropinirole, the patient experienced a sudden sleep attack whilst driving his car. Ropinirole was discontinued. The event outcome was unknown at the time of reporting.
B0228793A (Austria)	58	F	6	Restless Leg Syndrome	Sudden Sleep Attack	Concurrent medical conditions: difficulty sleeping and depression. Concomitant medications: alprazolam and paroxetine. The patient experienced two episodes of sudden sleep attack in an unspecified period of time after starting ropinirole. One of these occurred whilst the patient was driving. Ropinirole was discontinued. The event outcome was unknown at the time of reporting. The physician reporting the case considered the event may have been associated with alprazolam.

Continued

OCEANS Number	Age (years)	Sex	Total Daily Dose (mg)	Ropinirole Indication	Adverse Events (verbatim)	Comments
D0035037A (Germany)	37	M	15	Hyperactivity (Restless legs syndrome)	Panic attack, paresis, sudden onset of sleep, splenomegaly, sweating increased, nausea, vomiting, dizziness, weight decrease, insomnia, memory disturbance, concentration impaired and hyperlipidaemia	Medical history: smoking, psoriasis, severe headaches (suspected migraines), neurodermatitis, dragging paralgia in the legs, sleep disturbance (associated with restless legs), leg cramps, leg tremor and anxiety disease. Concomitant medications: tildine and naloxone. Panic attacks and increased sweating associated with nausea and vomiting started eight months after initiation of ropinirole. The patient reported that three months after a dose titration of ropinirole from 3.75 mg to 15 mg daily he experienced one to two episodes of sudden onset of sleep per day, and that this sometimes happened whilst he was driving. He experienced more episodes of sudden sleep when stressed and was aware of the symptoms before falling asleep. To deal with these episodes, the patient would stop what he was doing and sleep for half an hour. Following this, he reported waking up feeling refreshed. The patient was advised by his physician to discontinue ropinirole, however, the patient insisted on maintaining his treatment. The outcome of the patient was unknown at the time of reporting.
A0353258A (United States)	70	F	6	Parkinsonian-like-tremor	Falling asleep whilst driving, falling asleep during activities of daily living	Report received via a consumer and verified by a neurologist. Concurrent medical conditions: small vessel disease, restless leg syndrome, akinesia, bradykinesia, "pill rolling" type tremor, diabetes, coronary artery disease, hypertension, myocardial infarction, cerebrovascular accident and spinal stenosis. Concomitant medications: digoxin, potassium, metoprolol, ramipril, furosemide, conjugated estrogens, quinine, valproic acid and mometasone. The patient indicated that she did not feel sleepy before falling asleep during activities of daily living including driving. Ropinirole was maintained, and the events resolved. The patient's neurologist was of the opinion that other etiologies may account for the patient's excessive daytime sleepiness.
B0259186A (Canada)	62	M	0.75	Parkinson's disease	Sleepiness (sudden onset)	Case published in the medical literature [Hobson, 2002]. Medical history: sleep apnea, periodic leg movement during sleep[1] and REM sleep behavior disorder. Concomitant medication: levodopa. Ropinirole was administered for three months, in which time, the patient experienced a single episode of sudden onset of sleep whilst driving. Epworth Sleepiness Scale of 2 at time of event onset. Ropinirole was discontinued. The event outcome was not available at the time of reporting.

1. Although PLMS was specified as a concurrent medical condition for this patient a diagnosis of RLS was not reported.

Table 4 A Summary of Postmarketing Reports of All Serious Cases, Other Than Those Reporting Sudden Onset of Sleep, in Patients with Restless Legs Receiving Ropinirole

OCEANS No.	Age (years)	Sex	Total Daily Dose (mg)	Ropinirole Indication	Adverse Events (verbatim)	Comments
A0315288A (United States)	77	M	U	Restless leg syndrome	Decreased blood pressure, drug interaction (furosemide), edema	Report received from a consumer with no medical verification. Medical history: congestive heart failure, thyroid cancer, prostate cancer and hypertension. Concomitant medications: methadone, potassium and antihypertensive agents. Hypotension developed within one hour of taking furosemide. An emergency room physician considered that the combined use of ropinirole and furosemide may have caused the hypotension.
A0348281A (United States)	U	U	U	Restless leg syndrome	Melanoma	Very poorly documented report, with no details of the patient's medical history, concomitant medications, adverse event outcome or the action taken with respect to ropinirole were provided at the time of reporting.
A0379718A (United States)	70	M	U	Restless leg syndrome	Psychotic disorder, hallucinations	Concurrent medical conditions: lung cancer, hypertension and arthritis. Concomitant medications: terazosin, clonidine and rofecoxib. The patient experienced hallucinations three months after treatment with ropinirole was started. The event was reported resolved three months after discontinuation of ropinirole. The reporting physician considered the event possibly related to treatment with ropinirole or to the patient's concurrent lung cancer.
B0224381A (United States)	75	F	2	Restless leg syndrome	Mania	Report published in the medical literature [Ondo, 1999]. No details of the patient's medical history were provided. Concomitant medications: pergolide, temazepam, alprazolam, clonazepam, amitriptyline, fluoxetine and levodopa/carbidopa. Ropinirole was administered for five months. The event outcome was not reported.
B0227824A (United Kingdom)	33	F	0.25 – 3	Restless leg syndrome	Extrapyramidal effects, breathlessness, tremor and overdose effect	Medical history: depression. Concomitant medications: prochlorperazine, calcium, ergocalciferol, ferrous sulfate, propranolol and omeprazole. The patient took an overdose of ropinirole (dose unspecified) with alcohol In an unspecified period of time later, the patient developed extrapyramidal effects, breathlessness and tremor, which were severe in intensity and required hospitalization. Ropinirole was discontinued and the events resolved.
B0275020A (Austria)	U	U	U	Restless leg syndrome	Hemolytic anemia	Very poorly documented report with no details of the patient's medical history, concurrent illness, concomitant medications or the event provided.

Continued

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The other sixteen serious cases were consistent with the known safety profile or ropinirole (e.g., hypotension, edema, hallucinations, syncope, somnolence) or relevant concurrent conditions. Some reports were too poorly documented with respect to medical history and event details from which to conduct a valid medical assessment. The remaining 58 reports from the 80 retrieved were non-serious and were either consistent with the known safety profile of ropinirole or other factors including concomitant medical conditions or medications.

OCEANS No.	Age (years)	Sex	Total Daily Dose (mg)	Ropinirole Indication	Adverse Events (verbatim)	Comments
B0275676A (Austria)	75	M	1	Restless leg syndrome	Hypotension, electrocardiogram abnormal, chest pain	Concurrent medical conditions; hypertension, benign prostatic hyperplasia, spondylosis and neck pain. Concomitant medications: enalapril, finasteride, tamsulosin and tizanidine. The patient had received ropinirole in the past for treatment of Parkinson's disease with no reported adverse events. Fifteen days after restarting ropinirole, hypotension (systolic pressure of 87 mmHg) developed. Following discontinuation of treatment, the patient complained of left-sided thoracic pain and was hospitalized. A slight left ventricular hypertrophy was detected via an ECG. The events resolved a few days later (treatment unspecified). Ropinirole was restarted with no event recurrence.
B0289149A (Austria)	U	M	1	Restless legs	Restless legs syndrome, therapeutic response decreased.	Report received via the Austrian regulatory authority. In an unspecified period of time after starting ropinirole, the patient experienced aggravation of RLS described as disabling. Concomitant medications consisted of levodopa/benserazide. No information concerning the action taken with respect to ropinirole treatment was provided at the time of reporting. The event resolved with sequelae.
B0292565A (France)	61	F	0.75	Restless legs syndrome	Somnolence, confusional state	Excessive somnolence and confusion was reported in a 61-year-old female patient treated with ropinirole (**REQUIP**) for restless legs syndrome (unlicensed indication). The patient had no concurrent medical condition and no concurrent medication. In the middle of October 2002, the patient initiated ropinirole at a dosage of 0.75 mg daily. At an unspecified date, the patient developed severe somnolence approximately half an hour after each dose intake associated with confusion. The physician also initially reported a drug dependence described as "impossibility of not taking her medication". Upon follow-up the physician clarified this stating that it was not a drug dependence but rather the fact that the patient wanted to take her evening drug dose to decrease her symptoms of restless legs (pain and dysesthesia) which reappeared at evening time, despite the fact that she knew she would experience somnolence and confusion after drug intake. In August 2003, the patient moved abroad and consulted a neurologist. **REQUIP** was stopped abruptly without any problem. The patient was treated with vitamin E. In September, the events were reported as fully resolved and that her restless legs symptoms had improved. The reporting physician considered the events as probably related to ropinirole therapy.
B0295645A (United Kingdom)	U	F	0.5	Restless legs	Condition aggravated (multiple sclerosis)	Concurrent illness: multiple sclerosis. Approximately one year after starting ropinirole, the patient experienced a marked deterioration of her multiple sclerosis. The action taken with respect to ropinirole treatment, and the event outcome were not provided at the time of reporting.

Continued

OCEANS No.	Age (years)	Sex	Total Daily Dose (mg)	Ropinirole Indication	Adverse Events (verbatim)	Comments
D0034614A (Germany)	55	M	6	Restless legs syndrome	Convulsions, enuresis, syncope, bradycardia	Concurrent medical condition: sleep disorder. Concomitant medications: carbamazepine. No history of convulsions was noted. Three months after increasing the ropinirole dose from 0.75 to 6 mg daily, the patient was hospitalized due to syncope and convulsions. The syncope was suspected to be secondary to bradycardia. Two months later syncope recurred and was suspected to be due to hypotension. In the following month, ropinirole was decreased to and maintained at 2.5 mg/day. Carbamazepine was decreased from 400 to 200 mg daily. The patient fully recovered.
D0035295A (Germany)	69	F	2	Restless legs syndrome	Drug interaction (sevoflurane), hypotension, drug interaction (nitrous oxide)	The patient underwent vaginal surgery under anesthesia with inhaled sevoflurane and nitrous oxide, during which she experienced a decrease in blood pressure, with bradycardia, for 90 minutes. The patient fully recovered following an infusion with sodium chloride. The events were considered to be life threatening. The reporting physician diagnosed an interaction between ropinirole and the narcotic medications.
D0037414A (Germany)	69	F	1 – 1.5	Restless leg syndrome	Fatty liver, pancreatitis, abdominal discomfort, varicose veins	Report received from the consumer who is a physician. Concurrent medical conditions: goiter, chronic reflux esophagitis, arrhythmia and cholelithiasis. Concomitant medications: levothyroxine, sodium and potassium iodide, trapidil, digitoxin, estradiol valerate and esomeprazole. Approximately one year after starting treatment with ropinirole, the patient experienced intermittent upper abdominal discomfort. Esophageal varicose veins were diagnosed. An ultrasound of the abdomen and hepatic enzyme levels were normal. Two months later, a CT scan revealed a fatty liver. The patient was also found to have elevated lipase levels and was diagnosed with pancreatitis. Treatment with milk thistle extract, and a weight reduction program was initiated. Pancreatitis resolved after a short period, however, at the time of reporting all other events were persisting. It was unclear as to whether treatment with ropinirole was maintained.
D0038914A (Germany)	U	M	U	Restless leg syndrome	Idiopathic thrombocytopenic purpura	Poorly documented report. The patient was hospitalized with idiopathic thrombocytopenic purpura (Werlhof's disease) in an unspecified period of time after ropinirole was started. The event outcome and action taken with respect to ropinirole were unspecified at the time of reporting.
D0042900A (Germany)[1]	65	F	U	Restless legs syndrome	Syncope	Patient with a history of hypothyroidism and arthrosis, who was receiving concurrent thyrosine sodium and rofecoxib, developed a syncope more than three years after commencing treatment with ropinirole. The patient received unspecified shock treatment. A long-term electrocardiogram was uneventful. Treatment with ropinirole was continued and the event resolved the same day.

Continued

OCEANS No.	Age (years)	Sex	Total Daily Dose (mg)	Ropinirole Indication	Adverse Events (verbatim)	Comments
D0043476A (Germany)[1]	47	F	5.25	Restless legs syndrome	Vomiting, decreased body weight, reflux-oesophagitis, burning feeling in tongue and abnormal taste in mouth	Report received from a consumer with no medical verification. The patient's normal dosage was 0.25mg in the morning and 0.5 mg in the evening. In error the patient's pharmacist provided 5.0 mg Requip instead of 0.5 mg. The patient took the 5.0mg dose for three weeks and experienced the adverse events. On discontinuation of ropinirole: the vomiting resolved; outcome of decreased body weight was unknown and abnormal taste, burning feeling on tongue and reflux-oesophagitis were unresolved. This case is described as an overdose in Section 5.2.

U=Unknown
1. New report not previously reported in NDA 20-658/S013 or 120-day safety update.

7.4 Clinical Literature Searches

An updated clinical literature search was conducted and reviewed . No new safety information concerning ropinirole was uncovered. There was an informative paper "Diagnosis and Management of Pergolide-Inducd Fibrosis" Agarwal, Fahn, and Frucht 19 May 2004 regarding two patients treated with pergolide, one of whom developed pleural fibrosis and the other retroperitoneal fibrosis and how an extensive diagnostic evaluation and surgical intervention were required to reach a diagnosis.

8 SAFETY ISSUES RAISED FROM THE APPROVABLE LETTER (REVIEW BY DR. HERSHKOWITZ)

8.1 Pulmonary Fibrosis

An unexpected case of pulmonary fibrosis, which is usually associated with the class of ergot based dopamine agonist (bromocriptine and pergolide) and not the present drug or other non-ergot based dopamine agonists (pramipexole), was observed. There was also a report of another suspicious case reported in the present label.[6] Because of the unexpected and serious nature of this report the Sponsor was requested to:

> "…provide more information about the single case of pulmonary fibrosis in your submission. Specifically, address how the resolution of the fibrosis was documented, any specific treatment for the fibrosis, why it was not considered drug-related, and how the decision to continue Requip was made. Please examine your safety databases across all indications (Parkinson's disease, RLS, etc.) for any cases of fibrotic complications associated with the use of Requip. Please provide the results of your search."

The Sponsor has responded by providing the following: 1) a discussion of published reports, 2) additional information on the index case, 3) examination of the Sponsor's post-marketing safety data base (OCEANS)[7] and clinical trials database, 4) A Bayesian analysis comparing ergot and non-ergot dopamine agonist AERS reporting rates for fibrosis, 5) an examination of relative 5-HT receptor activity for dopamine agonists.

8.1.1 Published Studies and relative 5-HT receptor activity of dopamine agonists

The Sponsor notes there are no published epidemiological reports describing the incidence of fibrotic changes in Parkinson's patients or patients receiving Parkinson's medication. There are, however, study reports and case reports that include information on these patients. The total number of patients described in the literature for a variety of anti-Parkinson's drugs and other related agent are as follows: 33 for bromocriptine, 25 for pergolide, 1 for dihydroergocryptine, 1 for methysergide, and 0 for lisuride, pramipexole, and ropinirole. Also referenced is a published study that examined reports from the WHO Collaborative Centre for International Drug Monitoring (Uppsala) and published literature[8]. These authors reported that the onset is insidious and symptoms often emerge only after several years of well tolerated treatment with dopamine agonists. Most fibrotic reactions emerged after long-term treatment with bromocriptine and

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6 The following case is noted in the label under "PRECAUTIONS," "Fibrotic Complications": "In the *Requip* development program, a 69-year-old man with obstructive lung disease was treated with *Requip* for 16 months and developed pleural thickening and effusion accompanied by lower extremity edema, cardiomegaly, pleuritic pain, and shortness of breath. Pleural biopsy demonstrated chronic inflammation and sclerosis. The effusion resolved after medical therapy and discontinuation of *Requip* . The patient was lost to follow-up. The relationship of these events to Requip (ropinirole hydrochloride) cannot be established."

7 OCEANS (Operating Companies Event Accession and Notification System) is GSK's worldwide safety database. Data mining analyses of OCEANS data use only spontaneous adverse event reports for clinical marketed non-vaccine products; clinical trials reports are not included.

8 Mueller T, Fritze J. Fibrosis associated with dopamine agonist therapy in Parkinson's disease. *Clinical Neuropharmacology* 2003;26:109-111.

pergolide, often after a period of several years with good tolerability. According to this study there were no fibrotic syndromes associated with the compounds pramipexole, apomophine, selegiline, amantadine, entacapone, tolcapone, anticholinergics, or levodopa. The Sponsor states that "of note, the events referred to for ropinirole were all cases of effusion, as is the one case already described in the current US package insert." Upon examination of the reference it is noted that 7 cases were noted, 4 associated with pulmonary effusions, 2 with pericardial effusions and one reported as pericarditis (see Appendix A). The authors not they could not identify any ropinirole induced fibrosis in the literature. The Sponsor points out that the authors of this study concludes:

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Nonetheless the same authors recommend that:

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Included in the Sponsors review of the literature is the discussion of a number of papers reporting fibrosis complication of the ergot-based dopamine agonists (pergolide in specific). The Sponsor notes "while the authors recommend several interventions, including testing for fibrosis in patients exposed to ergot derivatives, they do not recommend these interventions for the non ergot-derivatives pramipexole and ropinirole." They also point out that authors have noted that the non-ergot-based agonists have not received long-term clinical use.

The Sponsor points out reports that describe two cases in the literature that describe fibrotic complications due to dihydroergocryptine and pergolide, respectively, who were switched to pramipexole and ropinirole, respectively, with regression of the fibrosis.

The Sponsor argues that one of the presumed mechanisms of fibrosis is related to the actions of agents on 5HT receptors. This is supported by the fibrotic syndromes associated with agents active at the serotonin receptor site and the fibrotic complications of the carcinoid syndrome that is associated serotonin secreting tumors. They point out that based upon this that while ergot-derivatives displayed diverse agonist and antagonist properties at multiple receptor sub-types, pramipexole and ropinirole showed a >100-fold affinity for the D2/D3 receptors versus the 5-HT sub-types.

8.1.1.1 Reviewers Comments

This reviewer feels that the literature search does not strongly indicate an association between ropinirole and fibrotic syndromes. The association certainly does not appear as strong as that associated with the ergot based substances. The higher incidence of pulmonary effusions and one case of pericarditis in the WHO database are difficult to interpret without additional information and not sufficient to lead to a conclusions of causality but should lead to continued vigilance for a potential association. The roles of 5-HT activity in the literature in producing fibrosis and the low activity of ropinirole at this site may lead to some comfort.

8.1.2 Additional Information on the Case of Fibrosis in the RLS patient

The Sponsor has provided additional information on fibrosis in the RLS patient (B0270261A). The information stresses specifically addresses requested information in the approvable letter of: 1) how the resolution of the single reported case of "pulmonary fibrosis" in a RLS clinical trial was documented, 2) any specific treatment for the fibrosis, 3) why it was not considered drug-related and 4) how the decision to continue Requip was made.

The patient was a 75 year old female participating in a trial on RLS, with a history of gastric ulcer, pulmonary embolism, hypothyroidism, hypertension and osteoarthritis, who was admitted to the hospital 3 months after the initiation of ropinirole for gastric hemorrhage. While in hospital the patient was also noted to have shortness of breath and wheezing. A chest x-ray revealed reasonably longstanding interstitial lung disease, which was suggestive of interstitial fibrosis and traction bronchiectasis. A subsequent chest x-ray demonstrated small pleural effusions, which were bilateral, and a few enlarged lymph nodes. The changes were ascribed as most likely due to idiopathic pulmonary fibrosis, with infection (interstitial pneumonitis), or less likely a result of a medicine-induced lung disease. Also diagnosed was ischemic hepatitis. The patient was treated with cisapride for the gastric condition and ropinirole treatment was interrupted for approximately two to three days while the patient was acutely ill. No specific treatment for fibrosis was documented. Sedative medication was started in the hospital. Because this was a violation to the protocol the patient was withdrawn from the study but Requip was restarted on a compassionate basis. The reason for continuing the medication was the patient's strong desire to continue the medication because of its perceived efficacy. The patient's gastric hemorrhage was reported as resolved approximately 16 days after hospitalization and the interstitial lung fibrosis and ischemic hepatitis resolved approximately three months after hospitalization. A chest x-ray approximately 10 months after the initial event showed a small number of "glands" visible in the aorto- pulmonary window, marginally enlarged. There was a bulla noted of 3cm in size in the posterior segment of the right upper lobe. Areas of cicatrical tissue with slight traction bronchiectasis were visible in the mid-lobe as were areas of cicatricial tissue in the lingula with slight overlying pleural thickening. No pulmonary thrombosis, infarction or other aberration was observed. On further follow up, approximately two years after the initial event, the investigator reported that the subject's lung condition had resolved completely and therefore that the patient had not developed pulmonary fibrosis as the initial x-ray report had stated. The Sponsor notes that patient was reported to be continuing treatment with ropinirole without further pulmonary problems.

Prior to the entry into the study the patient had discontinued treatment with nitrofurantoin, Lentogesic (dextropropoxyphene hydrochloride, paracetamol, pemoline and levo glutamide), hydroxyzine, temazepam, bromazepam, alprazolam, levodopa, benserazide and amytriptyline one week prior to starting ropinirole treatment.

The Sponsor concluded that Requip was not the cause of the observed lung pathology for the following reason:

- The initial x-ray revealed reasonably long standing interstitial lung disease, whereas ropinirole treatment started only three months prior to detection of the event.
- The investigator stated in follow-up report that the patient had developed interstitial lung disease caused by the use of nitrofurantoin
- The investigator reported that the subject's lung condition had resolved and the patient had not developed pulmonary fibrosis as original x-ray had indicated
- The patient continued treatment with ropinirole without further problems.

8.1.2.1 Reviewers Comments

The resolution of the lung pathology, in spite of continued treatment with Requip, strongly suggests that this is not Requip related. The previous history of nitrofurantoin use suggests a reasonable alternative explanation of fibrosis. Examination of the literature by this reviewer reveals that nitrofurantoin may cause lung disease ranging from symptoms that include fever, chills, cough, pleuritic chest pain, dyspnea to pleural effusion and/or pulmonary hemorrhage to irreversible pulmonary fibrosis (with chronic use). No information is provided about the liver pathology. Interesting there has been a reported case of pulmonary toxicity (fibrosis) and hepatitis caused by nitrofurantoin.[9] In summary the Sponsor presents additional information that strongly argues that the present report was confounded by the use of nitrofurantoin and was more likely due to this latter drug.

8.1.3 Sponsors Clinical Safety Data Base Search (OCEANS data base and Clinical Trials)

According to the Sponsor the OCEANS and clinical trials experience database includes adverse events from a total ropinirole exposure experience of more then 571,611 patient years. The Sponsor used a rather extensive search strategy from the OCEANS database so as to pick up pulmonary, cardiac or retroperitoneal fibrosis, in addition to other possible serous membrane complications normally associated with ergot-based agonists (e.g. pleural effusion and

9 Reinhart, HH et. al., Gastroenterology. 1992 Apr;102(4 Pt 1):1396-9.

pericarditis). Various key MedDRA search terms at a variety of levels where used. Along with this a text search for all Requip narratives where made using the following text search terms: "fibro", "pleur", "valv" and "pericardi".

Similar search strategies where used in the clinical trials as was used OCEANS search except that text searches were not possible. These searches used MedDRA terms identical to the OCEANS search as well as WHOAE terms (where appropriate). This database included 2,922 patients exposed to ropinirole with 1,452 patients exposed for at least six months and 927 patients exposed for at least one year. A few of these clinical trials (numbers not provided) ran for 5 years.

Only one case was identified in the clinical study database that was not included in the OCEANS database. As a result the Sponsor discuses all cases together. A list of the cases, with identification as to whether these were observed originally in trial database or spontaneous post marketing reports, are presented in the Table below. Six of these reports (4 pulmonary, 2 cardiac) specifically describe "fibrosis or fibrotic changes." Sixteen of the cases (11 pulmonary, 5 cardiac) did not note fibrosis or fibrotic changes but report events associated with "serous membrane complications of ergoline treatment (e.g. pleural effusion)." Ten cases were not included in the evaluation because they involved cancer, medical exam ruled out pathology or text search spuriously identified cases (e.g. "fibro" search picked up fibroscopy). Incidentally, of 355 patients exposed to bromocriptine in the clinical trials database, and not Requip, 3 cases of fibrosis or fibrotic associated events were identified.

OCEANS Number	Case type	Subject ID	Country of reporter	Fibrosis reported?	Cardiac or pulmonary case
B0202190A	Clinical trial	093.024.00209	Italy	Yes	Pulmonary
B0270261A	Clinical trial	188.015.02139	South Africa	Yes	Pulmonary
B0319267A	Spontaneous	-	UK	Yes	Pulmonary
B0287185A	Spontaneous	-	UK	Yes	Pulmonary
B0174202A	Clinical trial	043.015.01225	Belgium	Yes	Cardiac
B0240355A	Clinical trial	125.034.00713	Germany	Yes	Cardiac
A0235319A	Clinical trial	040.012.00063	USA	No	Pulmonary
B0168210A	Clinical trial	044.009.00031	USA	No	Pulmonary
B0178308A	Clinical trial	043.077.01415	Finland	No	Pulmonary
B0286324A	Clinical trial	43101	Netherlands	No	Pulmonary
B0220321A	Spontaneous	-	France	No	Pulmonary
B0223727A	Spontaneous	-	France	No	Pulmonary
B0238781A	Spontaneous	-	Austria	No	Pulmonary
B0296241A	Spontaneous	-	Spain	No	Pulmonary
D0033110A	Spontaneous	-	Germany	No	Pulmonary
D0033893A	Spontaneous	-	Germany	No	Pulmonary
D0033982A	Spontaneous	-	Germany	No	Pulmonary
A0290261A	Clinical trial	135.003.0E302	Canada	No	Cardiac
A0329072A	Spontaneous	-	USA	No	Cardiac
B0243787A	Spontaneous	-	France	No	Cardiac
B0285002A	Spontaneous	-	France	No	Cardiac
*	Clinical trial	040.005.00040	USA	No	Cardiac

*Non-serious event and therefore event not entered onto OCEANS.

Of the 15 pulmonary reports considered medically assessable (one report was considered to have inadequate documentation), six were from clinical trial trials and eight were spontaneous reports. Eleven reports were in male and three in female patients with ages ranging from 63 to 83 years old (median 69 years old). Ropinirole was prescribed for the treatment of Parkinson's disease in all but one of these reports in which it was prescribed for the treatment of restless legs syndrome (above noted case). Where recorded, the dose of ropinirole at the time of the event ranged from 0.5 to 20 mg daily and the time to onset following initiation of therapy ranged from 3 days to 4.5 years.

Below is a description of pulmonary cases described as "fibrosis" or "fibrotic changes." Amongst these is the case identified in the previous review that has already been discussed (B0270261A). The Sponsor feels that there may be confounding issues with each each reported case. Each bulleted item below contains a brief description of each case, the Sponsor's interpretation and this reviewer's comments. For a more in depth description of the actual cases the reader should refer to Appendix B.

- The Sponsor notes that in report B0270261A (previously discussed clinical trial case) other possible reasons for the suspected pulmonary fibrosis were documented (e.g. use of nitrofurantoin), treatment with ropinirole was continued and the patient recovered. This reviewer agrees that it is unlikely that the pulmonary changes are associated with Requip (see above).
- The Sponsor notes that in B0287185A (a spontaneous report), pulmonary fibrosis was suspected but not confirmed. This case consisted of a 58 year old male with a chest x-ray that revealed a left basal effusion with left lower lobe changes that were described as atelectasis versus fibrosis. The left lung showed only "small abnormalities" that were also considered possibly fibrotic or atelectasis. There is some question as to whether this may be related to tuberculosis, but no acid fast bacterium were observed in the pleural fluid. Nonetheless, it is reported that the patient was treated with anti-tuberculosis drugs. Furthermore this patient was an ex-smoker and had a medical history of myocardial infarction and pleural effusion. This reviewer believes the report is complicated by the lack of definitive diagnosis and the possibility of tuberculosis (although cultures were negative) and the potential description of atelectasis. There is no mention of prior use of other dopamine agonsists.. This is not an ideal case because of the lack of definitive diagnosis of fibrosis versus atelactasis and the suspicion of tuberculosis. It may be considered somewhat suspicious but with the prior caveats.
- The Sponsor notes that in report B0319267A (spontaneous report) other possible explanations for pulmonary fibrosis were not entirely ruled out. This, 69 year old male patient, who was receiving ropinirole for 4.5 years, presented with pneumonia and was also found to have bilateral pleural effusion, mediastinal and hilar lymphadenopathy, and features suggestive of basal fibrosis of an indeterminate cause. In the light of the adenopathy, the fibrosis was thought to be possibly of an infective type, but also conceivably of a malignant origin. A CT reading noted that the fibrosis may be idiopathic or drug related. This reviewer notes that there was a confounding issue as to whether the statement referring to preexisting asymptomatic pulmonary fibrosis is referring to an x-ray obtained before presentation or before treatment with Requip. The patient died 17 days after hospital admission. The report is not ideal as there is no x-ray prior to treatment. There is no mention of prior ergot-based compound therapy. This case is not easily attributed to ropinirole because of the finding of adenopathy and the issue of questionable previous fibrosis but with these caveats can be considered suspicious.
- The Sponsor notes that in report B0202190A (Clinical Trials, noted in labeling) the patient had a medical history of obstructive lung disease, concurrent arterial hypertension and had initiated several other medications just prior to starting ropinirole treatment. This case describes a 69 year old male with a previous 15 month history of exposure to ropinirole in a clinical trial who was enrolled in a second trial where treatment including ropinirole, selegiline, amlodipine and ticlopidine was initiated. A chest x-ray taken the same month of initiation of these drugs was normal. Nine months latter a chest x-ray revealed pleural effusion at the base of the right lung and evidence of fibrotic changes at both the basal and the apical field of the right lung. The left lung showed only "small abnormalities" that were also considered possibly fibrotic. Infectious, tumor, cardiac causes were ruled out. Ropinirole was discontinued. A chest x-ray 10 months latter

> revealed chronic obstructive bronchitis of moderate severity, sequelae of fibrosis at the right lung base and sclerosis of the aorta. The initial negative chest x-ray strongly suggests that this may be related to the drugs started over this period. This reviewer believes this is a suspicious case, but with some weakness. Thus in support there where there was a prior negative chest x-rays. Minor factors that may interfere with causality included histories of smoking and COPD. Also confounding was the starting of a number of medications simultaneously (selegiline hydrochloride, amlodipine and ticlopidine). None of these other medications note fibrosis in their labeling and as noted above selegiline is not noted to be associated with fibrosis in the WHOAE database. This is a suspicious case. This might be considered the most worrisome case.

This reviewer feels that 2 (B0202190A and B0319267A) of the 4 cases noted above are suspicious for symptoms and signs associated with a potential fibrotic syndrome. They are somewhat confounded by the absence of history of previous drug exposure, concomitant medication and some risk factors associated with fibrosis and importantly the presence of adenopathy in one case.. The Sponsor made no attempt to compare the rates seen here with background rates in the general population. If one assumes that the Sponsors ropinirole exposure calculation is correct (database includes at least 571,611 patient years) this would suggest an incidence of 2 cases/ 571,611 patient-years which is approximately 0.35/100,000 patients years. Even if one includes the case where there is a question as to the diagnosis of atelectasis versus fibrosis 3 cases/571,611 patient-years calculates out to be 0.52 cases/100,000 patient years. There is data on the background annual yearly incidence in the general population which can vary anywhere from roughly 0.74 to 23 per 100,000. Older patients however can experience greater rates. Thus, a study from New Mexico demonstrated that the incidence of pulmonary fibrosis in males and females between ages 65- 74 years were 22 and 12 per 100,000 per year, respectively. The incidences in patients older then 75 was 102 in males and 57 in females per 100,000. The calculated fibrotic incidence of cases observed in the Sponsors database is 0.35/1000 and is lower then the range described for the incidence of fibrosis in the general population. This is also true if you include the third more questionable case. These results, however are, substantially lower if one considers the fact that the Parkinson's population is generally an older population[10]. On the other hand, postmarking underreporting, may lead to an underestimation of the true value. This reviewer believes that no definitive association can be made at the present time but the issue needs continued vigilance. A more complete analysis is beyond the scope of the present review.

ODS is presently performing a more in depth analysis of the incidence of pulmonary fibrosis with all dopamine agonists in the AERs data base. Their results could change this reviewer's conclusion. Preliminary discussions with them revealed that 3 cases of fibrosis were identified. One case is unlikely to be caused by ropinirole as the fibrosis preceded exposure to ropinirole in but followed exposure to cabergoline (an ergot based dopamine agonist). The second case has already been described above (B0319267A). The third case is somewhat supecious. It involves a 75 year old women who received ropinirole for a period of 2 years (15 mg dsily). The pateints was noted to have a reduction in pulmonary function and a pulmonalogist felt this was

10 As previously noted the cases identified here varied from 63 to 83 years old.

consistent with pulmonary fibrosis. ESR, however, was normal. This is a suspicious case but slightly confounded by the normal ESR and lack of specific information. Out of these new cases identified by ODS only the last can be added to the collection of cases. The last case, however is a newly reported case from a different database (9/23/04) and cannot be added to the previous incidence calculation for comparison to the general public. It is a single new case and will likely not substantially change this value.

Ten additional cases mention pleural effusion or pleuritis without any note of fibrosis. Tables presenting a summary of these cases can be found in Appendix C. The Sponsor feels that all of these cases can be explained by other factors and are not drug related. Thus, The Sponsor notes that 5 of these cases can be dismissed based upon concomitant factors that include operative intubation following bypass surgery, congestive heart failure, renal failure following aneurysm surgery, acute renal failure and heart insufficiency and bronchopneumonia. In two additional reports, one was a clinical post trial event, the patients had received ergot-based agonists. In another two spontaneous reports Requip was continued with resolution of the event. The Sponsor discontents the last case (B0220321A) by noting the patient had a "history of congestive heart failure" for which he was on treatment (this is a clinical trials case). This reviewer does not feel this adequately explains this particular case. Nonetheless this reviewer feels there are other reasons to question the diagnosis. The patient's medical history included heart failure. The patient was hospitalized due to dyspnea. "Bilateral pleurisy and severe bilateral pleural effusion was detected." A diagnosis of cancer metastasis or tuberculosis was ruled out. Relevant examination showed an inflammatory hemorrhagic pleural effusion. Treatment with ropinirole was discontinued and an important improvement in pleural effusion occurred." The inflammatory infiltrate and plueritic nature of the presentation is inconsistent with exacerbation of CHF and could potentially be consistent with fibrosis but hemorrhage is inconsistent with fibrosis. Nonetheless, this case may be suspicious. If one includes this case as a potential case the calculation changes to 4/ 571,611 which comes to 0.7/100,000 patient years. This is close to the lowest value in the range of the mean background rate but still substantially lower then that in the aged population.

In summary, except for potentially one confusing case, this reviewer generally does not believe these additional pulmonary cases do not contribute largely contribute to additional suspicion between ropinirole and fibrosis. Many of these cases are complicated other severe medical conditions that may be associated with pulmonary effusions.

Of the seven cardiac reports retrieved by the Sponsor using terms possibly related to fibrosis, two reports (both from clinical trials) directly note fibrosis or sclerosis. The remaining five reports described pericarditis (2 reports), pericardial effusion (2 reports) and mitral valve disease (1 report), but not fibrosis. Four were from clinical trials reports and three were spontaneous reports. Ropinirole was prescribed for the treatment of Parkinson's disease in all of these reports. Where recorded, the dose of ropinirole at the time of the event ranged from 3 to 15 mg daily and the time to onset ranged from 2 to 35 months.

The two cases where fibrosis is specifically noted are presented in Appendix D. One case was associated with "fibrosis of the mitral valve" and the other with sclerosis of the aortic valve. The

Sponsor notes that in both cases other possible explanations for these events (e.g. previous cardiac history, previous bromocriptine treatment and/or short duration of ropinirole treatment) were also documented. The Sponsor therefore concludes that there is insufficient evidence to suggest an association between ropinirole treatment and the development of cardiac fibrosis. These two cases are described below:

- One clinical trials case (79 year old male-B0174202A) had a complex cardiac history with the placement of a pacemaker, sick sinus syndrome and bromocriptine exposure 36 months prior to Requip exposure. The patient presented 2 months after the initiation of ropininerole treatment. Little clinical information is presented except that noted here. This patient had very significant disease described on echo on presentation with fibrosis of the mitral valve ring, in addition to dilation of the left ventricle, global hypokinesia, reduced ejection fraction, mitral, aortic and tricuspid insufficiency and limited diameter of the ascending aorta. The patient was noted to suffer a fatal myocardial infarction. This case seems to be confounded by recent bromocritine exposure.
- The second case is from the clinical trials (B0240355A) and involves a 66 year old female with a history of an MI and presented who increasing dyspnea and chest pain 20 month following the initiation of ropinirole treatment (12 mg/day). On echo aortic sclerosis was identified. Single vessel disease was diagnosed and ropinirole was continued. A coronary artery bypass graft operation was performed. This reviewer agrees with the Sponsor that it is difficult to attribute this adverse event to ropinirol in that aortic sclerosis[11] is not that uncommon in this cardiac at risk population.

The remaining 5 cardiac cases constitute those where no fibrosis was noted. Other factors associated with drug induced fibrosis (e.g. pericarditis, pericardial effusion, valvular disease) were identified. These cases are summarized in the table in Appendix C. Two of these cases where from clinical trials. One of the two involved 73 year old female admitted for chest pain with a diagnosis of the cause as potentially dues to espohigitis or mitral valve disease. The Sponsor notes that mitral valve disease was not confirmed. There is really insufficient information in this case to determine causality. The second clinical case involved a 51 year old male with a history of mediastinal seminoma (s/p surgery and radiation) and previous pergolide exposure who presented with a pericardial effusion. This case is confounded by the previous history of mediatinal seminoma and exposure to pergolide. This reviewer believes causality with ropinirol is unlikely here. Included amongst the 5 cases are 3 spontaneous reports. One such case consisted of a 76 year old woman who presented with a pericardial effusion, likely secondary to an acute infarct. This reviewer feels that this case is not suspicious for drug involvement. The two additional spontaneous cases reported "pericarditis." The Sponsor notes that one of these reports had other potential causes that included "bronchopneumopathy, nicotinism and hypertension (B0243787A)." The latter case is somewhat confusing to this reviewer. It is described as pericarditis (pericardial detachment)." Also noted is persisting "mild pericardial effusion." The information provided in the table is somewhat sketchy (see the Appendix C). Nonetheless, this reviewer is somewhat uncertain as to how the Sponsor's description of the risk factors may lead to the pericarditis and effusion unless they are associated

11 Prasad Y, Bhalodkar NC, Clin Cardiol. 2004 Dec;27(12):671-3.

with a myocardial infarction or heart failure. There is insufficient information to determine this. The second case of pericarditis resolved despite a two day period of drug discontinuation and subsequent continuation, and according to the Sponsor, for which this reviewer agrees, is unlikely to result from drug.

The Sponsor concludes that there… "is, therefore, also insufficient evidence to suggest an association between ropinirole treatment and the development of pericardial events or valvulopathies possibly associated with fibrosis."

This reviewer feels that of 2 cardiac cases described with terms such as fibrosis, only one case suggested a potential drug induced effect, but even this case was confounded by the previous use of an ergot based dopamine agonist. Of the 5 cases identified without the description of fibrosis, but with associated factors, none stand out as definitively caused associated with a drug induced fibrotic syndrome. One case, however, did not include convincing definitive information as to an alternative cause. Analysis of the later case, however, was hampered by the paucity of information. In general all of the 5 cases were described only briefly.

It is noteworthy that ODS recently completed a reviw that compares the various dopamine agonists for valvulopathy (2/7/05). Five cases were identified. They concluded that "all five patients, cardiac valve (aortic, mitral, and/or tricuspid) disorders were unlikely related to ropinirole." These included"

- Three patients who were identified with valvular disorders in the presence of other cardiac myopathies and/or suspect medications. One of these 3 cases was of mild aortic insufficiency and was thought likely related to mild left ventricular hypertrophy from underlying hypertension. The remaining 2 of theses 3 cases developed congestive heart failure with other suspected drugs present; one with mitral valve incompetence and the other with triple valvulopathy (severe aortic disease and leaks in mitral and tricuspid valves). This latter case was the most suspicious amongst the ODS case as it involved multiple valves. ODS felt that causality may have been confounded by the use of Tegretol. This reviewer is unaware of a definitive association of the Tegretol with this pathology.
- Two patients were diagnosed with valvulopathy as a result of a comprehensive clinical work-up for other events. The first patient presented with a seizure and received an echocardiogram that revealed mild mitral valve insufficiency. The second patient presented with chest and abdominal pain. Evaluation revealed elevated liver enzymes and radiographic findings demonstrated pneumonia and aortic stenosis. The reviewer notes that "in the absence of baseline diagnostic tests, it is unknown what other events may have contributed to the valvulopathies (aortic insufficiency and valvular stenosis)."

This reviewer believes that of the ODS cases perhaps one is suspicious. This single case, however, does not lead to a definitive argument for causality but it reason for continued vigilance.

There were no cases identified by the Sponsor as retroperitoneal fibrosis in GSK database.

In conclusion the Sponsor notes: "Of the reports retrieved, only six mention fibrosis or fibrotic changes. Four of these six reports mention pulmonary fibrosis or fibrotic changes and two reports report cardiac valve fibrosis or sclerosis. Alternative reasons for the fibrosis, other than ropinirole treatment, were documented in at least three of these reports and pulmonary fibrosis was suspected but not confirmed in another. An additional report of interstitial lung disease was poorly documented and not medically assessable." Of the 15 reports that note symptoms and signs associated with fibrosis the Sponsor notes that "Again, there were other explanations for the adverse events in most of these reports and in several the adverse events were suspected but not confirmed. There is therefore insufficient evidence, from review of the relevant case reports, to support an association between ropinirole and the development of fibrosis or fibrotic complications." In conclusion, the Sponsor notes, "There is therefore insufficient evidence, from review of the relevant case reports, to support an association between ropinirole and the development of fibrosis or fibrotic complications."

8.1.3.1 Reviewer's Comments

This reviewer believes that the best evidence of fibrosis comes from 3 cases described as pulmonary fibrosis and 1 potential case that described associated events. Two of these cases are complicated by other factors. One case of these is complicated by the uncertain diagnosis of fibrosis versus atelectasis. Nonetheless, if you compare an incidence based upon these the 2 remaining cases (or even include the third case) the calculated incidence would be in the lower range (0.7/ 100,000 patient years) of what might be expected for the background rate in the general population, but more importantly it is substantially lower then what may be expected in the elderly population who likely make up the majority of treated patients.

8.1.4 Disproportionality analysis of post-marketing (AERS and OCEANS databases)

The Sponsor performed a Bayesian analysis of disproportionality, i.e. the Multi-item Gamma Poisson Shrinker (MGPS) analysis. This allowed the comparison of post-marketing events for ropinirole with the two ergoline dopamine agonists (bromocriptine and pergolide) for reports identified in the AERS database (up to the second quarter of 2003). A second similar analysis was performed using reports from the OCEANS database.

MGPS is a Bayesian data mining method that uses all of the data on drugs and events in a particular database to detect safety signals. For each drug-event pair observed in a database, MGPS computes internal expected counts using a stratified full independence model and derives the empirical Bayes geometric mean (EBGM). The EBGM value or signal score represents the relative reporting rate (adjusted ratio of observed to expected counts, after Bayesian smoothing) for the drug-event pair. For example, an EBGM value of 5 for a drug-event pair can be interpreted to mean that the pair has been reported to a given database 5 times more frequently

than would be expected if the drug and the event were reported independently. The lower and upper bounds of the two-sided 90% CI around EBGM are denoted EB05 and EB95, respectively. For this analysis, the threshold for signal detection is defined as an EB05 value equal to or greater than 2. This threshold ensures with a high degree of confidence that regardless of the number of reports, a particular drug-event combination was reported at least twice as often as it would be if there were no association between the drug and the event. EB05-EB95 intervals that do not overlap between drug-event pairs provide assurance that the differences in relative reporting rate are not just due to small sample size, and can be considered potentially different.

The adverse events search terms included: pulmonary fibrosis, pleural fibrosis, interstitial lung disease, pleurisy, pleural effusion, retroperitoneal fibrosis, peritoneal fibrosis, mitral valve incompetence, mitral valve disease, tricuspid valve incompetence, tricuspid valve disease, aortic valve disease, valvular heart disease, pericarditis and pericardial effusion.

This analysis of MPGS scores is presented in the table below. The Sponsor selects an EOB5 as 2 or greater as an arbitrary measure of significant elevation. No EOB5 values for ropinirole, however, are observed to be greater then 2. The Sponsor notes that while many values are positive for the ergot based compound none are for ropinirole. The Sponsor also notes that data similar to ropinirole was obtained for pramipexole. These latter data are not presented. A similar analysis for ropinirole in the OCEANS database was performed and no EOB5 was observed to be greater then 2.

PT	Bromocriptine				Pergolide				Ropinirole			
	N	EBGM	EB05	EB95	N	EBGM	EB05	EB95	N	EBGM	EB05	EB95
Interstitial lung disease	2	1.07	0.328	2.782	11	3.949	2.364	6.282	0	--	--	--
Mitral valve disease NOS	0	--	--	--	4	3.847	1.634	8.018	0	--	--	--
Mitral valve incompetence	1	0.724	0.149	2.434	10	4.489	2.619	7.297	2	1.106	0.339	2.878
Pericardial effusion	8	3.436	1.88	5.873	9	4.286	2.427	7.138	2	1.393	0.427	3.623
Pericarditis	22	12.601	7.995	20.348	4	2.8	1.195	5.787	2	1.905	0.584	4.958
Peritoneal fibrosis	0	--	--	--	1	1.769	0.36	6.023	0	--	--	--
Pleural effusion	65	13.73	10.845	17.311	58	10.454	8.327	13.069	8	1.812	0.992	3.096
Pleural fibrosis	6	53.324	20.272	108.678	17	83.7	54.941	123.253	0	--	--	--
Pleurisy	10	53.177	30.232	88.176	6	7.221	3.231	21.847	1	1.269	0.261	4.268
Pulmonary fibrosis	29	9.389	6.785	12.921	19	6.076	4.116	8.726	0	--	--	--
Retroperitoneal fibrosis	35	63.325	47.483	83.082	23	67.915	47.445	94.816	0	--	--	--
Tricuspid valve disease NOS	1	1.681	0.344	5.684	2	3.138	0.919	8.804	0	--	--	--
Tricuspid valve incompetence	1	0.942	0.193	3.164	12	8.275	4.882	14.458	0	--	--	--
Valvular heart disease NOS	0	--	--	--	6	2.896	1.443	5.324	0	--	--	--
Aortic valve disease NOS	0	--	--	--	2	2.502	0.765	6.544	0	--	--	--

MGPS (Multi-item Gamma Poisson Shrinker) scores for various events, previously associated with the use of ergot based dopamine agonists, for bromocriptine, pergolide and the non ergot based dopamine agonist ropinirole. EBGM: the relative reporting rate (adjusted ratio of observed to expected counts, after Bayesian smoothing) for the drug-event pair. EB05 and EB95: the lower and upper bounds of the two-sided 90% CI around the EBGM respectively. N = number of events recorded for each drug-event pairing.

The Sponsor justifiably summarizes the limitation of this technique by noting:

- Disproportionality analysis provides information about the relative reporting of adverse events in the post-marketing setting. The analysis does not provide estimates of the

incidence of adverse events. A high relative reporting rate does not necessarily indicate a high incidence of the event or suggest a causal relationship between the drug and the event. Relative reporting rates provide a measure of the relative frequency of reporting, but review of case reports is needed to evaluate causality.

- The absence of a signal (low signal score) indicates that a drug-event pair has not been reported more frequently than expected. It does not guarantee the absence of a causal relationship between a drug and an event.
- Reporting rates may vary between drugs and events and may be affected by many different factors, including publicity (e.g., media attention, class-action lawsuits, Dear Doctor letters). Hence, caution should be used in comparing EBGM values, as they may reflect biases due to differential reporting.
- Comparisons of signal scores across and between drugs or drug combinations should be made cautiously and should be interpreted as hypothesis-generating rather than confirmatory. A number of factors may impact the reporting frequency for adverse events including amount of time that a medication has been available in a market, association of an adverse event with another drug in the same or similar class, publicity, labeling and label changes.

The interpretation of these may therefore assist in looking for signals but alone cannot be used to definitively identify an effect. Other data (e.g. individual cases, estimation of incidences) need to be included in the interpretation. While a positive association in this type of analysis would require further investigation a negative study does not prove lack of association.

This reviewer would note that this analysis supports those performed in the above sections and it emphasizes the fact that comparison of the approximated observed to expected rates of ropinirole with that of ergot based agonists generally demonstrates a rather dramatic difference. Thus, these rates where much higher with bromocriptine and pergolide.

The Sponsor's concludes:

> "… based on the results of the extensive searches, analyses and evaluations conducted for this review, there is insufficient evidence to support an association between ropinirole treatment and the development of fibrosis or fibrotic complications. GlaxoSmithKline will, however, continue to monitor this area closely."

8.1.4.1 Reviewer's General Conclusions

This reviewer agrees that there does not appear to be an obvious signal for fibrosis syndromes with ropinerol. There are very few suspicious cases, but generally the lack of complete information and their small number does not permit one to conclude a casual relation to drug. The Sponsor makes no effort to compare incidences seen in the Sponsors database with that

observed in the general population. A rudimentary attempt was made by this reviewer in the above discussions and was not found to be remarkable. At the present time this adverse event should not prevent the approval of this new indication, but continued vigilance is necessary. ODS is presently performing an analysis of a comparison of fibrotic syndromes between all of the dopamine agonist. Preliminary examination of their identified cases does not suggest a change in conclusions but this issue will have to be revisited if this analysis indicates a relation of ropinirole with such syndromes. Information in the labeling, however, should be expanded upon so as to indicate that more then one case has been identified.

8.2 ECG Analysis

In the approvable letter this division expressed concern about the absence of ECG data timed to dose escalation, particularly considering the expected expansion of use of Requip that will result from this new indication. It was suggested that the Sponsor obtain and submit additional "ECG data in patients with RLS at multiple time points after dosing…" The division was particularly interested in examining "QTc, at Tmax of parent drug and any active metabolites." It was advised that the Sponsor may be able to accomplish this by incorporating the ongoing efficacy trial, 249, and that the total number of patients should include an adequate sample of patients at the highest daily dose examined (4 mg/kg).

To accomplish the Sponsor added an amendment that established an additional experimental phase that examined a subset of patients who had a more thorough ECG evaluation. During this phase patients were to return to the clinic 1 to 2 days following the administration of the last study dose on week 12 or after early withdrawal for EKG monitoring. At this time, pre-dose baseline EKGs and one and two hour posts dose EKGs were examined. Patients were administered a single dose of Requip that was previously observed to be optimally therapeutic. A latter EKG was evaluated at a follow-up visit 7 ± 3 days following the ECG Visit. All of EKGs, during the cardiac phase and follow-up visit, were obtained in triplicate. EKG recording was controlled for activity and time after a meal. All EKGs were performed and digitally collected using the same instruments. The follow up EKG was not controlled for the time of day. The EKGs were manually read using on-screen calipers, by a blinded cardiologist. A single screening EKG was obtained for all patients who participated in the study. This EKG was collected using uncontrolled instruments and in an otherwise uncontrolled fashion. The EKG, however, was converted to a digital record and included in the analysis, by the blinded cardiologist.

Not all patients participated in the cardiac phase amendment because a number had already completed the protocol at the time of its establishment. A total of 86 patients participated (41 ropinirole and 45 placebo patients). Four patients (2 drug and 2 placebo) were found to be lacking triplicate EKG measures at some time points, having only one or two recordings. Demographic characterization of this trial was similar to that of the total efficacy trial and relatively well balanced across treatment groups.

Mean baseline screening EKGs values for both placebo and drug groups where relatively similar for heart rate, RR interval, PR interval and QRS duration. There was slightly greater interval duration (5-10 msec) of various measures of the baseline QT interval (uncorrected, QTF and QTB) for the placebo group as compared to the ropinirole group. The distribution of test dosage of drug (or presumed dosage for placebo) is presented in the table below. Twenty-seven percent of patients were on the highest dosage of 4 mg/day. The median dosage was 2.5 mg/day.

Study Medication Dose (mg/day)	Ropinirole N=41		Placebo[1] N=45	
	n	%	n	%
0.25	1	(2.4)	0	
0.5	3	(7.3)	1	(2.2)
1.0	4	(9.8)	1	(2.2)
1.5	7	(17.1)	4	(8.9)
2.0	5	(12.2)	3	(6.7)
2.5	4	(9.8)	3	(6.7)
3.0	6	(14.6)	4	(8.9)
4.0	11	(26.8)	29	(64.4)

Data Source: Section 11, Table 11.4.5

1. Patients in the placebo group received 0 mg of active study medication.

The Sponsor provides the following table for uncorrected and corrected QT intervals during the EKG phase for pre-dose and 1and 2 hour post-dose readings in drug and placebo.

Interval/Time	Ropinirole N=41		Placebo N=45	
	n	Mean (SD) (range)	n	Mean (SD) (range)
QT (msec)				
ECG Visit pre-dose	41	390.8 (32.09) (324,464)	45	393.3 (30.12) (332,469)
ECG Visit, 1 hr post-dose	39	399.2 (29.40) (344,464)	45	404.5 (31.97) (352,474)
ECG Visit, 2 hr post-dose	40	404.7 (32.10) (348,487)	45	404.3 (30.39) (357,477)
QTcF (msec)				
ECG Visit pre-dose	41	405.7 (23.04) (366,489)	45	406.1 (19.22) (375,463)
ECG Visit, 1 hr post-dose	39	412.2 (23.60) (362,487)	45	410.4 (23.53) (375,472)
ECG Visit, 2 hr post-dose	40	416.0 (26.74) (363,498)	45	412.3 (21.22) (375,466)
QTcB (msec)				
ECG Visit pre-dose	41	413.9 (25.95) (363,523)	45	413.2 (21.94) (375,467)
ECG Visit, 1 hr post-dose	39	419.4 (28.36) (362,518)	45	413.9 (26.46) (367,478)
ECG Visit, 2 hr post-dose	40	422.0 (28.79) (362,527)	45	416.9 (24.50) (373,476)

Data Source: Section 13, Table 13.3.1.
ECG Visit ECGs were triplicate digital recordings using ECG equipment standardized across centers.

The Sponsor presents additional information on the mean change in the QTcF 1 and 2 hours after treatment as well as the maximal change (1 or 2 hours post dose). This is presented in the table below. Differences in mean scores when drug was compared to placebo demonstrated a 1.1 msec to 4.4 msec QTcF prolongation (drug – placebo). A prolongation of 5 msec or greater is usually considered significant.

Change from:	Ropinirole N=41		Placebo N=45	
	n	Mean (SD) Median (range)	n	Mean (SD) Median (range)
Pre-dose to 1hr post-dose	39	5.9 (9.58) 6.0 (-12,31)	45	4.3 (10.43) 5.0 (–17,27)
Pre-dose to 2hr post-dose	40	10.6 (13.39) 8.0 (–16,58)	45	6.2 (9.81) 5.0 (-19,22)
Pre-dose to maximum post-dose	41	11.6 (12.73) 9.0 (–11,58)	45	8.8 (9.39) 12.0 (-13,27)

Data Source: Section 13, Table 13.3.2.

When this data was adjusted for a center effect and a center effect plus the removal of a patient who experienced a Mobitz 1 type block the difference with placebo was further reduced. Thus, without such an adjustment the treatment difference when using the maximal prolongation was 2.8 but was 2.3 and 1.5 when adjusted for center effect and when adjusted for a center effect plus the removal of a patient who experienced a Mobitz 1 type block, respectively.

An examination of the number of patients with increases in QT and corrected QT intervals was contained in the submission of the final report and later supplemented by additional corrected information in an e-mail (2/25/05): i.e. because only QTcF was included in the original submission the Sponsor was requested to include an additional analysis of QTcB. This analysis is contained in the table below. Increases were divided into two groups, 30-60 msec and >60 msec. Analysis was performed for maximum change from pre-dose and change from pre-dose to 1 and 2 hours post-dose. As can be observed there were a slightly greater number of patients in the 30-60 msec group for drug then for placebos using the various measures: e.g. 3 Vs 1 (drug to placebo) for the QTcB and 3 Vs 0 (drug to placebo) for the QTcF maximal post-dose response. There was only one case of a patient with a greater then 60 msec change for QTcB (64 msec change) in the post-dose maximal response. This patient's EKG, as noted above was complicated by the development of heart block. It is noteworthy that of the 3 patients who exhibited an increase in the QTcF by 30-60 msec 2 patients were on the highest dose (4 mg/day) and 1 was on an intermediate dose (2 mg/day). The Sponsor notes that, with the exception of the one patient who experienced heart block, these patient's post-dose QTcF values were "within gender-specific normal ranges (upper limit of 460msec for males and 470msec for females)."

Number of Patients by Change in QT (msec) at ECG Visit
(ECG Population in Protocol SK&F-101468/249)

Treatment Group	Assessment	n	Change 30-60msec			Change >60msec		
			QT	QTcF	QTcB	QT	QTcF	QTcB
Ropinirole (N=41)	Maximum Post-dose minus pre-dose	41	8	3	3	0	0	1 [1]
	1 hr Post-dose minus pre-dose	39	3	1	3	0	0	0
	2hr Post-dose minus pre-dose	39	6	3 [1]	2	0	0	1 [1]
Placebo (N=45)	Maximum Post-dose minus pre-dose	45	8	0	1	0	0	0
	1 hr Post-dose minus pre-dose	45	4	0	1	0	0	0
	2hr Post-dose minus pre-dose	45	6	0	0	0	0	0

Data Source: Section 13, Table 13.16.12

1. Patient 249.028.00270 experienced Mobitz Type 1 block simultaneous with a variable PP interval suggestive of hypervagal tone during the previously reported in the 101468/249 Clinical Study Report.

Although there appears to be a trend in corrected QT prolongation this effect is small and the data is sufficiently limited that no definitive conclusions can be made.

Examination of the raw data by this reviewer revealed that the QT intervals during the single screening (prior to the initiation of study) and follow up period (7 ± 3 days following the ECG Visit) where substantially lower then the intervals measured at pre- and post-drug time periods during the EKG test phase. This begs the question as to whether the 1 to 2 day period was sufficient time to allow for drug, as well as metabolite, washout. According to the label the half-life of Requip is 6 hours. As a result of a Telecom with the Sponsor on 1/24/05 the Sponsor provided more accurate information as to the time patients were off of drug prior to the EKG phase of study 249. Thus, Patients were off of drug from 12 hours 40 minutes to 2 days 20 hours 35 minutes. Median time off drug was 1 day 23 hours 30 minutes. This would suggest that much of the parent drug should completely metabolized at the time of the initiation of the EKG phase of the study. However, discussions with Dr. Yasuda (PK reviewer) revealed that mass balance studies indicated that some metabolites may potentially be present at the time of measurement (e.g. see metabolite F in the record of a mass balance study in Appendix F). For this reason this reviewer considered a comparison to screening and follow-up recordings as justified.

It may not be completely justifiable to utilize the EKG performed during screening as a baseline for a number of reasons including the fact that it was performed as a single measure, was not controlled for the time of day and the recording utilized completely different instrumentation[12]. The follow up EKG, however, was performed in triplicate using the same instrumentation. The caveat for this analysis is that the EKG was not controlled for the time of day and it represented a smaller sub-sample of patients who participated in the EKG phase and made the follow-up appointment (28 of 41 in drug and 28 of 45 in placebo). The Sponsor was requested, in a telecom on 1/25/05, to perform an analysis of changes in EKG using the follow up as baseline. The analysis was received in an e-mail on 2/2/05, and is presented in the table below. Differences between placebo and drug treatment groups in corrected QT intervals are significant when the follow-up is used as a baseline with: i.e. the differences of the means of drug-placebo are greater then 5 msec. The increases were greatest during the post-dose then the pre-dose period. While this analysis should be interpreted with caution it does suggest the possibility of a potential metabolite effect as discussed above.

12 For analysis the recording was subsequently digitized and evaluated in the same fashion as were other EKGs.

Summary Statistics for Change in QT, QTcF, and QTcB (msec) Relative to Follow-Up Visit for Patients with ECG Measures at Follow-Up Visit (ECG Follow-Up Visit Population in Protocol SK&F-101468/249

Change[1] from Follow-Up Visit to:	Ropinirole N=28		Placebo N=28	
	n	Mean (SD) Median (range)	n	Mean (SD) Median (range)
QT (msec)				
Pre-dose ECG Visit[3]	27	2.3 (19.83) 2.0 (-46,35)	28	-1.3 (17.62) 1.0 (–28,33)
1 hr post-dose ECG Visit[3]	26	11.5 (20.18) 12.5 (–31,60)	28	10.4 (18.67) 13.5 (-28,39)
2 hr post-dose ECG Visit[3]	26	16.4 (23.64) 12.5 (–20,70)	28	10.9 (17.11) 10.0 (-15,43)
QTcF (msec)				
Pre-dose ECG Visit[3]	27	4.1 (11.89) 5.0 (-24,30)	28	-3.3 (9.80) -3.0 (–32,14)
1 hr post-dose ECG Visit[3]	26	11.0 (13.68) 10.5 (–16,41)	28	2.6 (12.19) 1.5 (–25,28)
2 hr post-dose ECG Visit[3]	26	15.4 (16.01) 14.0 (–16,54)	28	3.5 (9.18) 4.0 (-15,23)
QTcB (msec)				
Pre-dose ECG Visit[3]	27	5.1 (12.86) 3.0 (–23,30)	28	–4.2 (13.16) –4.5 (–38,22)
1 hr post-dose ECG Visit[3]	26	10.5 (15.65) 7.5 (–20,40)	28	–1.5 (14.41) –1.0 (–31,26)
2 hr post-dose ECG Visit[3]	26	14.4 (16.20) 15.5 (–14,55)	28	–0.4 (13.35) 0.5 (–27,24)

Data Source: Section 13, Table 13.16.41,Table 13.16.42, Table 13.16.43.

1. Change=ECG Visit or Screening Visit minus Follow-Up Visit.

3. ECG Visit and Follow-Up ECGs were triplicate digital recordings using ECG equipment standardized across centers. Time of last meal and level of activity were controlled, but time of day was not controlled.

A categorical outlier analysis of change in QTc using the follow-up as baseline was also requested in the aforementioned e-mail. These data are presented in the table below. This analysis resulted in a much larger percent of patients in drug treatment groups falling into the 30-

60 msec change group. Thus 4 out of 26 (or 15% of total drug) patients were observed to have increases falling into the 30-60 msec range at 2 hour post-dose for boyt QTcF and QTc B. This compares to 5 to 8% falling in this bin at 2-hours post dose based upon the difference with pre-dose baseline for QTcF.

The Sponsor notes that 2 of the patients who demonstrated post-dose corrected QT increases greater then 30 msec also experience nausea and vomiting approximately 30 minutes after drug administration. It is unclear to this reviwer how this may relate to causality of these changes.

Number of Patients by Change in QT, QTcF, and QTcB (msec) at ECG Visit Relative to Follow-Up Visit (ECG Follow-Up Visit Population in Protocol SK&F-101468/249)

Treatment Group	Assessment	n	Change 30-60msec			Change >60msec		
			QT	QTcF	QTcB	QT	QTcF	QTcB
Ropinirole (N=28)	Pre-dose minus follow-up	27	2	1	1	0	0	0
	1 hr Post-dose minus follow-up	26	5	2	4	0	0	0
	2hr Post-dose minus follow-up	26	7	4	4	1 [1]	0	0
Placebo (N=28)	Pre-dose minus follow-up	28	1	0	0	0	0	0
	1 hr Post-dose minus follow-up	28	4	0	0	0	0	0
	2hr Post-dose minus follow-up	28	3	0	0	0	0	0

Data Source: Section 13, Table,13.16.63,Table 13.16.61,Table 13.16.62

1 Patient 249.004.00429 reported nausea and dry heaves 30 min after the 4 mg ECG Visit dose and was previously reported in 101468/249 Clin Study Report.

The Sponsor feels that this analysis is "limited as it is based on the reduced subset of 28 patients per group who participated in the Follow Up visit." The reviewer agrees that this is a small number of patients. They also cannot be considered a true random sample. Hhowever, the consistent difference between placebo and drug group is suspicious for a potential effect. The Sponsor also notes that "additional new concomitant medications after the On-Treatment and ECG Visit study phases might affect changes in the intervals relative to the Follow-Up Visit." These medications are not noted and it would appear to this reviewer are as just as likely to effect the analysis during the within the EKG phase as between follow-up and EKG phase.

No patients at any point in any treatment group exhibited a QTcF of greater then 500 msec. The longest on-treatment QTcF intervals (in the 480-499 msec range) were reported in a single

ropinirole patient with a pacemaker with a fully paced QRS complex. This patient did not have a post-drug change from pre-drug EKG period in QTcF of greater then 30 msec.

The Sponsor concludes that "the ECG data in this study did not demonstrate a clinically significant effect of ropinirole on the measured QTcF interval."

To further explore for potential relation between drug and the prolongation of the corrected QTc interval the Sponsor was requested, in a telecom on 2/7/05, to plot the dose versus the post dose maximum change in QTcF and QTcB change from pre-dose baseline during the EKG phase. These plots were received in an e-mail on 2/11/05 and are contained in the two graphs below. It is difficult to determine whether there is a dose dependent effect because of the limited number of observations.

Maximum Change Post-Dose from Pre-Dose for QTcF versus Dose at the time of the Maximum Change in ropinirole and placebo (0 mg) patients.

Maximum Change Post-Dose from Pre-Dose for QTcB versus Dose at the time of the Maximum Change in ropinirole and placebo (0 mg) patients.

A similar analysis to that used in the above was performed using the follow-up as a baseline. Except for a more obvious prolongation in the 4 mg groups, these plots, like those above, did not show an obvious dose dependent effect.

Maximum Change Post-Dose from Follow-Up Visit for QTcF versus Dose at the time of the Maximum Change in ropinirole and placebo (0 mg) patients.

Maximum Change Post-Dose from Follow-Up Visit for QTcB versus Dose at the time of the Maximum Change in ropinirole and placebo (0 mg) patients.

This reviewer feels that these data are suspicious for a potential prolongation in the QT interval. It is, however, not proof as the analysis is post-hoc and the present study was not designed to definitively answer this question this question. If such changes occur, this reviwer feels that they most likely will be observed at doses of 4 mg/day and higher.

Additional EKG measured parameters during the study are presented in the table below. Most notable, in relation to the analysis of the QT interval, is the observation that there was no significant change in heart rate. It should be noted that an analysis for the subset follow-up sample is not included in this table. Other measures, including PR interval and the QRS segment, did not appear to be significantly altered.

ECG Parameter	Ropinirole N=41		Placebo N=45	
	n	Mean (SD) (range)	n	Mean (SD) (range)
HR (beats/min)				
ECG Visit pre-dose	41	68.5 (11.27) (48-90)	45	67.3 (11.27) (39-95)
ECG Visit 1 hr post-dose	39	67.1 (10.87) (47-91)	45	63.8 (9.92) (40-79)
ECG Visit 2 hr post-dose	40	66.0 (8.75) (48-84)	45	65.0 (10.52) (43-85)
Follow-up	28	67.0 (11.24) (50-89)	28	69.5 (9.89) (52-88)
RR (msec)				
ECG Visit pre-dose	41	901.5 (154.64) (663-1259)	45	917.8 (162.76) (634-1517)
ECG Visit 1 hr post-dose	39	919.2 (153.88) (662-1276)	45	968.2 (171.94) (759-1500)
ECG Visit 2 hr post-dose	40	927.8 (126.96) (715-1263)	45	953.9 (168.56) (708-1416)
Follow-up	28	920.4 (152.12) (672-1187)	28	881.3 (123.97) (686-1151)
PR (msec)				
ECG Visit pre-dose	40	161.5 (23.87) (127-240)	44	161.2 (24.47) (124-228)
ECG Visit 1 hr post-dose	38	162.9 (23.57) (125-218)	44	160.8 (24.38) (126-230)
ECG Visit 2 hr post-dose	39	162.9 (22.70) (125-206)	44	161.1 (23.78) (123-230)
Follow-up	27	158.8 (22.55) (123-204)	28	152.5 (23.69) (117-221)
QRS (msec)				
ECG Visit pre-dose	41	85.6 (16.42) (74-178)	45	86.5 (14.28) (72-148)
ECG Visit 1 hr post-dose	39	87.8 (15.86) (76-178)	45	87.6 (14.79) (71-153)
ECG Visit 2 hr post-dose	40	87.3 (14.92) (71-171)	45	87.1 (14.12) (72-144)
Follow-up	28	86.4 (17.06) (73-166)	28	84.6 (7.22) (72-98)

A latter analysis by the Sponsor, which examined heart rate changes for the follow-up subset analysis for patients included in the above follow-up QT measurements, was provided as a result of a telecom (2/2/05) in a submission provided through e-mail (2/8/05). There were no substantial difference in heart rates between follow-up and EKG phase testing periods

8.2.1 Relevant cardiac post-marketing issues (Torsades de Point)

Because of the equivocal, but somewhat suggestive EKG results noted above this reviewer performed a post-marketing data search of MEDwatch reports using the AERS datamart. The term Torsades de Pointe was cross-referenced to ropinirole and other dopamine agonists including pergolide, pramipexole and bromocriptine. Three non-domestic cases were identified for ropinirole. No cases were found for pergolide, pramipexole or bromocriptine.

The three cases, all foreign, are summarized below:

- AERS report # 308997 (Denmark): This case was of 69 year old female with a history of coronary artery disease, recurrent atrial fibrillation and "hypertensive cardiac disease." . The patient was started on Requip at "approximately Oct-1997." On (b) (6) the Patient experienced "ventricular fibrillation and cardiac arrest which was treated with defibrillation, heart massage, cardioversion, got artificial respiration and increasing dosage with Cordarex (Amiodarone) and Laxis 40mg, Digimerck 0.1mg, Isoptin 40m, Corversum (4mg)." Latter on (b) (6), the patient experienced several runs of "torsades de pointe-tachycardia, which was considered life-threatening" These resolve the following day. Echocardiography demonstrated moderate dilatation of left and right atrium/ left and right chamber of the heart; reduced pumping function and serum potassium was noted to be 3.3 mmole/l. No other laboratories are noted. Dose of ropinirol was not noted. The patient's concomitant medications were noted to include Coversum (an ACE inhibitor), Isoptin (verapamil), Digimerck (digitoxin) for CAD and Madopar, Nacom (levodopa), Madopar (levodopa/benserazide) and Parkinsan (budipin) for Parkinson's disease. The reporter accessed the event as possibly related to drug. It is unclear from this report as to whether Amiodarone was present at the time of the reporting of Torsades de Point, but if so this combined with low potassium (albeit borderline low) and apparent heart failure (based upon echo) are very reasonable alternative causes and confound casual relation with ropinirole.
- AERS report # 3215227 (Germany): This is a case of a 67 year old female with a history of Parkinson's disease (times 5 years) colon cancer (s/p bowel resection with no "reactivation") and latent hyperthyroidism. The patient was started on ropinirole in "December 1998" at a dose of 0.25 mg BID. Latter on (b) (6) patent lost consciousness and was hospitalized. Ventricular extra-systoles and Torsades de pointe was noted. The QTc interval at that time was reported to be 580 msec. Cardiac rhythm was stabilized by high-dose application of magnesium and potassium as well as low dosage of a beta-blocker (metoprolol) and temporary dose of Lidocain (Xylocain). The patient's concomitant medications at the time of the event included Nacom (Carbidopa/ Levodopa), Parkinsan (budipin, 60 mg qD), Tremarit (metixen, 10 mg QD) and Lexotanil (bromezepam 1.5 mg QOD). As drug history didn't reveal any other suspicious "remedy," ropininrole was suspected as causal factor of cardiac rhythm disorder. It was discontinued and the QT interval gradually shortened without complete normalization (QTc 480 msec). Tremarit was also discontinued (unclear as to when in relation to QT normailization). An echocardiogram, revealed good systolic function of left ventricle,

dimensions of left and right atrium at upper limit, mild insufficiency of the artrio-ventricular valves. The patient's hospital course was later complicated by the occurrence of pneumonia. This reviwer could not find any of the concomitant drugs association with Torsades de point when researched in the DRugdex database (Tremarit could not be found). Because of the absence of an obvious underlying risk factor and some normalization of the QT with resolution of the arrhythmia this case is suspicious for causality. The latter discontinuation of Tremarit slightly confounds the conclusions of causality.

- AERS report # 381231 (Great Britain): This is a case report of a 60 year old female with little in detail. All that is noted is that the patient developed Torsades de Point 2 month after ropinirole was started. The report notes under concomitants "no concomitants."

This search limited itself to simply looking for cases listed under Torsades de pointe. It is beyond the scope of this review to perform a more exhaustive search under other potential search items (loss of conscious, ventricular tachycardia, sudden death etc.) because of the lack of time.

In the cover letter of this submission the Sponsor notes that a "binding assay and functional; electrophysiology assay" in hERG analyses demonstrate that "ropininrole was very weak" and "will not prolog QT interval." Examination of this supporting information revealed that the IC50 in a binding assay and a "plate based electrophysiology assay" was 10.5 uM and 44.7 uM, respectively. According to the Sponsor, latter electrophysiology assay is not the conventional CHO-K1 assay but it correlates with it but may underestimate the potency of the drug. Examination of a positive control (E-4031) revealed that there was an underestimation of the IC50 compared to more conventional electrophysiology published studies; i.e. there was a 20 fold underestimation of potency. Indeed a more traditional published study that compared several anti-Parkinsons agents in the conventional CHO-K1 preparation[13] revealed an IC50 of 1.2 uM. This same study demonstrated a prolongation of the canine Purkinje action potential. By 41 to 106 msec at concentration s of 2.5 to 25 uM. I asked Dr. Yasuda (PK reviewer) to examine expected serum concentration of ropinirole in typical treatment regimens. She was able to provide me with an upper range of serum concentration, based upon population PK studies for the highest concentrations expected with the highest dosage in the treatment of Parkinson's disease. Thus the dosage of 8 mg TID may lead to a range of serum concentrations of 0.1 to 0.3 uM. This may not be considered too different from concentrations observed in hERG studies and certainly the presence of a 1A2 inhibitor may potentially lead to higher concentrations (i.e. in doses no higher then 4 mg).

8.2.2 Reviewer's Comments

In summary there appears to be a small signal based upon the EKG study provided by the Sponsor. This study, however, is inadequate. The Sponsor is presently performing a more definitive study. There is also a small signal in AERs as well as some indication from

13 Hurst et. al . European J. Phramacol, 31-37, 482, 2003.

electrophysiological studies that QT prolongation may be an issue. The ropinirole doses used to treat RLS are lower and therefore not expected to be as problematic as that of Parkinson's disease but therapeutic index should require that this issue be resolved before approval is allowed. Moreover, it is this reviewers understanding that the present EKG study is being performed at doses used in RLS. This reviewer feels that a second study should be initiated that examines higher doses in patients to better correlate to doses used in Parkinson's disease. It may also be helpful to ask ODS to perform a more through examination of the AERS data base for Torsades de pointe and associated presentations, particularly if the formal EKG studies are positive. A survey of other dopamine agonists may be helpful contingent on positive findings.

8.3 Blood Pressure Reanalysis

Ropinirole is vaso-active and may lead to orthostatic blood pressure changes. It has been suggested that this normal population may be at a greater risk in developing orthostatic changes then those with Parkinson's disease. Studies (191 and 194), which used a titration to optimal effect design, failed to reveal an orthostatic signal. Interpretation of these studies, however, may be obfuscated by the fact that titration was truncated as a result adjustment of doses because of competing adverse events. Blood pressure was monitored in two forced titration studies (207 and 208) in a non-Parkinson's patient population. This division has expressed the opinion that this design better represents the true potential of this drug to produce orthostatic changes in the in new intended therapeutic population. Previous analysis in these forced titration studies (pooled studies 207 and 208, see Appendix F for a description of experimental design of these studies) were reported but only at a given time point (2 hours post-dose). The results are presented in the table below in the form of number (and percent) of patients who experienced a "clinically significant post-dose orthostatic drop and systolic pressure" at the 2 hours measurement. Blood pressure measurements were actually obtained at 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours post dose. While 2 hours is approximately the mean Tmax, it was felt that the present analysis does not consider individual variability and the dose response do not adequately represent the true dose response for maximal potential orthostatic changes. In his review Dr. Feeney (Team Leader) recommended that the Sponsor be "asked to recreate the above table using the greatest post-dose change for each patient, regardless of timepoint, and including patients coded with an AE "orthostatic hypotension" even if no BP recordings were made."

Clinically Significant Orthostatic Decrease in Systolic BP During Dose Escalation		
Dose	Requip Number of Patients/Total (%)	Placebo Number of Patients/Total (%)
0.25	2/55 (4)	1/27 (4)
0.5	0/53 (0)	2/25 (8)
1.0	3/52 (6)	1/24 (4)
1.5	3/49 (6)	0/24 (0)
2.0	5/42 (12)	0/24 (0)
2.5	3/38 (8)	0/22 (0)
3.0	1/31 (3)	1/21 (5)
4.0	2/27 (7)	0/21 (0)

This was expressed in the approvable letter as follows:

> "In the forced titration studies, blood pressure data was collected at numerous timepoints post-dose, but you presented only the data collected at 2 hours post-dose. Therefore, we ask that you recreate the appropriate tables from your submission, using the greatest post-dose change for each patient, regardless of timepoint. You should include patients coded with an adverse event "orthostatic hypotension" in these tables at the appropriate dose, even if no BP recordings were made."

In response to this request the Sponsor provided this division with a number of tables that describe maximum decreases and increases in blood pressure similar to the one presented below that presents the maximum decreases from pre-dose in orthostatic (erect minus semi-supine) SBP, DBP and HR for each patient (all data irrespective of dosing day or time point). The means in such tables are meaningless in that they include only the sub-sample of patients who experienced the particular sign of change (increase or decrease). In the case of the table presented below, only patients who experienced decreases are analyzed.

Dose Level (mg)	Parameter	Ropinirole Group N	SBP (mmHg)	DBP (mmHg)	Heart rate (bpm)	AEs of hypo-tension[a]	Placebo Group N	SBP (mmHg)	DBP (mmHg)	Heart rate (bpm)
0.25	Mean (SD) Maximum	45-53	-13.8[b] (8.3) -31	-9.6 (6.4) -27	-8.4 (4.9) -26	03590[c] (6.1 h)	22-25	-13.7 (8.7) -37	-8.8 (5.3) -21	-7.7 (5.0) -20
0.5	Mean (SD) Maximum	47-53	-12.6 (7.1) -28	-6.9 (3.5) -14	-8.9 (6.7) -33	**00009[d] (1.7 h)**	22-25	-15.9 (9.8) -36	-10.2 (10.9) -48	-9.2 (5.3) -25
1.0	Mean (SD) Maximum	47-50	-16.0 (10.8) -56	-9.4 (5.7) -30	-9.1 (6.8) -32	03590 (0.6 h) 03635 (1.0 h)	21-24	-14.0 (8.4) -35	-10.3 (5.5) -25	-10.7 (9.3) -47
1.5	Mean (SD) Maximum	41-49	-15.5 (10.0) -53	-9.5 (7.7) -51	-8.6 (7.1) -38	03650[c] (1 h) 00008 (1 h) **00002[d] (1.2 h)**	21-23	-14.2 (7.4) -31	-10.7 (5.8) -25	-6.6 (4.5) -17
2.0	Mean (SD) Maximum	39-41	-18.1 (12.6) -61	-12.2 (7.8) -42	-8.4 (6.6) -33	03678 (0.5 h) 03696 (0.6 h) 03611 (1.5 h) 00009 (3.1 h)	21	-11.7 (5.8) -21	-9.4 (4.0) -16	-7.6 (4.4) -15
2.5	Mean (SD) Maximum	32-37	-16.1 (11.9) -55	-11.4 (8.5) -47	-7.6 (7.2) -39	03634 (1 h) 00012 (0.6 h)	19-21	-13.6 (8.7) -32	-8.3 (4.6) -18	-8.6 (6.4) -26
3.0	Mean (SD) Maximum	27-30	-16.3 (7.5) -34	-10.2 (5.4) -19	-8.1 (4.2) -20	03760 (1.5 h) **03611[d] (3 h)**	18-21	-13.4 (7.7) -31	-6.9 (4.6) -18	-8.5 (9.5) -41
4.0	Mean (SD) Maximum	21-27	-17.5 (7.4) -32	-12.6 (8.0) -41	-11.5 (8.4) -40	00010 (0.6 h) 03673 (1 h) **03550[d] (0.7 h)**	19-21	-14.4 (5.5) -31	-10.6 (4.9) -19	-10.5 (8.2) -37
All	*Mean (SD)* *Maximum*	*55*	*-28.8 (11.3)* *-61*	*-18.4 (9.8)* *-51*	*-16.6 (8.7)* *-40*		*26-27*	*-24.0 (7.6)* *-37*	*-17.5 (8.2)* *-48*	*-16.9 (10.5)* *-47*

Data source: CPStats Table 7, CPStats Table 8 and CPStats Table 9
SBP = systolic blood pressure; DBP = diastolic blood pressure
[a] = Patient ID (time of onset post-dose) for AEs of hypotension, postural hypotension or syncope
[b] = negative values indicate a decrease from pre-dose to post-dose
[c] = Patient had an AE of hypotension, but had a greater post-dose decrease in BP on a separate occasion
[d] = bold = Patient had an AE of postural hypotension or syncope, but missing BP recordings at the time of the event

What is really required is an outlier analysis. Such an analysis was requested in telecom with the Sponsor on 2/16/05 and was received through an e-mail on 2/17/05. The tables below presents this analysis of grouped data from forced titration study 207 and 218 using two different outlier endpoints; i.e. systolic or /diastolic pressures of $\geq$ 20 or /10 (first table) and systolic or/diastolic pressures of $\geq$ 40 or /20 (second table). Note information for number of patients and the number of measured episodes are presented in these tables. To be included as an outlier a patient need to fulfill only the criteria for diastolic or systolic alone. It should also be noted that not all patients reached higher dose levels. Moreover, the study could not be considered a true forced titration as some patients had dose reduced or were withdrawn because of an AE. In some cases this was the result of orthostasis (see below). Moreover, not all patients, included in the post-dose measures are included in the pre-dose measure. The Sponsor felt that such measures were not true pre-baseline controls as the blood pressure measures used a somewhat different paradigm in that these patients where also participating in a PK analysis; i.e. patients had simultaneous blood pressure and blood draw for PK assessments.

Summary of Orthostatic DECREASES in EITHER Systolic Blood Pressure = 20mmHg OR Diastolic Blood Pressure = 10mmHg (7-Week Forced Titration Clinical Pharmacology Combined for Study 207 and 218)

	Ropinirole		Placebo	
Dose[1] (mg)	**Number of episodes/number of measurements (%)[3]**	**Number of patients/total number of patients (%)[4]**	**Number of episodes/number of measurements (%)[3]**	**Number of patients/total number of patients (%)**

Pre-dose[2]	2[9]/56 (4)	2[9]/55 (4)	0/27 (0)	0/27 (0)
0.25[8]	19/343 (6)	13/49 (27)	12/153 (8)	7/22 (32)
0.5	13/392 (3)	8/53 (15)	15/173 (9)	9/25 (36)
1.0	13/410 (3)	10/52 (19)	9/165 (5)	7/24 (29)
1.5	21/367 (6)	13/49 (27)	10/165 (6)	7/24 (29)
2.0	23/362 (6)	13/42 (31)	3/165 (2)	3/24 (13)
2.5	20/335 (6)	12/38 (32)	6/149 (4)	4/22 (18)
3.0	11/239 (5)	8/31 (26)	10/144 (7)	4/21 (19)
4.0	28/343 (8)	12/27 (44)	19/261 (7)	8/21 (38)
Total[5]	148/2791 (5)[6]	39/55 (71)[7]	84/1375 (6)[6]	16/26 (62)[7]

1. Only post-dose measures are considered for each dose.
2. Pre-dose is the value taken pre-dose on Day 1 and is not included in the totals.
3. Each episode is counted only once for each measurement, even if both the SBP and DBP at that measurement meet criteria.
4. Each patient with either SBP or DBP that meet criteria is counted only once at each dose, even if both SBP and DBP meet criteria.
5. Total at any dose
6. Total number of episodes/total number of measurements
7. Total number of patients with a value at any timepoint and dose/total number of patients – this is not additive, one subject can only count once.
8. Blood pressure and heart rate assessments on pharmacokinetic visits have not been included in this summary. For study 218 at the 0.25 mg dose, 11 subjects (6 on ropinirole and 5 on placebo) had blood pressure and heart rate measurements taken in conjunction with PK sampling and did not have stand-alone blood pressure measurements. Therefore, to be consistent with the remaining doses, these subjects have been excluded from the summaries at this dose.
9. For study 207, subject 03630 had an episode at pre-dose and at 0.5mg (2 episodes), 2mg (2 episodes), 2.5mg (1 episode), 3mg (1 episode) and 4mg (1 episode). Subject 03736 had an episode at pre-dose and at 0.25mg (2 episodes), the subject was then withdrawn prior to receiving any higher doses as this subject was considered by the investigator to be "not co-operative". Please note subjects 03630 and 03736 had no episodes meeting the criteria in Table 3+8.

Summary of Orthostatic DECREASES in EITHER Systolic Blood Pressure = 40mmHg OR Diastolic Blood Pressure = 20mmHg (7-Week Forced Titration Clinical Pharmacology Combined for Study 207 and 218)

	Ropinirole		**Placebo**	
Dose[1] (mg)	**Number of episodes/number of measurements (%)[3]**	**Number of patients/total number of patients (%)[4]**	**Number of episodes/number of measurements (%)[3]**	**Number of patients/total number of patients (%)**
Pre-dose[2]	0/56 (0)	0/55 (0)	0/27 (0)	0/27 (0)
0.25[8]	1/343 (0)	1/49 (2)	1/153 (1)	1/22 (5)

0.5	0/392 (0)	0/53 (0)	0/173 (0)	0/25 (0)
1.0	4/410 (1)	2/52 (4)	0/165 (0)	0/24 (0)
1.5	2/367 (1)	1/49 (2)	0/165 (0)	0/24 (0)
2.0	5/362 (1)	3/42 (7)	0/165 (0)	0/24 (0)
2.5	2/335 (1)	2/38 (5)	0/149 (0)	0/22 (0)
3.0	0/239 (0)	0/31 (0)	1/144 (1)	1/21 (5)
4.0	5/343 (1)	2/27 (7)	1/261 (0)	1/21 (5)
Total[5]	19/2791 (1)[6]	11/55 (20)[7]	3/1375 (0)[6]	3/26 (12)[7]

1. Only post-dose measures are considered for each dose.
2. Pre-dose is the value taken pre-dose on Day 1 and is not included in the totals.
3. Each episode is counted only once for each measurement, even if both the SBP and DBP at that measurement meet criteria.
4. Each patient with either SBP or DBP that meet criteria is counted only once at each dose, even if both SBP and DBP meet criteria.
5. Total at any dose
6. Total number of episodes/total number of measurements
7. Total number of patients with a value at any timepoint and dose/total number of patients – this is not additive, one subject can only count once.
8. Blood pressure and heart rate assessments on pharmacokinetic visits have not been included in this summary. For study 218 at the 0.25 mg dose, 11 subjects (6 on ropinirole and 5 on placebo) had blood pressure and heart rate measurements taken in conjunction with PK sampling and did not have stand-alone blood pressure measurements. Therefore, to be consistent with the remaining doses, these subjects have been excluded from the summaries at this dose.

The tables shows little trend if one considers number of episodes for either criteria of orthostasis. If one considers individual patient experiences with orthostasis, the changes observed in the 20/10 criteria is rather complex with greater placebo patients meeting criteria at a "lower placebo dose" but with fewer at a "higher placebo dose." The meaning of this is difficult to interpret. This analysis is likely complicated by the fact that patients were withdrawn from the study or had their titration rate decreases as a result of AEs that included those related to the lowering of blood presume: i.e. this is not a true forced titration. More telling is the observation that a greater number of pateints in drug group tehn in the placebo group experienced blood pressure orthostatic changes in the higher range (20/40). Twelve percent of patients meet criteria in the placebo and 20% in the drug group. Theses analysis may be complicated by the fact that PK evaluations times where included in the some of the data collection times. The process of repetitive blood draws may contribute to vaso-instability and obscure differences between placebo and control. Significant alterations appeared to occur throughout the titration. This reviwer would speculate that this results from a combination of factors including differential sensitivity for different patients and tachyphalaxis to the blood pressure.

Included in the submission, and as requested in the approvable letter, is an accounting of AEs associated with hypotension, postural hypotension, orthostatic hypotension or syncope. These are presented in the table below. Eighteen such events occurred in 15 patients out of 55 studied in the drug treatment group. No such events occurred in the 27 placebo patients studied. Most of these events were labeled as orthostatic or postural hypotension. Events range in duration

from 2 minutes to 5 days with greater then 90% of events lasting less then 2 hours. Events were labeled as severe, moderate and mild in 5, 7 and 3 patients, respectively. Events lead to withdrawal from the study in 3 patients and reduction in dose in 7 patients. The majority of events occurred at doses 1.5 mg and greater although such events were observed at doses as low as 0.25 mg. In 4 instances complete orthostatic blood pressure changes were not documented. This occurred in 3 patients reported with "postural hypotension" (00009, 03550 and03611) and 1 patient with "vasovagal syncope" (00002). In the latter case no blood pressure measure was obtained. In the remaining 3 only semi-supine reading were obtained and in two of these this pressure was noted to be reduced. It is unclear if one was obtained in the third but this patient had a previous significant documented episode of orthostatic hypotension.

Patient ID	AE verbatim (severity)	Dose of ropinirole (mg)	Onset time post-dose	Decrease in SBP/DBP[a] (time post-dose)	Duration of AE	Withdrawal due to AE
00002	Vasovagal syncope (severe)[e]	1.5 mg (2nd dose)	1 h 10 min	No BP recordings at time of event	2 min	Yes
00008	Hypotension (severe)[c]	1.5 mg	1 h 2 min	O = -42/-51 mmHg (1 h)	43 min	No (DR)[b]
00009	Orthostatic hypotension (moderate)[c, e]	0.5 mg (PK day)	1 h 40 min	SS = -33/-25 mmHg (90 min) – no erect data	6 min	No
	Orthostatic hypotension (mild)[c]	2.0 mg (PK day)	3 h 7 min	E = -28/-34 mmHg (3 h)	9 min	No
00010	Hypotension (moderate)[c]	4.0 mg	33 min	E = -11/-24 mmHg O = -20/-41 mmHg (30 min)	23 min	No
00012	Orthostatic hypotension (moderate)[c]	2.5 mg	33 min	E = -58/-49 mmHg O = -55/-47 mmHg (30 min)	1 h 2 min	No
03550	Orthostatic hypotension (severe)[e]	4.0 mg	39 min	SS = -1/-11 mmHg (90 min) – no erect data	1 h 34 min	No
03590	Decline in DBP (mild)[d]	0.25 mg	6 h 4 min	E = +18/-14 mmHg O = 0/-27 (3 h)	I day 16 h	No
	Decline in DBP (moderate)[c]	1.0 mg	33 min	O = -39/-1 mmHg (30 min)	33 min	No (DR)
03611	Postural hypotension (mild)[c]	2.0 mg	1 h 32 min	E = -44/-26 mmHg O = -48/-30 mmHg (1 h 30 min)	2 min	No (DR)
	Postural hypotension (severe)[e]	3.0 mg	3 h	No erect BP recordings at time of event	1 h	No (DR)
03634	Orthostatic hypotension (moderate)[c]	2.5 mg	1 h 2 min	E = -61/ -31mmHg O = -55/-26 mmHg (1 h)	29 min	No (DR)
03635	Orthostatic hypotension (severe)[c]	1.0 mg	1 h	E = -62/-37 mmHg O = -56/-30 mmHg (1 h)	4 h 25 min	Yes
03650	Hypotension (moderate)[d]	1.5 mg	1 h	E = -19/+3 mmHg O = -11/+12 mmHg (1 h)	14 h	Yes
03673	Orthostatic hypotension (mild)[c]	4.0 mg	1 h	E = -23/-26 mmHg O = -32/-22 mmHg (3 h)	5 days 22 min	No (DR)
03678	Hypotension (moderate)[c]	2.0 mg	30 min	E = -48/-27 mmHg O = -42/-24 mmHg (1 h)	35 min	No (DR)
03696	Orthostatic hypotension (mild)[c]	2.0 mg	33 min	E = -69/-41 mmHg O = -61/-42 mmHg (30 min)	1 h 27 min	No (DR)
03760	Systolic BP fall (mild)[c]	3.0 mg	1 h 32 min	E = -35/-11 mmHg O = -27/-10 mmHg (2 h)	25 min	No

[a] E = erect SBP/DBP O = orthostatic SBP/DBP SS = semi-supine
[b] DR = dose reduction
[c] + bold = associated with a maximum recorded BP decrease for that patient
[d] = not the maximum BP decrease for this patient
[e] = missing BP readings

8.3.1 Reviewer's Comments

Analysis of outliers changes in orthostatic blood pressure in forced titration studies revealed a higher incidence of large orthostatic changes (40/20) in the drug as compared to the placebo group. This effect was not so obvious in smaller orthostatic changes (20/10). Alteration in blood pressure, predominately orthostatic in nature, was a commonly reported adverse event seen in these studies occurring in 27% of patients receiving drug and 0 % receiving placebo. Sixty seven percent of patients experiencing such adverse events required withdrawal from study or reduction in dose. This information should be reflected in the labeling.

9 FOREIGN REGULATORY HISTORY (REVIEW BY DR. ROUZER)

(b) (4) . On June 30 2004 the French agency issued an approval for the following indication:

(b) (4)

(b) (4)

EFFICACY RESULTS

(b) (4)

BENEFIT/RISK ASSESSMENT

(b) (4)

LONG-TERM EFFICACY AND SAFETY

(b) (4)

(b) (4)

Efficacy

(b) (4)

BENEFIT/RISK ASSESSMENT

(b) (4)

SwissMedic issued a decision on March 16, 2004. SwissMedic approved the product under the following restrictions:

(b) (4)

In Australia, ropinirole in RLS was approved on 22 September 2004 and was launched as REPREVE on 01 February 2005. (b) (4).

10 APPENDICES

Appendix A

Table from Mueller T, Fritze J. Fibrosis associated with dopamine agonist therapy in Parkinson's disease. *Clinical Neuropharmacology* 2003;26:109-111.

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TABLE 1. *Synopsis of the frequencies of fibrotic syndromes during treatment with the various dopamine agonists based on the International Drug Monitoring Uppsala database and a MEDLINE search using the given terms** Reported numbers of the International Drug Monitoring Uppsala database.† Results of the MEDLINE search.DEC, dihydroergocriptine.
From: Muller: Clin Neuropharmacol, Volume 26(3).May/June 2003.109-111

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Appendix B

Clinical case narrations for pulmonary "fibrosis" or "fibrotic" changes:

Clinical trial report B0270261A (patient ID 188.015.02139) was the case which initiated this query and included interstitial lung disease as an adverse event. This was that one which raised the issue and has been previously discussed.

Clinical trial report B0202190A, reports the occurrence of bilateral pleural effusion in a 69-year-old male patient who started ropinirole (7.5mg daily) for the treatment of Parkinson's disease nine months prior to the event. The patient had also received ropinirole in a previous trial which started 15 months prior to the event. Concomitant drugs being taken by the patient at the time of the event and started before ropinirole treatment was initiated included selegiline hydrochloride, amlodipine and ticlopidine. The patient's relevant medical history included obstructive lung disease, arterial hypertension (also concurrent) and heavy smoking (the patient was reported as having stopped smoking 15 years prior to the event). A chest x-ray taken during the same month the patient started amlodipine, ticlodipine and ropinirole treatment and approximately one month after initiating selegiline treatment revealed no abnormalities. A chest x-ray at the time of the event showed pleural effusion at the base of the right lung and evidence of fibrotic changes at both the basal and the apical field of the right lung. The left lung showed only "small abnormalities" that were also considered possibly fibrotic. A cardiological examination ruled out congestive heart failure. In addition diagnostic procedures did not reveal tuberculosis, tumours or bronchopulmonary infection. During his hopitalisation the patient was treated with selegiline hydrochloride, fosinopril, prednisolone, cortisone and omeprazole. Treatment with ropinirole was discontinued and the outcome of the events was recorded as resolved. The final chest x-ray recorded, approximately 10 months after ropinirole was discontinued, revealed chronic obstructive bronchitis of moderate severity, sequelae of fibrosis at the right lung base and sclerosis of the aorta. The reporting physician considered the pleural effusion to be possibly related to ropinirole treatment. This clinical case is in the current US labeling.

Spontaneous report B0319267A referred to a 69-year-old male patient with Parkinson's disease, who was receiving ropinirole for approximately 4.5 years prior to hospitalization due to bilateral pneumonia. Concomitant drugs being taken by the patient at the time of the event included carbidopa, levodopa (both started prior to ropinirole) and entacapone (started 7 months prior to the event). In addition to pneumonia, the patient was found to have bilateral pleural effusion, mediastinal and hilar lymphadenopathy, and features suggestive of basal fibrosis of an indeterminate cause. In the light of the adenopathy, the fibrosis was thought to be possibly of an infective type, but also conceivably of a malignant origin. It was noted that lymphangitis could also have given these appearances. The investigations (CT scan and pulmonary angiography) ruled out primary pulmonary malignancy and pulmonary embolism as a possible cause of these pulmonary findings. Since there was no evidence of prior exposure to asbestos, the reporting radiologist commented that the pulmonary changes could be either idiopathic, or due to a connective tissue disorder or drug related. An early report of this case mentioned that the patient had pre-existing asymptomatic pulmonary fibrosis at the time of the pneumonia, however it

was unclear as to whether this condition was present prior to the patient starting treatment with ropinirole. The patient died 17 days after admission to hospital due to pneumonia.

In spontaneous report (B0287185A), pulmonary fibrosis was suspected but not confirmed. This case reports the occurrence of pleural effusion and pyrexia in a 58-year-old male patient who received ropinirole for the treatment of Parkinson's disease for approximately 18 months prior to the event. Concomitant medications being taken at the time of the event included atenolol, bezafibrate, lactulose and aspirin. This patient's medical history, which included myocardial infarction, smoking (previously smoked for 21 years) and pleural effusion, provides a possible explanation for the occurrence of pleural effusion. A chest x-ray revealed a persistent loculated left basal effusion with a left lower zone band opacity consistent with atelectasis or fibrosis (right lung field was clear). Although examination of the pleural fluid did not show the presence of acid fast bacteria, the patient was started on anti-tuberculosis treatment. The reporter considered the events to be possibly related to treatment with ropinirole or to tuberculosis or to other pulmonary disease. The events were unresolved at the time of the report.

Appendix C Pulmonary cases where there is no mention of fibrosis

Pulmonary cases which do not mention fibrosis

Case ID Case type (Subject ID)	Age (Yrs) Gender	Medical History/ Concurrent medical condition	Concurrent Drugs	Adverse events (MedDRA PTs)	Time to onset (approx.) to highlighted AE	Ropinirole dose (at time of event)	Event outcome	Comments
B0178308A Clinical trial (043.077.01415)	69 Male	None specified.	Levodopa and Benserazide hydrochloride, Selegiline hydrochloride	Atrial fibrillation, **Pleurisy**	11 months	Patient finished trial 5 months before pleuritis event..	Unknown	Initial report was of atrial fibrillation during clinical trial. Five months after the patient had finished the trial, and after the patient had started treatment with bromocriptine, pleuritis was diagnosed. The reporter specified that the event was highly likely to be related to bromocriptine therapy.
B0286324A Clinical trial (43101)	66 Male	Concurrent: Diabetes mellitus, Hypercholesterolaemia, Lacunar infarction		Renal insufficiency, Condition aggravated, Hypokalaemia, Vomiting, Dehydration, Pulmonary oedema, Metabolic encephalopathy, Pyelonephritis, Coma, Aneurysm ruptured, Back pain	Unknown	Unknown	Resolved	Patient admitted to hospital due to ruptured abdominal aneurism. Subject underwent surgical repair and was ventilated following surgery. Patient's physical condition subsequently worsened with the development of **pleural liquid**, hypokalaemia and at a later date fever and coma. The patient was diagnosed as having renal failure and the investigator indicated that the events experienced by the subject following aneurism surgery were symptoms of the renal failure.

Continued

Pulmonary and Cardiac Reports Which Mention Events Possibly Related to Fibrosis But Not Fibrosis

Pulmonary cases which do not mention fibrosis

Case ID Case type (Subject ID)	Age (Yrs) Gender	Medical History/ Concurrent medical condition	Concurrent Drugs	Adverse events (MedDRA PTs)	Time to onset (approx.) to highlighted AE	Ropinirole dose (at time of event)	Event outcome	Comments
A0235319A Clinical trial (040.012.00063)	63 Male	Concurrent condition: Atherosclerosis occlusive, mild cerebral atrophy, rheumatic fever.	Thyroxine sodium, Selegiline hydrochloride, Atenolol, Amantadine, Carbidopa and Levodopa, Amitriptyline hydrochloride	Myocardial ischaemia, Dyspnoea, Chest discomfort, Angina unstable, Atelectasis, **Pleural effusion**, Fluid retention, Triple vessel bypass graft, Hoarseness, Dysarthria	34 months (unknown if ropinirole treatment interupted between trials)	7.5 mg daily	Resolved	Patient had been admitted to hospital with shortness of breath and chest pain. Angiography revealed total occlusion of 4 cardiac vessels. Patient underwent by-pass surgery. Atelectasis secondary to post-operative intubation. Reduced atelectasis with a small left pleural effusion noted on repeat x-ray. Investigator reported the left lower lobe atelectasis as not related to treatment with ropinirole.
B0168210A Clinical trial (044.009.00031)	61 Male	Medical history: Abnormal liver function.	Benzhexol hydrochloride, Carbidopa and Levodopa, Sertraline hydrochloride, Zolpidem tartrate	Cardiac failure congestive, Mitral valve incompetence, Cardiomegaly, Rales, Oedema peripheral, Dyspnoea exertional, Dyspnoea paroxysmal nocturnal, **Pleural effusion**, Orthopnoea, Dyskinesia, Tremor, Hallucination, Dysphonia	8 months	7.5 mg daily	Resolved	Patient initially admitted to hospital for hallucinations and dyskinesias. Patient subsequently admitted to hospital due to congestive heart failure. On examination the patient had bibasilar rales, no wheezes, bilateral pleural effusions and pedal oedema felt to be consistent with congestive heart failure. Patient treated with furosemide and follow-up chest films showed no signs of CHF. Ropinirole treatment was continued for another 3 weeks.

Continued

Pulmonary and Cardiac Reports Which Mention Events Possibly Related to Fibrosis But Not Fibrosis (Continued)

Pulmonary cases which do not mention fibrosis								
Case ID Case type (Subject ID)	**Age (Yrs) Gender**	**Medical History/ Concurrent medical condition**	**Concurrent Drugs**	**Adverse events (MedDRA PTs)**	**Time to onset (approx.) to highlighted AE**	**Ropinirole dose (at time of event)**	**Event outcome**	**Comments**
B0220321A Spontaneous report	68 Male	Medical history: Colon cancer, left heart failure, cardiac arrhythmia, post-operative venous thrombosis, phlebitis, varix stripping, depression, hypertension.	Levodopa, Benseraside hydrochloride, Enalapril, Lysine aspirin, Furosemide, Gaviscon, Nitroglycerine, Molsidomine, Digoxin, Nicardipine	**Pleurisy, Pleural effusion**, Dyspnoea, Asthenia	5 months	2.5 or 2.75 mg daily	Improved	Patients medical history included heart failure. Patient hospitalised due to dyspnea. Bilateral pleurisy and severe bilateral pleural effusion detected. A diagnosis of cancer metastasis or tuberculosis was ruled out. Relevant examination showed inflammatory haemorrhagic pleural effusion. Treatment with ropinirole was discontinued and an important improvement in pleural effusion occurred.
B0223727A Spontaneous report	83 Female	Medical history: Childhood tuberculosis, hemiparesia (regressive), pulmonary embolism, atrial fibrillation.	Carbidopa and Levodopa, Levodopa and Benserazide hydrochloride, Paroxetine hydrochloride, Furosemide, Digoxin, Enalapril	**Pleural effusion**, Dyspnoea, Oedema	3 months	6 mg daily	Resolved	Patient admitted to hospital with dyspnea. Pleural effusion discovered (mild importance left lung). A pleural puncture revealed inflammatory fluid with negative results for mycobacterium tuberculosis and for tumoral aetiology. Ropinirole and concurrent drugs were continued and the patient recovered without sequelae.

Continued

Pulmonary cases which do not mention fibrosis								
Case ID Case type (Subject ID)	**Age (Yrs) Gender**	**Medical History/ Concurrent medical condition**	**Concurrent Drugs**	**Adverse events (MedDRA PTs)**	**Time to onset (approx.) to highlighted AE**	**Ropinirole dose (at time of event)**	**Event outcome**	**Comments**
B0296241A Spontaneous report	71 Male	Concurrent: Diabetes mellitus	Levodopa and Benserazide hydrochloride	**Pleural effusion**	26 months	18 mg daily	Improved	Patient admitted to hospital with pleural effusion. No malignancy was detected and infection was ruled out. Patient treated with diuretics and oxygen. The event improved and the patient was discharged from hospital. Treatment with ropinirole was discontinued approximately 5 weeks later.
D0033110A Spontaneous report	76 Male	Medical history/concurrent: Excicossis, urosepsis, peptic oesophagitis, postpyloric ulcer, status after multiple falls (contusions, haematoma), dehydration	Biperiden, Tolcapone, Levodopa, Carbidopa, Beta-acetyldigoxin	Rhabdomyolysis, Renal failure acute	Unknown	1.5 mg daily	Rhabdo myelosis and renal failure recorded as resolved.	Patient had underlying heart insufficiency. Patient hospitalised due to increased CK values. Patient developed rhabdomyolysis and acute renal failure. Ropinirole and concurrent Parkinson's remedies were discontinued. A **pleural effusion** was detected several days later. The reporter considered it was caused by an underlying heart insufficiency and not ropinirole treatment.

Continued

Pulmonary and Cardiac Reports Which Mention Events Possibly Related to Fibrosis But Not Fibrosis (Continued)

Pulmonary cases which do not mention fibrosis								
Case ID Case type (Subject ID)	Age (Yrs) Gender	Medical History/ Concurrent medical condition	Concurrent Drugs	Adverse events (MedDRA PTs)	Time to onset (approx.) to highlighted AE	Ropinirole dose (at time of event)	Event outcome	Comments
D0033893A Spontaneous report	67 Female	Hemicolectomy for colon cancer, latent hyperthyreosis.	Carbidopa, Levodopa, Budipine, Methixene hydrochloride, Bromazepam	Electrocardiogram QT prolonged, Torsade de pointes	1 month	0.5 mg daily	Bronchop neumonia improved promply with treatment. Outcome of cardiac events unknown	Patient admitted to hospital due to repeated falls. Ventricular extra systoles, QT prolongation and torsades de points were detected by ECG. Patient developed fever one day after hospitalisation. Bronchopneumonia was diagnosed and a small **pleural effusion** was found. Staphylococcus hominus also detected.

Continued

Pulmonary and Cardiac Reports Which Mention Events Possibly Related to Fibrosis But Not Fibrosis (Continued)

Cardiac cases which do not mention fibrosis								
Case ID Case type (Subject ID)	Age (Yrs) Gender	Medical History/ Concurrent medical condition	Concurrent Drugs	Adverse events (MedDRA PTs)	Time to onset (approx.) to highlighted AE	Ropinirole dose (at time of event)	Event outcome	Comments
A0290261A Clinical trial (135.003.0E302)	73 Female	Concurrent: Mitral valve prolapse, Ventricular arrhythmia	Domperidone, Nexiletine, Alprazolam, Oxazepam	Chest pain	5 months	12 mg daily	Resolved	Patient admitted to emergency room with chest pain. Investigator indicated the chest pain could be associated with **mitral valve disease** or oesophagitis. Mitral valve disease was not recorded as an event and the investigator reported that the chest pain was not related to treatment with ropinirole.

Continued

Pulmonary and Cardiac Reports Which Mention Events Possibly Related to Fibrosis But Not Fibrosis (Continued)

Cardiac cases which do not mention fibrosis								
Case ID Case type (Subject ID)	Age (Yrs) Gender	Medical History/ Concurrent medical condition	Concurrent Drugs	Adverse events (MedDRA PTs)	Time to onset (approx.) to highlighted AE	Ropinirole dose (at time of event)	Event outcome	Comments
A0290261A Clinical trial (135.003.0E302)	73 Female	Concurrent: Mitral valve prolapse, Ventricular arrhythmia	Domperidone, Nexiletine, Alprazolam, Oxazepam	Chest pain	5 months	12 mg daily	Resolved	Patient admitted to emergency room with chest pain. Investigator indicated the chest pain could be associated with **mitral valve disease** or oesophagitis. Mitral valve disease was not recorded as an event and the investigator reported that the chest pain was not related to treatment with ropinirole.

Continued

Pulmonary and Cardiac Reports Which Mention Events Possibly Related to Fibrosis But Not Fibrosis (Continued)

Cardiac cases which do not mention fibrosis								
Case ID Case type (Subject ID)	**Age (Yrs) Gender**	**Medical History/ Concurrent medical condition**	**Concurrent Drugs**	**Adverse events (MedDRA PTs)**	**Time to onset (approx.) to highlighted AE**	**Ropinirole dose (at time of event)**	**Event outcome**	**Comments**
Clinical trial (040.005.00040)	51 Male	Medical history: Mediastinal seminoma removed and treated with radiation	Unknown at time of event but previously recorded to have received Pergolide prior to initiating ropinirole trials and Amantadine, Selegiline hydrochloride, Carbidopa, Levodopa, Profenamne hydrochloride, diphenhydramine hydrochloride and Quinine as concurrent drugs during the trial	**Pericardial effusion**	35 months from initiation of ropinirole but with interruptions to treatment	Unknown	Unknown	Pericardial effusion (mild) recorded as a non-serious event in a patient with a medical history of mediastinal seminoma, who had previously been recorded as having a congenital cardiac septal defect and subpleural lesions indicated to be unrelated to ropinirole.

Continued

93

Pulmonary and Cardiac Reports Which Mention Events Possibly Related to Fibrosis But Not Fibrosis (Continued)

Cardiac cases which do not mention fibrosis								
Case ID Case type (Subject ID)	**Age (Yrs) Gender**	**Medical History/ Concurrent medical condition**	**Concurrent Drugs**	**Adverse events (MedDRA PTs)**	**Time to onset (approx.) to highlighted AE**	**Ropinirole dose (at time of event)**	**Event outcome**	**Comments**
A0329072A Spontaneous report	76 Female	Medical history: Drug hypersensitivity. Concurrent: Sleep problems.	Carbidopa and Levodopa, Imipramine	Myocardial infarction, Cardiogenic shock, Cardiomegaly, Syncope, Asthenia, Dizziness, Sinus tachycardia, Mediastinal disorder, Atelectasis, **Pericardial effusion**, Ventricular dysfunction, Aortic calcification, Hypotension, Dyspnoea, Hyperhidrosis, Cyanosis	1year after ropinirole started and 1W after discontinuation.	Unknown	Fatal	Pericardial effusion reported as a symptom of myocardial infarction. Patient died following onset of cardiogenic shock.

Continued

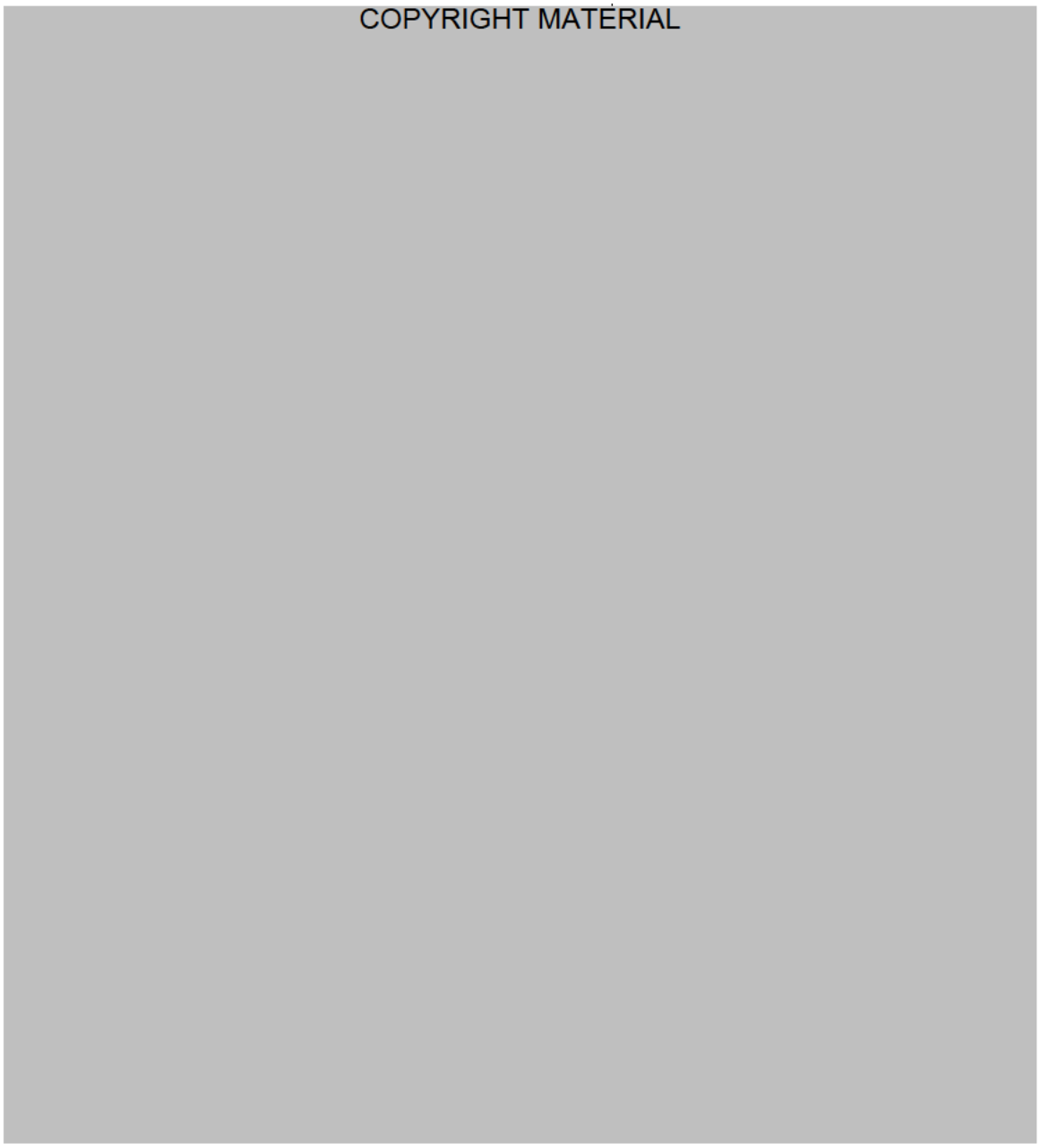
Appendix D Cardiac cases where fibrosis and Sclerosis are specifically noted.

Clinical trial report B0174202A, describes the occurrence of a fatal myocardial infarction in a 79-year-old male patient who had received ropinirole for the treatment of Parkinson's disease for approximately two months prior to the event. Concomitant medications included isosorbide dinitrate, benzhexol hydrochloride, frusemide and nitroglycerine. The patient's medical history included sick sinus syndrome and an operation to fit a cardiac pacemaker. Echocardiographic and Doppler examination of the patient had noted fibrosis of the mitral valve ring, in addition to dilation of the left ventricle, global hypokinesia, reduced ejection fraction, mitral, aortic and tricuspid insufficiency and limited diameter of the ascending aorta, one day prior to the myocardial infarction. Due to the patient's previous cardiac history, the investigator's causality assessment for the fatal myocardial infarction was 'unrelated to ropinirole'. The patient had also been treated with bromocriptine for approximately 36 months prior to starting ropinirole.

Clinical trial report B0240355A reports the occurrence of cardiopulmonary failure in a 66-year-old female patient who had received ropinirole (12mg daily) for approximately 20 months prior to the event. Concomitant medications at the time of the event included aspirin, ramipril, metoprolol succinate, molsidomine and danthron + docusate sodium. The patient was hospitalized following a six month history of increasing exert ional dypnea with thoracic pressure radiating into the left arm. The patient also developed bilateral leg edema and cardio-pulmonary de-compensation. Relevant investigations, including blood lipids, electrocardiogram, echocardiography, angiography, magnetic resonance imaging and an x-ray led to a diagnosis of coronary one vessel disease with occlusion of the left anterior descending artery and the patient was referred for by-pass surgery. Of relevance to this report, the echocardiography examination revealed sclerosis of the aortic valve. However, since the patient had a history of coronary heart disease and had had a previous myocardial infarction prior to initiating ropinirole treatment, the investigator reported the worsening coronary heart disease as not related to ropinirole treatment. Treatment with ropinirole was continued and the patient subsequently underwent coronary artery by-pass surgery.

Appendix E

TABLE 14. Composition of radioactivity in urine samples following single oral and single intravenous administration of ^{14}C-SK&F 101468-A



Appendix F: Description of blood pressure measurement design for forced titration studies 207 and 208.

A forced titration was performed from 0.25 to 4 mg qD over 7 weeks in RLS patients[14]. Orthostatic pressures and heart rate were evaluated by examining patients in semi-supine (for 10 minutes) followed by erect position (for 1 minute) at screening, baseline, the first day of each up titration, the last dose of the study and at follow-up. The pre-drug measure consisted of the average of three stable pre-drug evaluations. In one study (218) orthostatics were also taken on days that pharmacokinetic samples were obtained. The table below summarizes the timing of blood pressure evaluations as well as the number of patients examined in each study.

Study	Number of Patients		Assessment Visit	Timing of Measurements
	Ropinirole	Placebo		
207	37	17	Screening, Day 1, 3, 8, 15, 22, 29, 36, 43, 49 Follow-up or withdrawal	Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, and 6 h post-dose
218	18	10	Screening, Day 1, 3, 8, 15, 22, 29, 36, 43, 49 Follow-up or withdrawal plus pharmacokinetic days	Pre-dose 0.5, 1, 1.5, 2, and 3 h post-dose

14 Patients with a DBP > 110 mmHg or < 50 mmHg or a SBP > 180 mmHg or < 90 mmHg at baseline were excluded from study participation.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Hershkowitz
2/24/05 02:52:41 PM
MEDICAL OFFICER

John Feeney
2/25/05 12:25:35 PM
MEDICAL OFFICER
see my memo

MEMORANDUM

NDA 20-658/S-013 Requip (ropinirole)

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: Efficacy of Requip for the Treatment of Restless Legs Syndrome/Response to Approvable Letter

DATE: February 24, 2005

Requip is currently approved for the treatment of Parkinson's disease. On December 24, 2003, the sponsor was sent an Approvable Letter for the new indication Restless Legs Syndrome. In that letter, the sponsor was asked to submit evidence that Requip is effective in U.S. patients. Previous studies had demonstrated effectiveness, but not in the small subgroup of patients from North America. The letter also requested: 1) further analyses of blood pressure data, 2) further analyses of possible fibrotic complications with Requip, 3) ECG data timed to dosing with an adequate sample of patients at the highest targeted dose for RLS (4mg). Although draft labeling did not accompany the letter, comments were included about carton/container labeling and the sponsor's proposed indication-specific patient package insert (PPI).

The clinical review of this submission was performed by Dr. Norman Hershkowitz (with some contributions from Dr. Janeth Rouzer). The statistical review was performed by Dr. Kun He. Additionally, pharm/tox issues (specifically the need for further preclinical retinal studies) were discussed with Dr. Paul Roney and Dr. Lois Freed. Biopharm labeling was reviewed by Dr. Sally Yasuda. During the review period, Felicia Duffy from DMETS resolved carton/container labeling concerns with the sponsor, although she deferred the medical need for the proposed (b) (4) to DNDP. DMETS thought a (b) (4) . Jeanine Best, the Patient Product Information Specialist in DSRCS, reviewed the sponsor's PPI proposal.

In the Approvable Letter, the sponsor was asked to make a Phase 4 commitment to perform a retinal toxicity study in pigmented rats using morphometric techniques. [Ropinirole has already been associated with retinal toxicity in albino rats.] The sponsor, instead, has submitted the results of ophthalmological monitoring from a 2-year controlled trial in which patients with early Parkinson's disease were randomized to either L-dopa or Requip. Dr. Wiley Chambers has reviewed the ophthalmological results.

Efficacy

The sponsor has submitted the results of a large controlled trial performed exclusively in RLS patients in the U.S. Dr. Hershkowitz and Dr. He have reviewed that study. The results of that study, in conjunction with the results from previously reviewed multinational studies, provide substantial evidence of the effectiveness of Requip in RLS.

Analyses of Orthostatic Hypotension

Dr. Hershkowitz has reviewed the new analyses of orthostatic hypotension during the forced titration studies. These analyses better characterize the potential for orthostatic hypotension during treatment of RLS. The results of these analyses are reflected in draft labeling.

Fibrotic Complications

In the Approvable Letter, the sponsor was asked to address the one case of pulmonary fibrosis in the RLS clinical trials. The details of the case were presented and, I agree with Dr. Hershkowitz, the case is most likely attributable to nitrofurantoin use.

In addition to the case of fibrosis already described in labeling, 2 additional cases of pulmonary fibrosis, reasonably attributable to Requip, are discussed in Dr. Hershkowitz's review. These 2 additional cases are from postmarketing surveillance. An additional postmarketing case, a woman in her seventies, was received from the sponsor in November 2004 and is in the FDA AERS database. All these total 4 cases.

No cases specifically labeled retroperitoneal fibrosis, pericardial fibrosis, or valvular fibrosis have been described in postmarketing surveillance. But there is a case of cardiac valvulopathy associated with Requip in the AERS database. A woman in her seventies had a normal cardiac echo shortly before starting Requip. Two years later she had aortic, mitral, and tricuspid valvulopathy. Her only medications were Requip and carbamazepine.

There are other cases labeled pleural effusion, pulmonary infiltrates, pericardial effusion, pericarditis, and valvular heart disease. But, with the rare exception of several cases of pleural effusion, the rest of these cases are either poorly documented or documented in such a way to clarify a more reasonable explanation (other than Requip use).

Therefore, after exhaustive search, it appears that only very rarely has Requip been reasonably linked to fibrotic complications, pulmonary fibrosis in 4 cases and cardiac valvulopathy in 1 case. As Dr. Hershkowitz notes in his review, even these rare cases might only represent the background occurrence of these disorders in a predominantly elderly population.

ECG Data

The sponsor performed an ECG sub-study in the new U.S. controlled trial, collecting ECG data timed to dosing. Dr. Hershkowitz has reviewed that data and concluded that there is a signal for an increase in QT interval with ropinirole, especially at a dose of 4mg.

The study is far from optimal. The patients enrolled were a subset of a randomized sample. The pre-dose baseline ECGs were performed within a few days of stopping Requip, so that circulating metabolites might still have been present. And patients in the Requip arm were treated with a flexible-dose regimen. Using post-dose baseline ECGs, Dr. Hershkowitz found that the magnitude of the QT-prolongation signal was even greater, a mean change of 10-15msec with evidence of even greater effects in patients dosed at 4mg.

At the same time, a review of postmarketing data for Requip has revealed 3 cases of torsades over the 8 years of marketing. One of the cases of torsades is confounded, one case is poorly documented, and one case is well-documented and appears possibly due to Requip.

The sponsor is already conducting a formal QT study in normal volunteers, incorporating a placebo group and a positive control arm.

In considering the relevance of the increase in QT noted by Dr. Hershkowitz, I asked the DNDP safety group to obtain use data for Requip. Requip is approved in Parkinson's disease with a recommended dose up to 8mg tid. I was provided NDTI data (this data is not to be shared with anyone outside of the agency) for the years 1999-2004. My review of that data suggests that about 10% of the use of Requip has been at a dose of 4mg tid or greater. From labeling, I also note that the mean dose of Requip in 2 of the pivotal trials for Parkinson's disease was 4-5mg tid.

I then asked our biopharm team how the expected exposure data at that dose ($\geq$ 4mg tid) would compare to the exposure at 4mg once daily (the proposed maximum recommended dose for RLS). A single daily dose of Requip 4mg produces a mean Cmax of about 6-8ng/mL. At steady state, Requip 4mg tid is expected to produce a Cmax of about 16ng/mL.

My conclusion is that a significant part of the postmarketing experience with Requip over the past 8 years has been at systemic exposures similar to or greater than what will be expected in RLS patients. Even with concomitant CYP1A2 inhibitors, the exposures expected at a dose of 4mg once daily are no greater than what has been seen in postmarketing experience to date. Therefore, one could maintain that postmarketing experience with Requip has provided an adequate opportunity to clarify a risk of torsades, yet has produced only one well-documented case of torsades. Against this notion, however, is the expected substantial underreporting of cardiac arrhythmias in a generally frail elderly population (Parkinson's disease).

Given that a QT study, better designed to formally address QT prolongation with Requip, is already ongoing, it seems only reasonable to ask the sponsor to complete the ongoing formal QT study and submit the results as expeditiously as possible for our review.

Ophthalmological Data

Dr. Chambers has reviewed the data from a 2-year prospective controlled trial comparing patients with early Parkinson's disease started on L-dopa to similar patients started on ropinirole. According to Dr. Chambers, most patients completed the 1 and 2 year evaluations in the study and no clinically significant changes were noted. However, some additional records from that study are needed before Dr. Chambers can complete his review. Those records should be requested. After final review, if there are no findings in this study, the request for further preclinical retinal toxicity studies seems unnecessary.

Inspections

Inspections of 2 clinical sites in the U.S. study were performed. Overall, the data were deemed acceptable, although I have not seen the final report of the inspections.

(b) (4)

Labeling

I have the following specific comments about labeling.

1. Indication: The controlled trials included patients with moderate-severe primary RLS. The approved indication should reflect the population studied.

2. PRECAUTIONS: Augmentation and Rebound in RLS: (b) (4)

(b) (4)

3. ANIMAL TOXICOLOGY: (b) (4)

4. Indication-specific PPIs: The sponsor has proposed a 2-sided leaflet with each side devoted to a separate indication. The agency has advocated a single leaflet incorporating all indications. The primary reason for a single leaflet is to avoid the situation where a patient refers to the wrong indication by mistake. In keeping with this approach, the current sponsor should be asked to develop a single Patient Leaflet. At the same time, the agency has not opposed the development of indication-specific information leaflets to be distributed by health care practitioners to the appropriate patients. These would be developed based on the single leaflet attached to labeling.

Recommendations

The sponsor should be sent an Approvable Letter with draft labeling.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Feeney
2/24/05 01:09:58 PM
MEDICAL OFFICER

MEMORANDUM

DATE: February 24, 2005

FROM: Director
Division of Neuropharmacological Drug Product/HFD-120

TO: File, NDA 20-658/S-013

SUBJECT: Action Memo for NDA 20-658/S-013, for the use of Requip (Ropinerole HCl) Tablets as treatment for Restless Legs Syndrome (RLS)

NDA 20-658/S-013, for the use of Requip (Ropinerole HCl) Tablets as treatment for Restless Legs Syndrome (RLS), was submitted by GlaxoSmithKline on 7/3/03. The division issued an Approvable letter on 12/24/03, which included the following main questions to the sponsor:

1) Although the drug-placebo differences were statistically significant for the four randomized controlled trials submitted by the sponsor, the data raised serious questions about whether or not the drug was effective in patients in North America (US and Canada). Specifically, in Study 194, analysis of the sub-set of patients from the US and Canada showed numerical superiority in the placebo patients on the International RLS scale, the primary outcome. In Study 191, a study done in the US, which primarily examined the effects of Requip on symptoms of Periodic Leg Movements of Sleep (PLMS), examination of the IRLS scale and the CGI, both secondary measures, also failed to demonstrate a significant difference favoring ropinerole. For these reasons, we asked the sponsor to submit the results of a controlled trial in North American patients; such a trial was on-going at the time of the original action.
2) A case of apparent pleural fibrosis was noted in a patient with RLS. Because this is a serious event, one which might, if it were found to be drug related, have the potential to affect a decision about whether this symptomatic treatment for this condition should be approved, we asked the sponsor for more information about this case, as well as a discussion about ropinerole's capacity to cause fibrotic complications generally.
3) Because detailed information about ropinerole's capacity to prolong the QT interval was not available at the time of its approval for Parkinson's Disease, we asked the sponsor to provide valid information on this point at doses relevant for the RLS population (a population significantly younger than the PD population).
4) We asked the sponsor to further evaluate ropinerole's capacity to induce orthostatic hypotension in the RLS population.
5) Because of the similarity of ropinerole to pramipexole, a drug known to cause eye pathology in pigmented rats, we asked the sponsor to provide information

about ropinerole's capacity to produce a similar toxicity in pigmented rats in Phase 4.

6) We had several comments about the carton and container labeling.
7) We had several comments related to the Patient Package Insert (PPI).

The sponsor responded to the Approvable letter on 8/23/04. This submission contains the results of another randomized controlled study, Study 249, as well as analyses of the other issues raised in our letter. The submission has been reviewed by Dr. Norman Hershkowitz, medical officer, Dr. Janeth Rouzer, medical officer, Dr. Kun He, statistician, Dr. Wiley Chambers, supervisory medical officer, ophthalmology, Dr. Michael Brony, Division of Drug Marketing, Advertising, and Communications, Jeanine Best, Division of Surveillance, Research, and Communication Support, Felicia Duffy, Division of Medication Errors and Technical Support, and Dr. John Feeney, Neurology Drugs Team Leader. I will briefly review the pertinent findings, and offer the rationale for the Division's decision.

Effectiveness

Study 249

This was a multi-center, double-blind, parallel group trial in which patients were randomized to receive either ropinerole in a flexible dose regimen or placebo. The study had a one week screening phase, a 12 week treatment phase, and a one week follow-up phase. This study was performed in the US, and the primary outcome measure was the mean change from baseline in the RLS at 12 weeks, using a last observation carried forward (LOCF) population. In addition, we required that the sponsor evaluate a global measure (in this case, the CGI) as a co-primary measure, even though in the protocol this was considered one of several secondary outcomes.

The following table presents patient flow in this study:

	Drug	Placebo
Randomized	187	193
Completed	164 (88%)	167 (87%)
Reasons for D/C		
Adverse Event	7 (3.7%)	9 (4.7%)
Lost to F/U	6 (3.2%)	1 (0.5%)
Protocol Deviation	4 (2.1%)	9 (4.7%)
Other	4 (2.1%)	2 (1%)
Inadequate Response	2 (1.1%)	5 (2.6%)

The following table displays the results of the primary outcomes:

	Drug	Placebo	P-value
Mean Change from Baseline RLS	-13.6	-9.6	<0.0001
CGI (% Very Much or Much Improved)	73%	57%	0.0006

Safety

Fibrotic Events

As noted above, the sponsor provided additional information about the single case in an RLS patient about which the division had questions, as well as additional data addressing the general question of ropinerole's capacity to cause fibrotic complications.

With regard to the aforementioned patient, the sponsor noted that this was a 75 year old woman who was admitted to the hospital for a gastric hemorrhage three months after the initiation of ropinerole. Chest x-rays revealed longstanding interstitial lung disease, suggestive of interstitial fibrosis and traction bronchiectasis, and bilateral pleural effusions and enlarged lymph nodes. Ischemic hepatitis was diagnosed, along with possible pulmonary infection. Although the patient had a complicated medical course (see Dr. Hershkowitz's detailed description of the case), a critical fact is that the patient continued treatment with ropinerole, and that two years later the lung pathology had completely resolved.

As far as evaluating the general issue of ropinerole's capacity to produce fibrotic complications, the sponsor performed numerous analyses to address this concern. In particular, they evaluated all of the cases in their database, both those occurring in clinical trials as well as post-marketing reports. Dr. Hershkowitz has described in detail, and evaluated, the sponsor's analyses.

In brief, based on a detailed search of their databases (see Dr. Hershkowitz's description of the sponsor's search methodology), the sponsor identified 22 potential cases; in 6 of these cases, fibrosis was specifically mentioned (4 pulmonary, 2 cardiac) and in 16 (11 pulmonary, 5 cardiac), fibrosis was not noted, but "serous membrane complications" were noted (for example, pleural effusions). Of all of these cases, 10 cases occurred in clinical trials and 12 were reports of post-marketing events.

Dr. Hershkowitz has reviewed the descriptions of these cases in detail. In his view, of the four pulmonary cases in which fibrosis was mentioned, two were reasonably likely to have been true fibrotic events (one of the cases was the case about which we asked, and described above, and in one, the diagnosis of fibrosis was not clearly made). Of these two, one is mentioned in labeling (and occurred

in a clinical trial) and one was a spontaneous report. In Dr. Hershkowitz's view, these two cases are consistent with being drug related, but he believes additional information should be provided. In my view, the third case is also a potential case of fibrosis, despite the fact that the diagnosis of fibrosis was not clearly made. I believe (as does Dr. Hershkowitz) that additional data could help clarify the details of these cases. Even so, however, I do not believe that additional details of the individual cases are likely to shed light on the question of whether or not the cases are drug-related.

Of the pulmonary cases in which fibrosis was not mentioned, but in which potentially relevant signs and symptoms were presumably present (pleural effusion or pleuritis), Dr. Hershkowitz has found that in all but one, other factors were present that made attribution to ropinerole essentially impossible (e.g., other obvious confounders were present [CHF, treatment with ergots] or continued treatment with ropinerole was associated with resolution of the problem). In the one remaining case (in which the patient was reported to have had bilateral effusions and pleurisy), this patient was being treated for CHF, was admitted to the hospital for dyspnea, and examination revealed inflammatory hemorrhagic effusions and the effusions improved coincident with discontinuation of the ropinerole. As Dr. Hershkowitz notes, an inflammatory effusion is not typical of CHF, but a hemorrhagic effusion is probably not typical of fibrosis. As a result, he cannot rule out a contribution of ropinerole. He is correct, although it is clear that the patient had numerous medical problems that could be responsible for the effusions and symptoms.

With regard to the cardiac fibrosis cases, one was reported as "fibrosis of the mitral valve" and one was reported as "sclerosis of the aortic valve".

The patient with the mitral valve fibrosis was a 79 year old man with a history of bromocriptine use, and who had been treated with ropinerole for 2 months at the time of the diagnosis of the valvulopathy. The valvulopathy was associated with significant other cardiac pathology (see Dr. Hershkowitz's detailed description of this case). The second case was a 66 year old woman with dyspnea and aortic sclerosis diagnosed 20 months after the initiation of ropinerole treatment.

Of the remaining 5 non-fibrotic cardiac cases, 2 were reported as pericarditis, 2 as pericardial effusions, and one as mitral valve disease (this latter case was reported by the sponsor as "not confirmed"). One of the cases of effusion had a history of a mediastinal seminoma and previous exposure to pergolide. The other effusion case was in a woman with a myocardial infarction. One of the pericarditis cases appeared to have other possible causes, and the remaining case is unclear as to the event (it is described as pericardial detachment). In both of the pericarditis cases, additional information would be helpful to clarify the event and/or other potential confounders.

As further information, the sponsor has also searched the literature for reports or studies about fibrotic complications of dopamine agonists. As described by Dr. Hershkowitz, there are no studies of this question described in the literature, although there are numerous case reports and case series. According to Dr. Hershkowitz, there are a total of 33 patients with fibrotic events described for bromocriptine, 25 for pergolide, 1 each for dihydroergotamine and methysergide, and none for lisuride, pramipexole, or ropinerole. Dr. Hershkowitz also referenced a publication of the WHO Collaborative Centre for Drug Monitoring in which no reports of fibrotic complications were seen for non-ergot PD treatments (although ropinerole is not mentioned specifically).

Although the sponsor has not, Dr. Hershkowitz has provided estimates of the background rate of pulmonary fibrosis in the general population. These estimates vary from 0.74-102 cases/100,000 patient years of exposure, with the higher rates (12-102/100,000 patient years) seen in older patients (greater than 65 years of age). Although detailed age data are not available, the sponsor estimates that there is about 570,000 patient years of exposure to ropinerole, the vast majority of it in PD (i.e., older) patients. If we consider 2 of the pulmonary fibrosis cases as possibly drug related, this results in a reporting rate of about 0.35 cases/100,000 patient years of exposure, far below most of the estimates of the incidence of pulmonary fibrosis in the (older) population. Even with any reasonable estimate of underreporting, this is still likely to be well below the background rate.

EKG

As noted above, at the time of the approval of ropinerole for PD, detailed data on the effect of ropinerole on the QT interval was not available. As a result, we asked the sponsor to address this concern.

The sponsor performed an analysis of EKG in a subset of the patients enrolled in Study 249. Specifically, after 1-2 days off of treatment at the end of the study, patients received either a single dose of ropinerole or placebo (patients received the drug, and dose, they received in the controlled trial). Patients then had a 12 lead EKG measured at 1 and 2 hours after dosing. Further, patients had another EKG done at 4-10 days after the single dose. We and the sponsor agreed that performing an EKG after a single dose was appropriate, given that patients with RLS will take the drug (and took it in the trials) only once a day (at night), and, given the approximately 6 hour $T_{1/2}$, there is no appreciable accumulation with chronic dosing (that is, the Cmax after a single dose should be about the same as the Cmax after multiple single daily dosing). The median dose in these patients was 2.5 mg; about 27% of patients received the maximum recommended dose of 4 mg.

The relevant findings are described by Dr. Hershkowitz. In particular, there was about a 1.6 msec increase from baseline in QTcF on drug (N=39), compared to

placebo (N=45) at 1 hour post-dosing and about a 4.4 msec increase on drug (N=40) compared to placebo (N=45) at 2 hours post-dosing. There were 3 patients on drug who had an increase of between 30-60 msec at 2 hours compared to none on placebo. No patients had a QTcF increase of 60 msec or more at any time point.

However, as Dr. Hershkowitz notes, different results were seen when the 1 and 2 hour post-dosing intervals were compared to the EKG done 7-10 days after the dosing. As described by Dr. Hershkowitz, these differences in QTcF were about 9 msec at 1 hour post dose for drug compared to placebo (N=26 on drug, N=28 on placebo) and about 10 msec at 2 hour post dose for drug compared to placebo (N=26 on drug, N=28 on placebo). A total of 2 ropinerole patients had a QTcF increase of between 30-60 msec at 1 hour post dosing and 4 ropinerole patients had a QTcF increase of between 30-60 msec at 2 hour post dosing. No placebo patients had such an increase, and no patients had an increase of 60 msec or more.

Although it appears odd to compare the post-dosing EKGs to a "baseline" taken 7 days after the dosing, Dr. Hershkowitz points out that there are several metabolites that persist for several days after dosing is discontinued. As he notes, given that we do not know if these metabolites are active, their persistence may have had an effect on the EKGs performed only 1-2 days after dosing in Study 259 was stopped. For this reason, it is possible that a "baseline" EKG done at least one week after the EKG dosing was performed may have given a more reliable baseline (we would expect that by this time there would be no circulating metabolites).

No patient had an increase of 500 msec or more at any time point.

The sponsor did not present mean QT changes by dose. However, they did perform analyses in which they plotted the maximum post-dose change in QTcF (and B) compared to dose. As can be seen in Dr. Hershkowitz's review, the plot of the maximum increase in QTcF post dose compared to the 1 week post-dosing "baseline" by dose strongly suggests a dose response, particularly at the 4 mg dose (although the number of patients at 4 mg in this analysis [N=6] is quite small; the plot of the same metric but compared to the "baseline" performed before the dosing for the EKG phase also appears to demonstrate a dose trend, and here the number of patients at the 4 mg dose is 11).

Because of these findings, Dr. Hershkowitz searched the Agency's post-marketing reports for cases of torsades de pointes. He found three cases in ropinerole treated patients (one in Denmark, one in Germany, and one in Great Britain), and none for pergolide, pramipexole, or bromocriptine. He describes the three cases in detail.

Briefly, in one of the cases (from Denmark), a 69 year old woman, there were

multiple confounders. However, there were no obvious confounders in the German case, and there was very little information for the British case (for this case, the report only states that this 60 year old woman developed torsades 2 months after ropinerole was started, apparently with no concomitant medications).

Although the results of the analyses of QTc interval data are clearly not definitive, they do raise questions about ropinerole's capacity to prolong the QTc interval, especially at a dose of 4 mg. Further, these data raise questions about QTc prolongation at plasma levels potentially seen in patients receiving treatment with concomitant CYP 1A2 inhibitors, as well as at the higher doses used in patients with Parkinson's Disease.

Dr. Feeney has estimated that about 10% of the use of ropinerole has been at doses of 4 mg TID or greater (see his review for a discussion of this point). Doses of 4 mg TID are expected (based on pharmacokinetic modeling) to give rise to a Cmax of about 16 ng/ml, whereas a single daily dose of 4 mg is expected to give a Cmax of about 6-8 ng/ml. In the presence of a potent CYP 1A2 inhibitor, the Cmax is expected to increase about 60%. Of the approximately 570,000 patient years of world wide exposure, we do not know how much represents domestic compared to foreign exposure. Any estimate of the reporting rate for torsades de pointes must take into account not only the geographic distribution of the exposure, but also the relevant dose exposure, as described. In addition, although we have identified only 3 (or 2 unconfounded) cases of torsades, we have not (nor has the sponsor) undertaken a search for post-marketing reports of other events that might represent other relevant malignant ventricular arrhythmias.

In my view, the sponsor should better characterize the effect, if any, of ropinerole on the QTc interval prior to approval for RLS, a non-life threatening condition for which the drug has a modest symptomatic effect. Should it be determined that the drug, especially at the higher doses, has an important prolonging effect, this would require, at least, a description in labeling, and may affect the decision to approve it for this indication.

Hypotension

We noted in the Approvable letter that the sponsor had presented blood pressure data only at 2 hours post dosing in 2 forced titration study in patients with RLS, but that they had obtained such data at multiple time points. We asked them, therefore, to provide further analyses of the additional data collected at these time points.

As described by Dr. Hershkowitz, the sponsor performed multiple additional analyses. In an analysis by dose (confounded with time), anywhere from 6-12% of patients on ropinerole between doses of 1-4 mg experienced clinically

significant orthostatic systolic hypotension compared to 0% of placebo patients at most doses, although the number of patients experiencing these changes at any given dose were small.

In other analyses, the sponsor examined the proportion of patients who experienced a decrease in systolic blood pressure of at least 40 mg Hg and/or a decrease in diastolic blood pressure of at least 20 mm Hg at any time during the study: a total of 20% of ropinerole patients and 12% of placebo patients experienced such changes (71% and 62% of ropinerole and placebo patients, respectively, experienced decreases in SBP of at least 20 mm Hg and/or decreases in DBP of at least 10 mm Hg). In these two studies, a total of 14/55 (25%) ropinerole patients experienced adverse events consistent with hypotension, compared to 0/27 placebo patients. A total of 12 of these events were considered moderate or severe. Although it is difficult to formally assess the dose relatedness of these changes, it is clear that some patients could not be titrated to the maximum dose of 4 mg because of these (and other) adverse events. Although I do not believe that these findings should preclude approval of ropinerole for RLS, they would need to be prominently described in labeling.

Carton Labeling and Patient Package Insert (PPI)

In our Approvable letter, we had also asked the sponsor to address several issues related to carton and container labeling, in addition to requesting that the sponsor produce a patient package insert (PPI).

The sponsor has responded adequately to most of our concerns related to the carton and container labeling. However, the sponsor has proposed language for a patient starter kit (containing dosage strengths appropriate for initial titration to be given to the patient by the physician) that describes the drug as being "for restless legs syndrome". Given that the proposed indication is for the treatment of (moderate to severe) primary restless legs syndrome, we will ask the sponsor to change the carton label to "primary restless legs syndrome". In addition, the sponsor has included no adverse event information on the carton label; we will ask them to add relatively prominent language to the carton label directing the patient to read the enclosed PPI in order to learn about potential adverse events.

The sponsor has proposed a 2 sided PPI, one side containing information about PD, the other containing information about RLS, with language directing patients to read the side appropriate for them. We believe that this may be confusing for patients, and that therefore the sponsor should produce one comprehensive document including language for both indications. Much of the language in their current proposal for each indication is identical, so producing one, relatively concise, comprehensive document should be possible.

Finally, in our Approvable letter, we asked the sponsor to commit to performing a study in pigmented rats in Phase 4 to assess for retinal toxicity, as described

above. In response, the sponsor has submitted the results of Study 125, a 2 year study in which patients with early PD were randomized to receive treatment with either ropinerole or Sinemet. During this study, patients' ophthalmologic function was tested, including with electroretinogram (ERG). About 70 patients were randomized to each group; the mean dose of ropinirole was about 12 mg/day. The study was reviewed by Dr. Wiley Chambers, who has provisionally concluded that there were no clinically significant differences between ropinirole and Sinemet; however, he has several questions for the sponsor that will need to be addressed before he will be able to definitively conclude that these are, in fact, the findings. In his view, if the study is negative, the sponsor need not perform the previously requested animal toxicity study.

In summary, the sponsor has provided substantial evidence of effectiveness for ropinirole in the treatment of moderate to severe primary restless legs syndrome. They have adequately responded to most of the requests included in our 12/24/03 Approvable letter. However, the submitted analyses of the EKG data suggest an increase in the QTc interval, especially at the 4 mg dose. Although these analyses are not definitive, I believe that they raise sufficient suspicions to require that this issue be definitively addressed before the application is approved for patients with RLS. For this reason, I will issue the attached Approvable letter, with appended draft labeling.

Russell Katz, M.D.

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/s/

Russell Katz
2/24/05 12:48:39 PM
MEDICAL OFFICER

Medical Officer's Consultation Review of NDA 20-658/S-013
Ophthalmology Consult

NDA #20-658/S-13 Submission date: 8/23/04
Ophthalmology Review date: 2/22/05

Drug name: Ropinirole

Sponsor: SmithKline Beecham

Indication: Parkinson's disease

Submitted: Supplement including study evaluating retinal safety from Study 125.

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on Approvability

From an ophthalmology prospective, the supplement is not recommended for approval because the submitted study report does not contain items specified in the Code of Federal Regulations to be submitted (21 CFR 314.50(f)(2)). The supplement is missing the Case Report Forms (CFR) for patients who dropped out of the study. The shift table for visual fields does not include an adequate description of the information contained in the table. Only the initial part of the investigator's comments with respect to the ophthalmologic data has been provided. The full text of the comments should be provided.

B. Recommendation on Phase 4 Studies and Risk Management Steps

No Phase 4 studies are recommended from an ophthalmologic prospective.

II. Summary of Clinical Findings

Although there are numerical differences favoring L-dopa in comparision to ropinirole, the differences are not statistically or clinically significant.

III. Labeling (limited to areas of ophthalmologic concern)

Pending review of the case report forms, there is no objection to the proposed labeling addition concerning the ophthalmic findings.

(b) (4)

HUMAN OPHTHALMIC DATA

Ocular safety assessments were conducted during a 2-year, double-blind, multicenter, flexible dose, L-dopa controlled clinical study of REQUIP in patients with Parkinson's disease. A total of 156 patients (78 on ropinirole, mean dose 11.9 mg/day and 78 on L-dopa, mean dose 555.2 mg/day) were evaluated for evidence of retinal dysfunction through ophthalmological examinations and electroretinograms. There was no difference between the treatment groups in retinal function over the duration of the study."

STUDY 125

Comments in this review are limited to areas of ophthalmologic concern.

STUDY DESIGN/PLAN

This was a 2-year double-blind, double-dummy, multicentre, parallel group, flexible dose study in patients with early-onset parkinson's disease (PD). Male and female out-patients, 30 to 75 years of age with idiopathic PD (Hoehn and Yahr stage I-II.5) of less than 2 years duration, who required dopaminergic therapy and who satisfied all other entrance criteria were eligible for the study.

Both double-blind medications (ropinirole and l-dopa), were provided in a double-dummy presentation and therefore all patients received both tablets and capsules.

Following a 1 to 2 week placebo run-in period, eligible patients were randomly assigned (1:1) to ropinirole or l-dopa. All randomised patients initiated therapy at dose level 1 (0.75 mg/day ropinirole or 50 mg/day l-dopa). Mandatory up titration occurred during the first 4 weeks of the study up to either 3 mg/day Ropinirole or 200 mg/day l-dopa. At the week 4 visit, patients received dose level 5 (4 mg/day ropinirole or 300 mg/day l-dopa). Thereafter the dose was flexible with the potential to be titrated up in increments to a maximum of 24 mg/day (ropinirole) or 1,000 mg/day (l-dopa) (dose level 12), according to the judgement of the investigator based on the efficacy and tolerability of the study medication. Titration to the maximum tolerated dose was encouraged. However, if patient symptoms were inadequately controlled, supplementary open-label ldopa medication in either group was permitted and the patients were allowed to continue in the study.

Patients who completed the study or who withdrew after at least 12 months were given the option to enter a voluntary 1 week down-titration and then unmedicated washout phase lasting up to 2 weeks, with assessments at the end of each week. At the investigators discretion, patients were allowed to continue on double-blind medication until the study was unblinded.

Reviewer's Comments: *Acceptable.*

Efficacy Parameters
The primary efficacy parameter was the percentage decrease in putamen 18Fdopa influx constant (Ki) using 18F-dopa 3D PET scanning techniques. These images were analysed by a central region of interest (ROI) analysis on spatially transformed data by a single investigator.
The PET scan data were also analysed using statistical parametric mapping (SPM) on spatially transformed data and by each individual centre on nonspatially transformed data (i.e., local ROI analysis).

The secondary efficacy parameters were:
- Unified Parkinson's Disease Rating Scale (UPDRS) total motor score.
- Requirement for supplementary L-dopa medication.
- Increases in "offs" duration.
- Time to withdrawal.
- Clinical Global Impression (CGI) improvement scale.

Safety Parameters
The primary safety parameter was the incidence of retinal dysfunction as assessed by ERG.

The secondary safety parameter was dyskinesia (assessed from AEs and the UPDRS Part IV score).

Safety was also assessed by AE monitoring, vital signs and laboratory data.

Reviewer's Comments: *Acceptable from an ophthalmic prospective.*

RESULTS

	Left Eye			Right Eye		
	L-dopa	**Ropinirole**	**L-dopa – Ropinirole (p)**	**L-dopa**	**Ropinirole**	**L-dopa – Ropinirole (p)**
Scotopic Rod ERG						
b-wave amplitude (μV)	71	68		73	71	
[F1.1.3]	174.0	160.1		175.1	170.1	
	(91.5)	(83.3)		(91.1)	(91.8)	
	-3.6	+0.9	+5.5	-3.8	-2.9	+2.6
	(76.1)	(47.1)	(0.55)	(63.8)	(51.1)	(0.74)
b-wave latency (msec)	71	68		73	71	
[F1.2.3]	96.7	91.8		94.7	90.7	
	(21.2)	(23.3)		(21.1)	(23.6)	
	-3.2	-1.2	-1.1	-0.9	-2.0	+0.4
	(15.8)	(9.2)	(0.45)	(13.2)	(11.0)	(0.76)
Standard Flash (DA)						
b-wave amplitude (μV)	72	69		74	72	
[F2.1.3]	386.6	344.5		383.6	347.8	
	(169.2)	(144.3)		(171.0)	(145.6)	
	-8.8	-6.6	+11.7	-9.6	-13.4	+15.2
	(82.4)	(74.7)	(0.33)	(78.3)	(74.9)	(0.19)
b-wave latency (msec)	72	69		74	72	
	(7.6)	(7.7)		(7.1)	(8.1)	
	+0.5	+1.1	-1.3	+0.9	+1.0	-0.7
	(4.5)	(5.9)	(0.12)	(4.4)	(6.6)	(0.37)
a-wave amplitude (μV)	72	69		74	72	
[F2.3.3]	225.1	192.2		227.5	190.6	
	(120.5)	(103.2)		(119.9)	(106.0)	
	-4.8	+1.2	+9.9	-15.0	-1.4	+3.6
	(55.3)	(59.8)	(0.23)	(49.7)	(60.7)	(0.64)
a-wave latency (msec)	72	69		74	72	
[F2.4.3]	21.3	21.3		21.2	21.2	
	(8.2)	(8.1)		(8.3)	(8.1)	
	+0.1	+0.1	-0.2	+0.1	+0.1	-0.2
	(3.4)	(3.7)	(0.69)	(3.7)	(3.8)	(0.72)

	Left Eye			Right Eye		
	L-dopa	**Ropinirole**	**L-dopa – Ropinirole (p)**	**L-dopa**	**Ropinirole**	**L-dopa – Ropinirole (p)**
30Hz Cone Flicker						
Implicit time (msec)	66	64		67	66	
[F4.7.3]	26.7	26.0		26.7	26.3	
	(6.9)	(5.8)		(6.5)	(5.8)	
	-1.0	+0.5	-0.8	-0.8	-0.3	-0.4
	(7.2)	(5.1)	(0.35)	(5.8)	(3.8)	(0.50)
Amplitude (µV)	72	69		74	72	
[F4.8.3]	94.4	86.8		94.6	85.7	
	-3.3	-6.3	+6.4	-2.2	-4.0	+5.6
	(27.3)	(25.0)	(0.085)	(26.0)	(22.8)	(0.11)
Photopic ERG						
b-wave amplitude (µV)	72	69		74	72	
[F5.1.3]	127.6	121.2		125.4	123.4	
	(62.3)	(59.6)		(60.8)	(62.2)	
	-12.1	-15.9	+4.9	-10.0	-18.6	+7.7
	(31.3)	(28.7)	(0.27)	(33.6)	(28.7)	(0.088)
b-wave latency (msec)	72	69		74	72	
[F5.2.3]	34.3	34.9		34.1	35.0	
	(6.6)	(7.6)		(6.2)	(7.0)	
	+1.8	+1.8	-0.8	+1.9	+2.1	-1.1
	(5.2)	(5.1)	(0.14)	(5.7)	(5.6)	(0.045)
a-wave amplitude (µV)	72	69		74	72	
[F5.3.3]	43.4	41.3		45.0	41.4	
	(20.3)	(20.8)		(18.7)	(23.8)	
	-0.3	-1.6	+1.8	-1.1	-2.6	+3.0
	(14.6)	(16.3)	(0.41)	(15.5)	(19.6)	(0.20)
a-wave latency (msec)	72	69		74	72	
[F5.4.3]	17.0	17.8		17.1	17.9	
	(5.2)	(5.8)		(5.3)	(6.9)	
	(3.2)	(3.2)	(0.82)	(3.9)	(3.7)	(0.65)
Colour Contrast Thresholds						
Protan (%)	18	10		18	10	
[F6.9.3]	7.9	19.2		7.3	17.9	
	(3.1)	(22.3)		(2.9)	(22.1)	

	Left Eye			Right Eye		
	L-dopa	**Ropinirole**	**L-dopa – Ropinirole (p)**	**L-dopa**	**Ropinirole**	**L-dopa – Ropinirole (p)**
	-0.8	-1.5	-3.4	-0.6	-3.9	-1.1
	(2.8)	(11.8)	(0.22)	(1.9)	(10.3)	(0.61)
Deutan (%)	18	10		18	10	
[F6.10.3]	9.1	19.1		9.7	19.5	
	(4.1)	(21.2)		(5.8)	(23.8)	
	-0.9	-5.8	-1.2	-1.8	-1.5	-3.5
	(3.0)	(11.2)	(0.40)	(1.9)	(10.3)	(0.37)
Tritan (%)	18	10		18	10	
[F6.11.3]	12.9	13.7		12.2	13.3	
	(9.1)	(3.1)		(5.3)	(3.0)	
	-0.1	-2.7	+2.8	-1.6	-1.2	-0.8
	(3.1)	(3.2)	(0.031)	(5.1)	(3.0)	(0.53)
Electro-oculogram						
Dark trough (μV)	18	10		18	10	
[F7.12.3]	200.8	162.5		199.4	169.6	
	-17.2	+11.7	+0.8	-28.3	-0.5	-2.1
	(75.6)	(66.1)	(0.97)	(76.2)	(47.9)	(0.92)
Light peak (μV)	18	10		18	10	
[F7.13.3]	493.1	370.4		500.3	368.2	
	(160.8)	(143.0)		(175.0)	(368.2)	
	-1.1	+8.0	+76.2	-48.6	-0.5	+16.6.
	(158.1)	(157.6)	(0.20)	(149.6)	(101.1)	(0.75)
Arden ratio (%)	18	10		18	10	
[F7.14.3]	262.2	226.4		264.7	219.3	
	(64.4)	(37.9)		(54.3)	(35.1)	
	+13.3	-4.5	+31.6	+13.3	+4.0	+26.3
	(56.0)	(61.2)	(0.15)	(59.7)	(68.6)	(0.31)
Pattern						
Electroretinography						
P50 amplitude (μV)	18	10		18	10	
[F8.15.3]	2.4	2.1		2.3	2.2	
	(0.9)	(0.8)		(0.8)	(0.5)	
	0.0	-0.2	+0.3	+0.1	-0.1	+0.3
	(0.6)	(0.2)	(0.10)	(0.7)	(0.3)	(0.20)

	Left Eye			Right Eye		
	L-dopa	**Ropinirole**	**L-dopa – Ropinirole (p)**	**L-dopa**	**Ropinirole**	**L-dopa – Ropinirole (p)**
N95 amplitude (μV)	18	10		18	10	
[F8.16.3]	3.6	3.0		3.4	3.3	
	+0.2	-0.2	+0.6	+0.4	+0.2	+0.4
	(0.9)	(0.6)	(0.060)	(0.9)	(0.8)	(0.22)
P50 latency (msec)	18	10		18	10	
[F8.17.3]	50.1	50.3		49.8	51.1	
	(3.6)	(2.5)		(3.5)	(2.6)	
	+1.2	+1.6	-0.6	+0.7	+0.5	-0.7
	(3.8)	(3.7)	(0.70)	(3.4)	(2.9)	(0.53)

Reviewer's Comments: *The vast majority of values show mild differences clinically in favor of L-dopa for most values measured (i.e., positive amplitudes and negative latencies). The values are not statistically or clinically significant.*

Evidence of Retinal Dysfunction

Analysis Group	N to Y	Same	Y to N	Total
L-dopa	2	64	1	67
Ropinirole	1	58	2	61

Reviewer's Comments: *There is no significant difference between groups.*

VISUAL FIELD TEST

L-Dopa Baseline		N	Final X	Y	Total
N	10	11	7	0	28
X	0	14	34	1	49
Y	0	0	0	1	1

Ropinirole Baseline		N	Final X	Y	Total
N	7	15	6	0	28
X	10	6	29	2	47
Y	0	0	0	3	3

Reviewer's Comments: *The meaning of the categories in these shift tables has not been provided. An explanation should be provided.*

ADVERSE EVENTS

Reviewer's Comments: *There were no recognizable clinically significant adverse events that were not present at baseline or not likely to be directly related to Parkinsonism.*

The printed comments in Appendix H, pages 1834-1859 are not complete. The size of the data field appears to limit the comment. The full comments should be provided.

RECOMMENDATIONS:

A final evaluation of Study 125 cannot be completed due to missing information. The following information should be provided:

1. Case Report Forms for all patients who did not complete the study.
2. An explanation of the headings used to display the shift tables for the visual fields.
3. The full text of the investigator's comments with respect to the ophthalmologic data (Appendix H, pages 1834-1859).

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wiley Chambers
2/23/05 09:13:19 AM
MEDICAL OFFICER

MEMORANDUM

DATE: December 24, 2003

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-658/S-013

SUBJECT: Action Memo for NDA 20-658/S-013, for the use of Requip (ropinerole hydrochloride) in the treatment of patients with Restless Legs Syndrome (RLS)

NDA 20-658/S-013, for the use of Requip (ropinerole hydrochloride) in the treatment of patients with Restless Legs Syndrome (RLS), was submitted by SmithKline Beecham Corp., on 7/3/03. Requip is currently approved for use in patients with Parkinson's Disease.

The application contains the results of four adequate and well-controlled clinical trials that the sponsor believes establish the safety and effectiveness of ropinerole in patients with RLS. The application has been reviewed by Dr. Janeth Rouzer-Kammeyer, medical reviewer (review dated 12/23/03), Dr. Kun He, statistician (review dated 12/16/03), Dr. Thomas Broadbent, chemist (review dated 8/11/03), Ms. Alina Mahmud, Division of Medication Errors and Technical Support (review dated 12/18/03), Ms. Jeanine Best, Division of Surveillance, Research, and Communication Support (review dated 12/16/03), Dr. Sally Yasuda, Office of Clinical Pharmacology and Biopharmaceutics (review dated 12/5/03), Dr. Paul Roney, pharmacologist (review dated 12/18/03), and Dr. John Feeney, Neurology Team Leader (memo dated 12/23/03). The clinical team has concluded that there is an absence of adequate effectiveness data in patients in the United States. I will very briefly review the data bearing on effectiveness, and offer the rationale for the division's action.

Effectiveness

As noted above, the sponsor has submitted four randomized controlled trials (Studies 190, 191, 194, and 188) that purport to establish the effectiveness of ropinerole as a treatment for RLS. These studies have been reviewed in detail by Drs. Rouzer-Kammeyer, Feeney, and He.

Study 190

Study 190 was a multi-center study performed in 10 Western European countries in which 286 patients were randomized to either ropinerole or placebo and treated for 12 weeks. The primary outcome measure was the change from baseline in the IRLS total scale score. The between treatment comparison on

the primary outcome yielded a p-value of p=0.0036 (ITT population, LOCF analysis). Statistically significant between treatment differences were also seen on the CGI-I scale.

Study 194

This study utilized the same design as Study 190. In this study, a total of 267 patients were randomized. This study was performed in 46 centers in the US, Canada, Australia, Germany, and Norway. In this study, ropinerole was statistically significantly superior to placebo on both the change from baseline in the IRLS scale and CGI-I.

However, in this study, the results in the North American centers (US [N=59] and Canada [N=55]) numerically favored placebo (though not significantly).

Study 191

This was a study in patients with RLS in which the primary outcome measure was the mean change from baseline in the number of Periodic Leg Movements of Sleep (PLMS) as measured by polysomnography. In this study, 65 patients were randomized at 15 sites in the US to ropinerole or placebo, and treated for 12 weeks. There was a statistically significant between treatment difference on the primary outcome in favor of ropinerole, but, again, placebo was numerically superior to ropinerole on the IRLS scale, which was a secondary outcome measure in this study, and there was an essentially identical proportion of responders on the CGI-I in the drug and placebo groups (53.1% and 51.5%, respectively).

Study 188

This was a randomized withdrawal study in which patients treated in an open label phase who met responder criteria by Week 24 were randomized to continue ropinerole or placebo. The double blind period was 12 weeks long. In this study, 92 patients were randomized to drug or placebo at 26 sites in South America, Australia, Austria, Germany, and Canada. There were no US patients. The primary outcome was the proportion of patients who met relapse criteria (variously defined). There was a statistically significant difference in the relapse rate, in favor of ropinerole (p=0.016; results were favorable in Canada as well, with a total of 23 patients).

COMMENTS

The sponsor has submitted the results of four randomized controlled trials that they believe provide substantial evidence of effectiveness for ropinerole as a treatment for patients with Restless Legs Syndrome (RLS). In three trials, ropinerole is statistically superior to placebo on the IRLS scale and the CGI,

outcome measures that we have agreed are appropriate to assess treatments for this condition. In study 191, the primary outcome was a measure of PLMS, an outcome we have not agreed is an appropriate outcome on which a claim for the treatment of RLS can be based. PLMS are phenomena that are common in patients with RLS, but they do not represent the core phenomena of RLS; we have previously informed the sponsor that this would not be acceptable as an outcome to support their proposed claim.

While the studies are all "positive" by protocol, a striking finding is that in the two studies in which US centers were included (Studies 194 and 191), no differences between drug and placebo were detected on the IRLS, the primary clinical measure of the core symptoms of the disease. Indeed, in these studies, placebo was (very slightly) numerically superior to drug (each study had about 30 patients on ropinerole). The sponsor argues that this finding is not relevant to a regulatory decision, primarily because 1) they have been unable to identify any important differences at baseline between US and other patients, and 2) it is not unexpected that in multi-center studies, certain centers do not distinguish drug from placebo; further, trials are meant to be analyzed as a whole (not within each center), and there is no significant treatment by region interaction.

I agree that there are no obvious explanations for the results in the US centers. However, the lack of such an obvious explanation does not, of course, establish that no relevant differences exist, or that the finding is not present (and in need of explanation). Further, I find the statistical argument unsatisfying. It is true that no statistically significant interaction exists, but this too cannot be considered to definitively dispense with the observation. The fact remains that, in the two studies in which US patients were enrolled (each with about 30 patients on drug and 30 patients on placebo), there is no discernible difference between drug and placebo as measured on the primary clinical outcome measure.

Of course, this could represent variation, and be entirely a chance, and therefore spurious, finding. However, we have no experience with clinical trials in patients with this diagnosis, nor do we have information about differences between countries in patients' responses to this or any other treatment (although it is true that the results are generally favorable across a wide range of countries and cultures in these studies). If we had a robust experience with this condition and treatment in this country, we might be in a position to attribute the findings seen in US patients in this NDA to chance, but we do not have this experience, and it is always possible that some "real" difference between patients in this country and those in other countries (either intrinsic or extrinsic factor[s]) accounts for the results. For this reason, it seems ill-advised to approve the drug for use in this country until the sponsor submits affirmative evidence that ropinerole is effective in patients in the US. Indeed, the sponsor is conducting such a study at this time, entirely within the US.

Finally, while there are no safety issues that would appear to preclude approval, the clinical team is requesting additional information about orthostatic

hypotension and EKG parameters. Of particular interest to me, however, is the report of a patient diagnosed with pulmonary fibrosis after treatment with ropinerole for 3 months; we will ask for additional information on this patient. While Requip labeling currently describes a case of pleural fibrosis in a patient with Parkinson's Disease (PD), the occurrence of a case in this relatively small database (about 700 RLS patients received at least one dose of drug) and in a population that is generally younger and healthier than patients with PD is worrisome. Further consideration of how this will impact on the ultimate action on this application will await the additional data.

For the reasons given above, then, I will issue the attached Approvable letter, requesting evidence that ropinerole is effective in patients in the US.

Russell Katz, M.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
12/24/03 01:43:57 PM
MEDICAL OFFICER

MEMORANDUM

NDA 20-658/S-013 Requip (ropinirole)

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: Efficacy of Requip for the Treatment of Restless Legs Syndrome

DATE: December 18, 2003

Requip is currently approved for the treatment of Parkinson's disease. Several years ago, the sponsor approached DNDP with a plan to develop Requip for the treatment of Restless Legs Syndrome (RLS). RLS was described in the medical literature in 1945 by Ekbom and is sometimes referred to as Ekbom's Syndrome, although descriptions of the clinical symptoms of RLS apparently were described even before that time. Criteria for the diagnosis of RLS were published in 1995 by the International Restless Legs Syndrome Study Group (IRLSSG) and used in the clinical trials described in this submission. These diagnostic criteria were more recently slightly modified by the IRLSSG in 2002.

In the current submission, the sponsor has provided the results of 3 pivotal studies, Study 190, Study 194, and Study 188 to support the efficacy of Requip in RLS. Studies 190 and 194 are almost identical in design. Both are 12-week, randomized, placebo-controlled, parallel-group studies of Requip in patients diagnosed with RLS. Study 188 was designed to demonstrate the continued efficacy of Requip after a 24-week treatment period. In Study 188, patients were all treated in a single-blind fashion with Requip for 24 weeks and then the responders underwent a double-blind randomized withdrawal to either Requip or placebo for 12 weeks.

Also included in the submission is Study 191, a 12-week, randomized, placebo-controlled, parallel-group study. In this study, the primary outcome was the number of period limb movements observed during sleep in patients with RLS. Period limb movements are a frequent, but not necessary accompaniment in RLS. Because PLMS are so common in RLS (80% of patients), it is valuable to know the effect of an RLS drug on PLMS. In addition, the study of PLMS addressed another concern previously raised by DNDP. Because dopamine agonists are known to cause somnolence, an effect of Requip reflected on the IRLS Scale might only reflect these sedative-hypnotic effects, being no different than any other sedative drug. A demonstrated effect on PLMS suggests an effect of Requip in RLS beyond simply shortening the time of sleep onset. DNDP had also suggested the use of a sedative/hypnotic arm in the trials for the same reason, but the sponsor has not done that.

Two more studies were done, Study 207 and Study 218. These were both small randomized trials that incorporated a forced titration dosing regimen. Even though

Requip was an approved drug product when the RLS studies began, DNDP had asked the sponsor to address the safety of the proposed dosing regimen in patients with RLS before conducting large controlled trials. The Parkinson's disease development program had suggested that normal volunteers might be more susceptible to the hypotensive effects of ropinirole than patients with PD. Patients with early PD were more susceptible than patients with advanced PD. While the total daily dose in RLS was small (it is only given once daily in RLS, in the evening), the size of the single doses was comparable to the single doses used in PD. Therefore, in Studies 207 and 218, the proposed dose titration was used, advancing patients to a maximum tolerated dose based on blood pressure, nausea, and vomiting. With the first dose of each dose escalation, patients' vital signs were monitored frequently for several hours after the dose.

The clinical review of this efficacy supplement was performed by Dr. Janeth Rouzer. The statistical review was performed by Dr. Kun He. Additionally, a pharm/tox review was written by Dr. Paul Roney and a biopharm review was written by Dr. Sally Yasuda.

Diagnostic Criteria

Restless Legs Syndrome (RLS) is a disorder characterized by an uncomfortable sensation in the legs brought on at night while resting in bed prior to sleep onset. The uncomfortable sensation is relieved by movement of the legs. While often described as a disorder of sleep, it might better be thought of as a movement disorder, like akathesia. It differs from akathesia in that it is associated with discomfort in the legs and it has a circadian rhythm.

It is a clinical diagnosis. The IRLSSG defines 4 diagnostic criteria:

1. Desire to move the limbs usually associated with uncomfortable or unpleasant sensations;
2. Motor restlessness;
3. Symptoms worse or exclusively present at rest with at least partial and temporary relief with activity;
4. Symptoms worse in the evening/night.

A number of characteristics associated with RLS have also been described. These include:

1. Difficulty initiating and maintaining sleep. This can lead to excessive daytime somnolence (EDS). The EDS associated with RLS is usually not as severe as with other sleep disorders, such as sleep apnea.
2. Involuntary movements during sleep. These so-called periodic limb movements of sleep (PLMS) can be recorded on overnight polysomnograms using surface limb leads to record the electrical muscle activity. It is estimated that as many as 80% of patients with RLS also will have PLMS. If these limb movements are associated with arousals from sleep, they may contribute to the EDS seen with RLS. More than

5/hour is usually considered abnormal and more than 20/hour usually warrants treatment.
3. Frequent family history
4. Normal neurologic exam in idiopathic RLS
5. Variable age of onset. Symptoms increase in frequency and severity with age. Up to 20% of older age groups may meet the criteria for RLS.

There are no laboratory tests to confirm the diagnosis. Objective tests to measure severity during symptomatic episodes have been developed. In these tests, patients are asked to remain immobile while resting or sitting and the time to movement is measured.

Augmentation and Rebound

With treatment, especially with short-acting dopaminergic drugs, investigators have described a worsening of symptoms in the early morning hours, similar to the end-of-dose failure seen in advanced Parkinson's disease. This is referred to as rebound. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. Augmentation is also described with therapy for RLS.

International Restless Legs Syndrome Rating Scale (IRLS Scale)

The International RLS Rating Scale (IRLS Scale) was developed by the IRLSSG to measure the core manifestations of RLS. The scale reflects the patient's assessment of his or her own symptoms. The scale is made up of 10 questions, each rated from 0 to 4, with 0 reflecting no symptoms. The total score ranges from 0-40. The sponsor chose the IRLS Scale as the primary outcome in their clinical trials and has previously submitted the validation information to DNDP (November 6, 2002).

The first 5 questions on the scale ask the patient to rate their overall discomfort, need to move, relief from movement, sleep disturbance, and daytime somnolence, all over the past week. The next 3 questions ask the patient to rate the frequency (days per week), severity (hours per day), and overall severity of RLS symptoms. And the final 2 questions ask the patient the overall effect of RLS on their lives and the overall effect of RLS on their mood.

The scale does not specifically address the occurrence of rebound or augmentation.

The IRLSSG performed a large validation study including 196 patients with RLS and 209 controls. The patients remained on stable doses of RLS medications throughout. On testing days, patients rated themselves twice on the scale. The severity of RLS symptoms was also rated on a global scale, from 0 (no symptoms) to 8 (most severe),

and these results correlated with the IRLS scale. The correlation between the CGI scores and the IRLS scale scores is shown below:

CGI Score	Mean IRLS Score
0-2, Mild	12
3-4, Moderate	20
5-6, Severe	27
7-8, Very Severe	30

In the trials described below, the inclusion criteria required that patients have a score on the IRLS scale of at least 15 at baseline. The mean score at baseline in these studies was about 24 with a range of 15-40. The completed controlled trials discussed below were originally powered to show a between-group difference of 6 on the change-from-baseline on the IRLS scale. The observed difference was about 3.

Because the novelty of the IRLS scale and the lack of familiarity with its properties, DNDP asked the sponsor to consider the use of a co-primary outcome, the CGI. The CGI used by the sponsor is a 7-point patient-rated assessment of the overall effect. As in the regulatory approach to Alzheimer's drug development, the CGI was recommended in part to assure that a small, clinically insignificant change on the IRLS scale did not become the basis for approval.

Requip Dose Regimen in the RLS Clinical Trials

In the RLS studies, patients received 0.25 mg for the first 2 days, followed by 0.5 mg for the next 5 days, followed by 1.0 mg for the second week, followed by weekly increments of 0.5mg until a dose of 3.0 mg was reached. An increase to 4.0 mg was allowed for the final increment. Dosing was once daily, 1-3 hours before bedtime. The actual doses achieved in the RLS trials are discussed in detail in the safety section, later in this review.

Study 190

This was a 12-week randomized, double-blind, placebo-controlled multinational trial of Requip vs placebo. None of the sites were in North America. There were 146 patients randomized to Requip and 138 to placebo. Patients randomized to Requip were titrated to a dose that provided moderate to marked improvement with acceptable side effects, or to a maximum dose of 4mg. Patients all had a diagnosis of primary idiopathic RLS and met the criteria for diagnosis of moderate to severe RLS, defined as an IRLS scale score of 15 or greater at baseline and the presence (or presumed presence if left untreated) of symptoms on 15 or more nights in the past month. Fully half the patients enrolled had been previously treated with other agents for RLS. Almost half the patients enrolled had a family history of RLS. Patients with a previous history of augmentation or

rebound in response to therapy were excluded. The presence of other movement disorders such as Parkinson's disease led to exclusion.

The primary outcome measures were the IRLS scale and the CGI. The primary analysis was a sequential analysis with 4 steps. The first and second analyses compared patients at 12 weeks on the IRLS scale and then the CGI. The third and fourth analyses compared patients at 1 week on the IRLS scale and then the CGI. The study was powered to show a between-group difference on the change-from-baseline IRLS scale score of 6 points.

The mean change from baseline on the IRLS scale was –11 for the Requip group and –8.2 for the placebo group. The between-group difference, -2.8, was statistically significant, p=0.0036. The proportion of responders (defined as moderate or marked improvement on the CGI) was 53% for the Requip group and 41% for the placebo group, p=0.0416. The between-group differences were likewise statistically significant at 1 week.

Study 194

This study was almost identical in design to Study 190, but it included sites in Canada and the U.S. There were 131 patients randomized to Requip and 136 to placebo. The mean change from baseline on the IRLS scale was –10.9 for the Requip group and –9 for the placebo group. The between-group difference, -1.9, was statistically significant, p=0.0197. The proportion of responders (defined as moderate or marked improvement on the CGI) was 59% for the Requip group and 40% for the placebo group, p=0.001. The between-group differences were likewise statistically significant at 1 week.

Study 188

This was a multinational study, but it did not include any sites in the U.S. Patients were all treated in a single-blind fashion for 24 weeks. Patients who then met the definition of responder, a 6-point improvement on the IRLS scale, were randomized to placebo or continued treatment with Requip. Relapse was defined as a 6-point worsening on the IRLS scale after 12 weeks (and at least a total score of 15) or withdrawal due to lack of efficacy. In the single-blind phase, there were 202 patients, of which 92 were then randomized, 45 to Requip and 47 to placebo.

The proportions of patients who relapsed were 35% in the Requip group and 65% in the placebo group, p=0.0156.

Study 191

This was a U.S. study designed to examine the effect of Requip on PLMS in patients with RLS. It was a 12-week double-blind, randomized, placebo-controlled trial of Requip vs placebo. The primary outcome was the change in number of limb movements during sleep as measured on overnight polysomnograms (PSGs). The IRLS scale was a

secondary outcome measure as was the CGI. There were 32 patients randomized to Requip and 33 to placebo.

The change from baseline in the number of PLMS/hour was –33 for the Requip group and –6 for the placebo group, $p<0.0001$.

There was no difference between groups on the change from baseline on the IRLS scale. Likewise, there was no difference between groups on the proportion of responders on the CGI.

North American Sites

Study 191 included only U.S. sites. There was no difference between groups as measured by the IRLS scale.

Study 194 included sites in Canada and the U.S. No benefit of Requip was demonstrated on the IRLS scale in either Canada or the U.S. In fact, the results trended in favor of placebo on the IRLS scale.

The sponsor addressed the lack of effect in North America in their submission. Exploratory analyses did not reveal an obvious explanation for this discrepancy. In particular, given the flexible dose range allowed in the trials, there did not appear to be any significant differences in the doses achieved in the different countries to explain the discrepancy.

Study 249

This is a large ongoing controlled trial being conducted entirely in the U.S. Similar in design to Studies 190 and 194, this is a 12-week, randomized, double-blind, placebo-controlled study of Requip vs placebo in patients with RLS. Outcome measures include the IRLS scale and the CGI. There will be 360 patients randomized, 180 per treatment arm. The study is powered to show a between-group difference of 3 on the change-from-baseline on the IRLS scale. Thus, the study is powered, using the effect observed in Studies 190 and 194, to show half the effect size that was originally targeted in powering the previous trials.

As in Studies 191 and 194 (U.S. sites), orthostatic blood pressure measurements are planned pre-dose and at 2 hours post dose with each first new dose.

The first patient was randomized to Study 249 in September 2003. Already, 182 patients have been randomized (half the planned enrollment).

Safety

Requip is an approved drug product for the treatment of Parkinson's disease. The safety experience from the drug development program for that use and from postmarketing experience is summarized in currently approved labeling. In Parkinson's disease, Requip is started at a dose of 0.25 mg tid and titrated at weekly intervals. The titration schedule followed in the RLS development program differed in that only one dose per day was administered, but the size of these doses mirrored the individual doses administered in the Parkinson's titration schedule. In clinical trials in early and advanced PD patients, the mean dose achieved was about 5 mg tid.

The safety data from the RLS development program was presented in two parts, the original submission and a 4-month safety update.

In the original submission, the sponsor presents data on 677 patients who received at least one dose of Requip. The data is presented grouped by the type of study. There are 4 such groupings: the completed 12-week efficacy studies (190, 194, and 191), the maintenance of effect study (188; with a 24-week single-blind phase and a 12-week double blind phase), the clinical pharmacology studies (207 and 218; 7-week forced titration studies), and the open-label continuation studies (192 and 243). The cutoff date for the original submission was 29 January 2003.

In the 3 pooled efficacy studies, there were a total of 310 Requip-treated patients vs. 308 placebo-treated patients. In the 2 pooled 7-week forced titration studies, there were a total of 55 Requip-treated patients vs. 27 placebo-treated patients. In all the pooled efficacy studies, patients were titrated taking into account the level of improvement already experienced. In the forced titration studies, patients were titrated to a maximum tolerated dose as defined by unacceptable nausea, vomiting, or hypotension at the next highest dose. Unfortunately, neither design has the ability to fully characterize a dose-response relationship for any individual adverse event.

In the RLS studies, patients received 0.25 mg for the first 2 days, followed by 0.5 mg for the next 5 days, followed by 1.0 mg for the second week, followed by weekly increments of 0.5mg until a dose of 3.0 mg was reached. An increase to 4.0 mg was allowed for the final increment. Dosing was once daily, 1-3 hours before bedtime. It is clear from the forced titration studies that the maximum tolerated dose for half of all patients will be well below 4 mg.

The following table shows the number of patients in Study 207 with an MTD at each dose level.

MTD in Study 207	Number of Patients N=37
0	1 (3%)
0.5	4 (11%)
1.0	5 (14%)
1.5	1 (3%)
2.0	3 (8%)
2.5	3 (8%)
3.0	1 (3%)
4.0	16 (43%)

In the 4-month safety update, the sponsor presents cumulative data from the open-label continuation studies (Study 192, N=306; Study 243, N=81) through June 2003 (September 2003 for deaths and serious AEs). Because some patients entered the open-label continuation studies without exposure to Requip in the other studies, the safety update includes experience for some newly exposed individuals, bringing the total exposure to 725.

For these 725 RLS patients, 537 were exposed for $\geq$ 3 months, 353 were exposed for $\geq$ 6 months, 212 were exposed for $\geq$ 9 months, and 64 were exposed for $\geq$ 12 months.

The following two tables show the maximum doses achieved for the Requip patients in Studies 190 and 194, the pivotal studies:

Study 190		
Dose	Number of Patients	Percent of Patients
0.25	3	2
0.5	18	12
1.0	26	18
1.5	26	18
2.0	21	14
2.5	16	11
3.0	15	10
4.0	20	14

Study 194		
Dose	Number of Patients	Percent of Patients
0.25	4	3
0.5	18	14
1.0	23	18
1.5	26	20
2.0	17	13
2.5	10	8
3.0	9	7
4.0	21	16

The following table shows the total cumulative exposure by dose for the entire safety population:

Total Cumulative Exposure		
Dose	Number of Patients	Total Exposure to Dose (days)
0.25	722	10232
0.5	692	18178
1.0	640	27531
1.5	529	21526
2.0	401	19060
2.5	295	10321
3.0	194	7875
4.0	134	10320

In her review, Dr.Rouzer has presented the safety data from each individual study in the original submission separately, followed by a review of the new data in the safety update. The safety update also included a review of postmarketing data on Requip when used for RLS. Dr.Rouzer has reviewed this also.

Hypotension and Orthostatic Hypotension During Dose Titration

Early in the development of Requip for RLS, the division raised concern about the tolerability of Requip with respect to hypotension and orthostatic hypotension. Previous experience suggests that patients with Parkinson's disease may actually be more tolerant of these effects than normal volunteers. For this reason, the sponsor incorporated extensive blood pressure monitoring into some trials on the day of each dose escalation. Because patients with RLS are only dosed once daily, several hours before bedtime, this blood pressure monitoring necessitated home visits in some cases to capture blood pressure recordings timed to dosing.

The studies with this monitoring were Studies 207, 218, 191, and 194 (only U.S. sites in 194). In the two forced-titration studies, with each first new dose, orthostatic blood

pressure measurements were made pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours post dose. In Studies 191 and 194 (U.S. sites), orthostatic blood pressure measurements were made pre-dose and at 2 hours post dose with each first new dose. As mentioned earlier, the study designs did not allow for the true characterization of a dose-response relationship because titration was stopped for competing adverse events in all trials (207, 218,191, and 194) and for efficacy in some trials (191 and 194).

In Studies 191 and 194, using set criteria for a clinically significant post-dose orthostatic drop in blood pressure, there was no signal for orthostatic changes during dose titration.

When Studies 207 and 218 are pooled, the number (and percent) of patients in each group that met the criterion for a clinically significant post-dose orthostatic drop in systolic pressure (at 2 hours) is shown below:

Clinically Significant Orthostatic Decrease in Systolic BP During Dose Escalation		
Dose	Requip Number of Patients/Total (%)	Placebo Number of Patients/Total (%)
0.25	2/55 (4)	1/27 (4)
0.5	0/53 (0)	2/25 (8)
1.0	3/52 (6)	1/24 (4)
1.5	3/49 (6)	0/24 (0)
2.0	5/42 (12)	0/24 (0)
2.5	3/38 (8)	0/22 (0)
3.0	1/31 (3)	1/21 (5)
4.0	2/27 (7)	0/21 (0)

Note that during dose escalation patients dropped out for other reasons, so that a true dose response relationship cannot be described. It is not clear to me why the sponsor has only focused the above analysis on data collected 2 hours post-dose. While this is the Tmax, there is variability in Tmax among patients and data was collected at numerous timepoints post-dose in these forced-titration studies. The sponsor should be asked to recreate the above table using the greatest post-dose change for each patient, regardless of timepoint, and including patients coded with an AE “orthostatic hypotension” even if no BP recordings were made.

Adverse events related to lowered blood pressure were collected in the controlled trials. In the 12-week controlled trials:

	Requip N=309	Placebo N=307
Syncope	5 (1.6%)	1 (0.3%)
Hypotension	4 (1.3%)	1 (0.3%)
Postural hypotension	3 (1%)	2 (0.7%)

In the forced-titration studies:

	Requip N=55	Placebo N=27
Syncope	1 (1.8%)	0
Hypotension	6 (10.9%)	0
Postural hypotension	8 (14.5%)	0

In the 4-month safety update, the sponsor summarized the blood pressure data collected systematically in 80 patients enrolled in Study 243 during dose escalation. Study 243 was the open-label continuation study in the U.S. During dose escalation, patients had resting and orthostatic blood pressure measurements recorded pre-dose and 2 hours post-dose for each dose escalation. The numbers of patients at each dose escalation is shown below:

0.25mg	0.5mg	1mg	1.5mg	2mg	2.5mg	3mg	4mg
79	76	72	52	31	22	16	9

Of these, only 1 patient met the criterion for a clinically significant post-dose orthostatic drop in systolic blood pressure, even using a fairly conservative change of 20mmHg systolic as the criterion. This occurred at 1.5mg.

ECGs During Dose Titration

ECGs were only collected at screening in Studies 190, 191, 194, and 188. In Studies 207 and 218, ECGs were collected at baseline and at the end of the study, within 7 days of stopping study drug. Therefore, no information about the effect of Requip on ECG was presented in the submission.

I am not aware of any ECG data collected at post-dose timepoints comparable to the post-dose blood pressure data described above. Minutes of a pre-IND meeting held on January 24, 2001 state, “Safety data supporting tolerance to the proposed dosage regimen is necessary. Safety concerns, especially those that are cardiovascular in nature (ECG, othostatic blood pressure changes, and syncope) should be a primary focus.” Therefore, in the ongoing controlled trial of Requip in RLS, such ECG data should be requested as a Phase 4 commitment.

Deaths

There was only one death during the RLS studies. A 70-year-old woman died of anaplastic cancer of the thyroid, not reasonably attributable to Requip.

Serious Adverse Events

In the 12-week efficacy studies, there were 14 patients with serious AEs, 5 in the Requip group and 9 in the placebo group. The serious AEs reported by patients on Requip included injury (2 patients), gastrointestinal disorder, angina pectoris aggravated, and menstrual disorder.

In the maintenance of efficacy study (Study 188), there were 22 serious AEs reported by 18 patients during the single-blind phase and none in Requip patients during the double-blind phase. These included basal cell carcinoma (4 patients), thyroid neoplasm (discussed above), intestinal obstruction, malignant melanoma, prostatic disorder, chest pain, implantation complications (from shoulder prosthesis), increased drug level (3 patients), myocardial infarction, hematemesis, hepatitis, pulmonary fibrosis, injury, syncope, calcinosis (shoulder joint), and fatigue.

In the forced-titration studies, there was one serious AE, a patient with severe abdominal pain at a dose of 2 mg. This persisted until 2 months after the last dose of study medication.

In the extension studies, there were 7 serious AEs as of the original January 2003 cut-off date. These included arrhythmia, myocardial infarction, intestinal obstruction, edema, overdose, chest pain, and gastric polyp. In the 4-month safety update, a total of 24 patients from the extension studies are described with serious AEs. None of the additionally reported serious AEs significantly alter the safety profile of Requip.

From all those listed above, perhaps the most concerning at this point in time is the case of pulmonary fibrosis. This occurred in a 75-year-old woman. She was hospitalized with gastrointestinal bleeding after taking Requip for 3 months. During the hospitalization, she was noted to be short of breath. A CT scan of the chest revealed interstitial pulmonary fibrosis. The provided narrative does not note any specific treatment or outcome for the fibrosis. This case merits further investigation.

Pleuropulmonary fibrosis is a known complication of ergot alkaloid dopamine agonists. Requip is not an ergot, but current labeling describes a single case of pleural fibrosis in a patient treated for PD. Given that the RLS patient population is larger and perhaps generally healthier than the PD population, vigilance for fibrotic complications is certainly warranted. The ergot dopamine agonist pergolide has seen off-label use for RLS and has been linked to pulmonary fibrosis in at least one case report in an RLS patient (Danoff et al. Chest 2001;120:313-316). The authors of that report believe that the drug-relatedness of such reactions may go unrecognized and result in under-

reporting. Usually such cases are not diagnosed until treatment has continued for 6 months or longer. The case described above with Requip, however, was captured incidentally when the patient was hospitalized for another reason (gastrointestinal bleeding). Requip was not discontinued however. Therefore, follow-up is needed.

There are several cases of chest pain or myocardial infarction. While none of these events can be clearly linked to use of Requip, lowered blood pressure from Requip could certainly aggravate underlying coronary artery disease. Events of chest pain and myocardial infarction were noted in placebo patients as well.

Likewise, lowered blood pressure from Requip could predispose to falls and subsequent injury, but in most cases it is difficult to ascertain premonitory presyncopal symptoms.

The case of melanoma was a recurrence shortly after starting Requip in a patient with known melanoma and a previous recurrence.

Adverse Events Leading to Withdrawal

The table below shows the AEs leading to withdrawal of two or more Requip patients from the 12-week controlled trials:

	Requip N=309	Placebo N=307
Nausea	7 (2.3%)	1 (0.3%)
Dizziness	4 (1.3%)	1 (0.3%)
Headache	4 (1.3%)	0
Vomiting	3 (1%)	0

These are consistent with the overall adverse event profile seen in RLS patients.

Adverse Events of Special Interest

Aside from adverse events related to lowered blood pressure (discussed above), certain adverse events were designated to be of special interest based on previous experience with dopamine agonists in PD. The incidence of these events in the 12-week controlled trials are shown in the following table:

	Requip N=309	Placebo N=307
Somnolence	36 (11.7%)	20 (6.5%)
Edema	10 (3.2%)	3 (1%)
Sudden Onset of Sleep	0	1 (0.3%)
Hallucinations	0	1 (0.3%)
Augmentation	0	0
Vision Abnormal	6 (1.9%)	0
Melanoma	0	0
Retroperitoneal Fibrosis	0	0

The reported visual abnormalities were variable and non-specific, including blurred vision and sparkles in front of eyes. Because Requip is taken at bedtime in RLS, it is not clear that somnolence would be an *adverse* event unless it continued as daytime somnolence. I do not believe this distinction was sought out during adverse event data collection.

In the total development program, there were several cases of hallucinations, one case of melanoma, and one case of pleural fibrosis. Augmentation also occurred for ten patients during extension studies.

Postmarketing Data

In the 4-month safety update, the sponsor reviewed 69 reports for RLS patients, 4% of all postmarketing reports for Requip. Twenty were considered serious. Of these, 6 represented sudden sleep attacks. Two of these 6 had RLS along with PD. Among the remaining 14 reports were single cases of melanoma, hemolytic anemia, breathlessness, convulsion, pancreatitis, and idiopathic thrombocytopenia purpura. These cases are generally poorly documented. The report of convulsion may have been due to syncope.

Preclinical Finding of Retinal Toxicity

Current labeling for Requip describes the preclinical finding of retinal toxicity found in albino rats in 2-year carcinogenicity studies. This finding is also described with Mirapex (pramipexole), another non-ergot dopamine agonist. More recently, labeling for Mirapex was updated to describe a more subtle thinning of the outer nuclear layer of the retina in pigmented rats seen in 3-month studies. The latter finding was detected with morphometric techniques.

Dr.Roney, the pharm/tox reviewer, describes a 3-month study with pigmented and albino rats at various light intensities. No incidents of retinal degeneration were observed in the pigmented rats. However, morphometric techniques were not used. Dr. Roney believes a study with morphometric techniques should be done. Also, the sponsor has proposed a labeling change which implies that the retinal changes noted in albino rats were due to light exposure alone. However, there are clear differences between the Requip and vehicle groups. Dr.Roney disagrees with this change and recommends keeping the original labeling.

Inspections

Inspections of 2 clinical sites were performed. There were no objectionable findings and the data were deemed acceptable.

Labeling

The sponsor has proposed labeling describing the efficacy studies and the safety data. The sponsor also has proposed two separate Patient Information Leaflets, one for RLS and one for PD. The sponsor has proposed that both leaflets be attached to approved labeling. Recently, when sponsors of other applications have proposed separate leaflets for separate indications, the agency has advocated a single leaflet incorporating all indications. The primary reason for a single leaflet is to avoid the situation where a patient is provided the leaflet for the wrong indication. In keeping with this approach, the current sponsor should be asked to develop a single Patient Leaflet.

At the same time, the agency has not opposed the development of indication-specific information leaflets to be distributed by health care practitioners to the appropriate patients. These would be developed based on the single leaflet attached to labeling.

Conclusions

Overall, Requip has been shown to be effective for the treatment of *moderate-severe, primary* RLS. Given that only moderate-severe patients were studied, I believe labeling should limit the indication to patients with moderate-severe RLS.

The data from North America either trends in the wrong direction or shows no difference. This is true for the Canadian sites in Study 194, the U.S. sites in Study 194, and in Study 191 (a U.S. study). Note that Study 191 was primarily designed to assess the effect of Requip on PLMS, but included the IRLS scale as a secondary outcome. Even with a difference in favor of Requip on PLMS, there was no difference on the IRLS scale. Prior to approval in the U.S., I believe a U.S. trial showing an effect of Requip on RLS (using both the IRLS scale and CGI as co-primary outcomes) should be required. Such a trial, Study 249 is already ongoing.

While no signal of a clinically significant effect of ropinirole on ECG has been previously detected, ECG data timed to dosing through dose escalation should be collected. This should be added to the protocol for Study 249 as soon as possible.

In the forced titration studies, blood pressure data was collected at numerous timepoints post-dose, but the sponsor presented only the data collected at 2 hours post-dose. The sponsor should be asked to recreate the appropriate table in my memo, using the greatest post-dose change for each patient, regardless of timepoint.

More information should also be requested about the single case of pulmonary fibrosis. Specifically, the sponsor should address how resolution of the fibrosis was documented, any specific treatment for the fibrosis, why it was not considered drug-related, and how the decision to continue Requip was made. Meanwhile, a consult to the Office of Drug Safety (ODS) seeking additional postmarketing cases of fibrotic complications with Requip is pending at this time.

For labeling, given that PLMS is not considered necessary for the diagnosis of RLS and occurs without RLS, the results of Study 191 should probably not be described in the clinical trials section. Also, the sponsor should be asked to develop a single PPI, instead of the two indication-specific PPIs proposed.

Recommendations

The sponsor should be sent an Approvable Letter requesting the additional information described above.

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/s/

John Feeney
12/23/03 05:15:10 PM
MEDICAL OFFICER