CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20658

ADMINISTRATIVE DOCUMENTS

MEMORANDUM

DATE: August 21, 1997

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

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

Director
Office of Drug Evaluation I/HFD-101

File, NDA 20-658

SUBJECT: Supervisory Review of Response to Approvable Letter

On 1/2/97, the Agency sent an Approvable letter to SmithKline Beecham Pharmaceuticals for NDA 20-658, for the use of ropinerole as symptomatic treatment for patients with Parkinson's Disease (PD). The Approvable letter included several requests:

1) Clinical-We asked the sponsor to present a clearer picture of the experience at the higher daily doses (i.e., 12 mg/day or greater). Because the controlled trials were all titration designs, it was not clear if there was sufficient exposure to these higher doses to permit them to be included in labelling as recommended doses.

2) We asked the sponsor to examine the dose response, if any, for efficacy and for adverse events, especially postural effects and syncope.

3) Labelling-Draft labeling was included with the Approvable letter, with numerous areas to be addressed by the sponsor. The letter specifically highlighted our concerns regarding statements on Orthostatic Hypotension/Syncope and Hallucinations in the Warnings Section, Information for Patients in the Precautions Section, and the Dosage and Administration Section.

4) Biopharmaceutics-We proposed specific dissolution specifications

5) Environmental Assessment-3 issues were raised.

6) CMC-4 issues were raised

7) Safety Update-In addition to the routine requests, we had a number of specific concerns (e.g., relative risk of ADRs in patients with and without CV disease, further clarification of certain ADRs, specific format guidance, etc.)

8) Foreign Labeling/Update

The sponsor responded to the letter in a submission dated 3/28/97. This response contained answers, re-analyses, etc., that responded to the Approvable letter, as well as fairly extensively revised draft labeling. The resubmission was reviewed comprehensively by Dr. Burkhart of the Safety group in a review dated July 24, 1997, and by Dr. Rouzer-Kammeyer in a review dated 5/1/97. In addition, the response was reviewed by Dr. Safaa Ibrahim of The Division of Pharmaceutical Evaluation I (7/23/97), Dr. David Scarpetti, chemist (5/30/97, 7/15/97), and by Dr. Philip G. Vincent of the Environmental Assessment Team (6/3/97).

A copy of the Division's re-proposed draft labeling was faxed to the sponsor on 8/8/97. Further negotiations were held with the sponsor on August 19, 1997, and there is essentially complete agreement on the language contained in the labelling being forwarded with the draft Approval letter contained in this package. The labelling differs from the original draft labeling sent with the Approvable letter in the following important ways.

1) **CLINICAL PHARMACOLOGY**

Mechanism of Action-Minor wording changes. Slightly altered wording regarding activity at various dopamine receptor sub-types. Additional language regarding effects in animal models has been included,; this is similar in form to the pramipexole labeling.

Clinical Pharmacology Studies-Doses above which orthostatic symptoms appear have been added, as have doses associated with normal ECGs. Also, a statement about the effects on serum prolactin has been added.

Pharmacokinetics-Minor section heading and wording changes. A statement about the main P450 enzyme responsible for ropinerole's metabolism has been added.

Population Subgroups-A statement about the lack of necessity of adjusting the initial dose (similar to one in the pramipexole label) has been added. A statement about the likelihood of dialysis not being effective in drug removal has been added.

Clinical Trials-Minor wording changes were made. Statements describing the time (and dose) at which differences between treatments emerged in the trials were included, as were clarifications in the description of the titration schemes used. Tables of results have been replaced by narrative text, which is similar to the format used in the pramipexole label. In the section on adjunct trials, statements about the degree of decrease of the l-dopa dose achieved and the change in "off time" have been added.

2) **WARNINGS**

Symptomatic Hypotension/Syncope-Our original draft included this combined sub-section. The current version contains 2 sections: Syncope and Symptomatic Hypotension, in that order.

The language in the new Syncope sub-section is essentially unchanged from the relevant language in the original, with some slight alteration of numbers. Some additional clarifying language, as we requested, is included in the Symptomatic Hypotension sub-section.

Hallucinations-Several requested incidences were included.

3) **PRECAUTIONS**

General

Events Reported With Dopaminergic Therapy-The initial paragraph (which describes caveats about the absence of any of these findings in the development cohort) has been removed. Under Fibrotic Complications, the generic language that appears in the pramipexole labeling has been added, as has a description of a case of a 69 year old man who developed pleural fibrosis. While we agreed to the language included in the version accompanying the package in our phone meeting of 8/19/97, the firm subsequently phoned Mr. Nighswander and told him that after further internal discussion, they request that any description of this case be removed from the label. As noted, the version accompanying this package has the language included.

Two paragraphs describing retinal pathology in the rat and binding to melanin have been added.

Information for Patients-A statement describing the potential utility of taking ropinerole with food to decrease nausea has been amended, based on the fact that C_{max} is decreased with food, and a statement about the teratogenic potential of ropinerole has been added (a similar statement appears in pramipexole labeling).

Drug Interactions-Several drug specific interactions have been added, as has a generic statement about the route of metabolism of ropinerole.

4) **ADVERSE REACTIONS**

Various lists and tables of incidences of ADRs have been included, as requested in the AE letter. Descriptions of dose response for specific ADRs have been limited to those which are most likely dose related; no reliable statements could be made about the dose relatedness of others (see Dr. Burkhart's review).

5) **DOSAGE AND ADMINISTRATION**

An opening paragraph describing the fact that the controlled trials all employed a titration scheme, and advising the prescriber to titrate the dose to maximum therapeutic effect (balanced against the principle ADRs) has been added.

The same statement that appears in the Information for patients sub-section about the potential for increased GI tolerance when ropinerole is taken with food has been added.

The maximum daily dose that can be given is described as 24 mg/day (in our proposed labeling, we stated that the firm would need to support this statement with additional clinical experience; we believe they have done so adequately). A statement about lowering l-dopa dose related to ADRs has been added.

BIOPHARMACEUTICS

The division proposed dissolution methodology and specifications to be applied to all dosage strengths of ropinerole. The sponsor requested that different volumes be used depending upon the specific dosage strength being tested (500 mL for dosage strengths below 0.1 mg and 900 mL for dosage strengths of1.0 mg and greater). Dr. Ibrahim of the Division of Pharmaceutical Evaluation I concludes that 900 mL may be used for all dosage strengths. Subsequent discussions between Drs. Baweja and Ibrahim and the sponsor, as described in an e-mail from Dr. Baweja dated 8/14/97, have resulted in the sponsor agreeing to the specifications included in the Approvable letter for all dosage strengths.

CMC

All questions have been satisfactorily answered.

Clinical

The safety update contains additional exposure data at higher doses. Dr. Burkhart's review describes the data in detail; for example, a total of 103 patients were treated with 24 mg/day for 6 months or longer, with a total of 203 patients treated with this dose for any duration. In addition, approximately 41% of the total experience has been at doses greater than 12 mg/day (712 patient years/1740 patient years), with an approximately equal split between early and advance patients (including a similar split in the total exposure at 24 mg/day).

Regarding the dose response, there was not much useful information available in this submission due to a number of factors (small cell numbers, confounding of time and dose, inadequate methods applied to the data). In the face of this outcome, appropriate language has been included in the labeling.

Stratified analyses to evaluate the risk of specific ADRs in cohorts defined by specific factors (e.g., CVD, other concomitant diseases and medications) were not generally able to identify any difference in the risk of developing specific ADRs defined by these strata.

RECOMMENDATIONS

The attached labeling is acceptable. The Approval letter with attached labeling should be sent to the sponsor.

Russell Katz, M.D.

Cc:

NDA 20-658
HFD-120
HFD-120/Katz/Leber/Burkhart/Nighswander

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: September 7, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Requip™(ropinirole HCl) NDA 20-658 Approval Action

TO: File NDA 20-658
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys my endorsement of the Division review team's recommendation that SmithKline Beechman Pharmaceutical's NDA 20-658 for Requip™ (ropinirole HCl) be approved (see also my approvable action memorandum of December 13, 1996).

Issues affecting approval as enumerated in the agency's approvable action letter of January 2, 1997

The approvable action letter of January 2, 1997 noted that ultimate approval of the sponsor's application was contingent upon the firm's agreement to market Requip™ under product labeling developed in accordance with instructions and guidance given in that communication. The approvable action letter also announced that, prior to approval, the firm would have to provide reports of analyses exploring the relationship between the dose of ropinirole administered and the nature of the ensuing clinical response, especially in regard to the incidence of untoward events associated with doses exceeding 12 mg a day. The agency also asked the sponsor to determine whether the presence of cardiovascular disease affected the incidence of postural hypotension (and related phenomena) associated with the use of ropinirole.

Evaluation of information submitted following the issuance of the approvable action letter.

Dr. Rouzer-Kammeyer, Dr. Greg Burkhart and Dr. Russell Katz have provided review documents describing/analyzing information that has been submitted to the NDA file after the issuance of the approvable action letter. None of the 3 describe any fact or finding that would require the agency to rescind and/or modify its determination that ropinirole has been shown to be both safe for use and effective in use.

Dr. Kammeyer's 5/1/97 review calls attention, however, to two matters that are worthy of comment. First, drug regulatory authorities in Finland sought and gained withdrawal of the marketing application for ropinirole in their country because of what they deemed to be inadequate testing and evaluation of a finding of retinal degeneration that occurred in rats assigned to the high dose group in the 2 year lifetime CA study. Although the Division believes the finding should be described in product labeling, it does not believe additional investigation is required. (In fact, a similar finding is reported with pramipexole). Second, the file now contains a report of a 69 year old male who presented with bilateral pleural effusions. The details provided are sparse and the history allows no definite conclusion. Nonetheless, it is conceivable that the pleural effusions and signs of pleural thickening which resolved following ropinirole withdrawal might have been caused by the drug. Whether or not the case is an example of a pleuropulmonary fibrotic reaction of the kind reported to be sometimes associated with ergoline dopamine agonists is unknown, but the possibility cannot be dismissed. Dr. Kammeyer recommends, therefore, that the case be included in product labeling.

In his memorandum of July 24, 1997, Dr. Greg Burkhart, team leader of the Division's safety unit, provides a comprehensive evaluation of safety information submitted by the firm (March 28, 1997) in response to requests enumerated in the agency's approvable action letter.

Dr. Burkhart observes that although the firm went to considerable lengths to comply with the agency's requests, it failed to carry out as comprehensive an assessment as it might have of the role played by factors/covariates affecting (modifying) the incidence of adverse clinical events among ropinirole treated patients. The firm chose to restrict their evaluation to clinical adverse events for which the incidence of ropinirole associated events could be compared meaningfully to the incidence under a

control condition within both of the strata involved in each factor's assessment(i.e., within the stratum with and the stratum without the factor .of interest.). The limitation of this strategy is that it may exclude from consideration clinical events that occur exclusively among ropinirole exposed patients, a result that hardly serves the intent of the analyses requested.

I am not certain, however, as to which clinical events and potential modifiers were actually excluded. In any case, the exclusions led Dr. Burkhart to conduct a review of individual two by two tables to determine if a risk factor, including concomitant drug usage, might have affected the incidence of "confusion, hallucination, and syncope" among ropinirole treated subjects. His review failed to identify any previously undetected relationships.

The firm did not fully comply with agency requests regarding the presentation of safety update exposure information. Again, Dr. Burkhart attempted to overcome this by extrapolating from data that were provided. He calculates that the safety update provides about 500 to 550 additional person years of clinical experience with ropinirole and that more than 400 PD patients have been observed on the drug for at least a year. In toto, therefore, our understanding of ropinirole's risks are dependent upon experience gained from some 1740 patient-years of exposure. Importantly, there are now about 100 patient years at 24 mg/day, the maximum recommended daily dose.

This exposure is partitioned among PD patients that used ropinirole alone (ET or early therapy) or in combination with L-dopa (AT or advanced therapy)

It is Dr. Burkhart's view that the information provided in the post-approvable action period has not identified any new finding or risk that would cause the agency to revise it conclusion that the evidence shows ropinirole to be both safe for use and effective in use. He does concur with the recommendations of Drs. Kammeyer and Fitzgerald that mention be made in labeling of the retinal degeneration observed in high dose rats and with Dr. Kammeyer's suggestion that the case of possible pleural fibrosis be included as well.

Dr. Katz, who led the agency review team, explains in his memorandum of 8/21/97 how and why modifications have been made to the draft labeling that was forwarded to the firm at the time of the approvable action letter.

Conclusions and Recommendations.

Upon review of the findings and information submitted to the NDA file, the Division review team has concluded that the NDA for Requip™ which allows for the marketing of ropinirole under labeling jointly developed by the review team and the sponsor may be approved. I endorse this recommendation.

Paul Leber, M.D.
September 7, 1997

NDA 20-658
cc
HFD-101
Temple
HFD-120
Katz
Burkhart
Rouzer-Kammeyer
Fitzgerald
Steele
Wheelous
Nighswander

MEMORANDUM

DATE: September 18, 1997

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

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

Director
Office of Drug Evaluation I

File, NDA 20-658

SUBJECT: Final Revisions to Requip Labeling

In a memo dated 9/2/97, Dr. Temple asked us to consider including a statement in labeling describing at what time after the initiation of treatment syncopal events had been seen to occur. Further, he had several proposed changes to our draft labeling.

In response, we have added a sentence to the first paragraph of the Syncope sub-section in the Warnings section which describes when these events occurred, and describes the relationship between these events and recent dose changes.

We have added the identical sentence to the second paragraph in the Symptomatic Hypotension sub-section of the Warnings section, and removed statements about orthostatic symptoms from this paragraph.

In the Adverse Reactions section, we have changed the controlled trials ADR tables to included only those ADRs occurring at a rate of greater than or equal to 2%. Those events no longer listed in the table (the ones that had occurred at a rate of 1%), are now included in the list of ADRs occurring in the entire database. We have further collapsed the number of clinical categories in this portion of the ADR section (e.g., Red Blood Cell, Platelet Bleeding/Clotting, and White Blood Cell/Reticuloendothelial are now combined into a Hematologic category).

We have included a statement in this section noting that there were no important differences in ADR rates between men and women.

In response to Dr. DeGeorge's comments about the placement of several statements in the Pregnancy and Nursing Mothers sub-sections, we have made several changes.

First, we have removed any statements about the drug crossing the placenta in animals (the fact that the drug is teratogenic suffices in this regard). In the Nursing Mothers sub-section, have included a statement describing the effect of the drug on prolactin secretion in animals, and the possibility of its preventing lactation. Finally, we included a statement that the drug is excreted in rat milk, and standard (at least identical to pramipexole) language about the possibility/risks of it appearing in human breast milk.

All other indicated changes have been made.

Russell Katz, M.D.

Cc:
NDA 20-658
HFD-120
HFD-120/Katz/Leber/Nighswander/Burkhart/Fitzgerald/Steele

(476)

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair, (HFD-530), NLRC Room 224

From: Division of Neuropharmacological Drug Products HFD-120
Attention: Frederick J. Abramek, Phone: 301-594-5526

Date: 8 August 1995 8/8/95

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: REQUIP NDA/ANDA# IND

Company Name: SmithKline Beecham Pharmaceuticals

Established name, including dosage form: ropinirole HCl, SK&F 101468-A oral tablets

Other trademarks by the same firm for companion products: N/A

Indications for Use (may be a summary if proposed statement is lengthy): symptomatic treatment of Parkinson's disease (tentative)

Initial comments from the submitter (concerns, observations, etc.):
None

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev May.94

Subject: Consult 476 revised

nsult #476 (HFD-530)

QUIP Ropinirole Hydrochloride Tablets

A review revealed no names which sound like or look like the proposed name.

The Committee notes the proposed name has been submitted for review very early in the review process (IND stage). Under such circumstances, the Committee routinely recommends the proposed name be re-evaluated once an NDA has been submitted and the application is closer to approval since the universe of potential sound-alike/look-alike proprietary names is constantly changing.

The Committe has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

D Boring, Chair

NOTE: The Committee believes the established for this product is -

Ropinirole Hydrochloride Tablets

MEMORANDUM

DATE: November 25, 1996

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

TO: File, NDA 20-658

SUBJECT: Supervisory Review of NDA 20-658, for the use of Ropinerole as Mono- and Adjunctive Therapy for Patients With Parkinson's Disease

BACKGROUND

NDA 20-658, for the use of Ropinerole, a D2 agonist proposed as a treatment for patients with either early or late Parkinson's Disease (PD), was submitted by SmithKline Beecham on 12/29/95. The IND for this product was submitted in June of 1988, and was placed on Hold, due to CMC concerns, until March 1991, after which studies proceeded without interruption. Dr. Rouzer-Kammeyer of the Division has reviewed the effectiveness trials (review dated 7/15/96), and Dr. Kun Jin of the Division of Biometrics has reviewed a subset of the effectiveness trials (review dated 10/15/96). Dr. Gregory Burkhart of the Division has reviewed the safety data (review dated 10/11/96). This memo will present a brief overview of the relevant effectiveness and safety information,as adapted from the primary reviews, as well as my recommendations for action on the NDA.

EFFECTIVENESS

The sponsor intends to obtain approval for ropinerole as a treatment for patients with early onset PD (not currently receiving dopa) as well as for patients with poorly controlled PD; in essence, this translates into a claim for mono and adjunctive therapy (regarding concomitant dopa treatment). To support these proposed claims, the sponsor has submitted the results of a total of 10 randomized, controlled trials. Four (4) of the

trials were performed in patients with early (non-dopa treated) PD; 2 of these, Studies 32 and 54, were placebo controlled, while the remaining 2, Studies 53 and 56, were active controlled, in which ropinerole was compared to l-dopa or bromocriptine, respectively. The remaining 6 studies were placebo controlled trials, in which ropinerole was added on to l-dopa. This memo will focus on the 2 placebo controlled early studies, as well as on Study 44 for the late PD patients.

EARLY PD

STUDY 32

This was a multi-national, multi-center, randomized, double-blind, placebo controlled trial in which patients not currently receiving l-dopa treatment were randomized to receive ropinerole or placebo during a 12 week treatment phase.

Patients between the ages of 30-80 who had idiopathic PD at Hoehn and Yahr Stages I-IV (a staging instrument ranging from Stage I-unilateral involvement with minimal functional impairment to Stage V-confined to wheel chair or bed) with bradykinesia and at least tremor, rigidity, or postural instability were considered for enrollment. Patients could have received l-dopa as monotherapy for up to 6 months prior to enrollment, but had to have discontinued this treatment for at least 2 weeks prior to screening. At the time of enrollment, patients were permitted to be receiving other anti-PD drugs (e.g., anti-cholinergics, selegiline, amantadine), with the doses of these treatments having been constant for at least 1 month.

Patients meeting these criteria were to be randomized in a 2:1 ratio to ropinerole or placebo. A titration dosing regimen was employed, with all patients starting at 0.5 mg BID, with subsequent increments of 0.5 mg BID (total daily increment of 1.0 mg) weekly for 4 weeks and then at week 6. Additional increments at weeks 8 and 10 were permitted as well. The maximum daily dose was to be 5 mg BID (total daily dose of 10 mg). Dose decrements were permitted to control dopaminergic adverse events.

Patients were assessed at Weeks 1, 2, 3, 4, 6, 8, 10, and 12. Efficacy

assessment instruments included the Unified Parkinson's Disease Rating Scale (UPDRS), a clinician's global evaluation, and a finger tapping test.

The UPDRS is a scale in 8 parts designed to evaluate the following aspects of PD; 1) Mental function and status, 2) Activities of Daily Living, 3) Motor Examination, 4) Complications of therapy, 5) Clinical fluctuations, 6) Other complications, 7) modified Hoehn and Yahr Scale to assess disease stage, and 8) an Activities of Daily Living (ADL) assessment. Each part is composed of multiple items; items under parts 1-4 are scored from 0-normal, to 4-maximum disability.

The Motor section consists of 14 items, each rated from 0-4, and which includes assessment of both sides of the body, where relevant. The UPDRS, and in particular the Motor Subsection, have often been used as outcomes in studies of treatments for patients with PD.

The clinician's global evaluation was a 5 point scale with 1-Marked Improvement, 3-No Change, to 5-Markedly Worse.

In this study, the Motor section of the UPDRS was designated as the primary outcome measure, which was to be assessed at each visit 2 hours after dosing. The protocol specified the primary analysis to be a comparison between the treatment groups of the rate of responders. A responder was defined as a patient who experienced an improvement on the motor scale of at least 30% compared to their baseline.

The protocol was not specific regarding the method of analysis of the secondary measures.

RESULTS

A total of 63 patients were randomized to treatment at 9 centers in 6 countries, mostly in the UK.

The following table displays the disposition of patients in this study:

	Ropinerole (%)	Placebo (%)
Randomized	41	22
Completed	36 (88%)	19 (86%)

Three (3) and 1 patients withdrew from treatment for adverse events in the ropinerole and placebo groups, respectively, and 2 patients in the placebo group withdrew for insufficient effectiveness. Two (2) patients withdrew from ropinerole for "other" reasons.

There were no important differences between treatment groups at baseline in the factors examined, but there were sporadic differences. For example, 34/41 (83%) of the ropinerole patients entered with a Hoehn and Yahr score of II or less, compared to 14/22 (64%) with these grades in the placebo group. Patients in both groups had carried the diagnosis of PD for slightly greater than 2 years, and use of the following 2 most commonly used concomitant PD medications were distributed as follows:

	Ropinerole (%)	Placebo (%)
Selegiline	8 (20%)	7 (32%)
Amantadine	6 (15%)	8 (36%)

The following results on the primary outcome (Percent responders on the UPDRS Motor Score) are displayed in the table below. The analysis (chi-square test) was performed on the intent-to-treat cohort, utilizing the last observation carried forward data set:

	Ropinerole	Placebo	P-value
Responders	29 (71%)	9 (41%)	0.021

These numbers were devised using a somewhat complicated rule for grading the Motor scale, described as follows. For those measures assessed for both right and left sides, the side with the worst score at baseline was then utilized throughout the study. If both sides had the same score at baseline, the total motor score was calculated for both

sides, and status as a responder was determined on the basis of a showing of a 30% decrease from baseline on either side. Because of the complicated nature of this rule, Dr. Jin performed an analysis of Mean Percentage Change From Baseline in Total Motor Score, with the following results for the LOCF analysis of the intent-to-treat cohort:

	Baseline	Percent Change	P-value
Ropinerole (N=41)	18.6	-43.4%	
Placebo (N=22)	19.9	-21.0%	0.012

Secondary Measures

The following results were obtained for the secondary measures assessed in the trial for the LOCF analysis of the intent to treat population.

Finger Taps

No significant difference between treatments was seen in the Mean Percent Change Form Baseline in the Number of Finger Taps.

Clinician's Global Evaluation

In the Ropinerole treated group, 29/41 (71%) of the patients improved compared to baseline, with 9/22 (41%) of placebo patients improving. The between treatment comparison was significant with a P-value of 0.021.

UPDRS Subscales

No statistically significant between treatment differences were seen on either the Mental or Activities of Daily Living subscales of the UPDRS.

There is considerable discussion in the medical and statistical reviews about an apparent interaction with concomitant medication, specifically

selegiline. Dr. Jin ultimately concludes that a statistical interaction does not exist, though the small numbers may make this conclusion somewhat less than robust.

STUDY 54

This was a multi-center, randomized, parallel group, placebo controlled trial in patients with PD not currently taking l-dopa or dopamine agonists. Patients whose PD corresponded to Hoehn and Yahr stages I-III, who had not received treatment with dopa or dopamine agonists for more than 6 weeks, and who had received no PD medications except selegiline for 4 weeks prior to screening were eligible for enrollment.

Patients were to be entered into a 1 week placebo run-in period, after which they were randomized to ropinerole or placebo (randomization was stratified by selegiline use). All patients had treatment initiated at 0.25 mg TID (total daily dose of 0.75 mg), and then titrated weekly to a maximum of 8 mg TID. All patients were to be titrated to at least 1.5 mg TID (total daily dose of 4.5 mg). The study was to be 6 months long. In this trial, if the investigator felt that the patient had not received a maximal response even if the maximum dose of study drug was achieved, the patient could receive open label l-dopa. Patients who received l-dopa rescue were to have their last pre-l-dopa assessments carried forward in the LOCF analysis.

The primary outcome measure in this trial was the mean percent reduction from baseline in the UPDRS Motor score. Secondary measures were to include the responder rate (responder defined as in the previous study), the Clinical Global Impression, the number of patients receiving l-dopa rescue, the time to l-dopa rescue, and the number of patients with, and time to, insufficient response (presumably related to the need for l-dopa rescue).

The Clinical Global Impression appears to have consisted of 2 sub-parts: *Severity of Illness*, rated from 1-Normal to 7-Among the most extremely ill (0 for Not Assessed), and *Global Improvement*, symmetrically centered on 4-No Change, with 1-Very Much Improved and 7-Very Much Worse. For

this variable, the protocol stated that the percent of patients in each class of the CGI will be compared between the treatment groups and be assessed by a Mann Whitney analysis.

RESULTS

A total of 241 patients were randomized at 25 centers in the United States. The following chart displays the disposition and progress of patients in this study:

	Ropinerole	Placebo
Randomized	116	125
Completed		
Week 24	72 (62%)	73 (58%)

(Here, a completer is defined as a patient who was treated for 24 weeks who did not receive rescue l-dopa; I.e., those patients receiving rescue dopa were not considered completers.)

The following chart (Table 10.1.1 from Dr. Jin's review, page 21) displays the disposition of dropouts:

	Ropinerole	Placebo
L-dopa rescue only	5	29
Sponsor's dropouts only	28	15
Both	2	1
Total	35	45

Approximately 1/2 of the patients in each group were concomitantly

treated with selegiline.

The following presents the results of the analysis of the primary analysis, Percent Change From Baseline in Mean UPDRS Motor Score for the LOCF Analysis of the intent to treat cohort:

	Baseline	Percent Change	P-value
Ropinerole (N=107)	17.9	-22.0%	
Placebo (N=118)	17.7	+3.7%	<0.05

The numbers in this chart conform to those used by Dr. Jin, based on his imputation of missing data. He utilized a rule for imputation different from that used by the sponsor. The numbers here are almost identical to those used by the sponsor.

The sponsor detected, by at least one analysis, a significant treatment by selegiline interaction (patients in the placebo group receiving selegiline appeared, on average, to do significantly worse than placebo patients who were not receiving selegiline, the latter of whom actually slightly improved compared to baseline). Dr. Jin determined that this interaction appeared to be the result of the inclusion of 6 patients (3 ropinerole who were not receiving selegiline, 3 placebo patients who were) who were determined to be outliers (see his bootstrap analysis on pages 14-17). Re-analysis of the primary outcome measure with these 6 patients excluded yielded slightly different estimates of the percent change from baseline and, again, a statistically significant difference between treatments ($p<0.001$), as well as a resolution of the apparent treatment by selegiline interaction.

DROPOUTS

Because of the relatively large number of patients who did not complete the trial, Dr. Jin undertook an analysis of the effects of these censored patients on the estimate of the treatment effect as measured by the primary outcome variable. This review revealed little to no change in the

within group estimate of the treatment effect in both treatment groups in the completers at Weeks 12 and 24. The sponsor also performed analyses of the trial at the point at which 70% of patients still remained in the trial, as well as an analysis of the 24 week observed cases. These additional analyses yielded results that were essentially the same as those of the LOCF, ITT analysis.

SECONDARY MEASURES

Responder Rate

The following chart displays the results of the analysis of the proportion of responders in each treatment group:

	Ropinerole (N=107)	Placebo (N=118)	Odds Ratio
Responders	50 (47%)	23 (20%)	4.45

These results are statistically significant, although there was a statistically significant treatment by selegiline interaction, with a significant treatment effect seen only in the selegiline treated group.

CGI

A total of 38/115 (33%) ropinerole patients experienced improvement at endpoint compared to 15/123 (12%) of placebo patients, a statistically significant difference.

Proportion of Patients requiring l-dopa rescue

A total of 13/116 (11%) of ropinerole patients required rescue, as opposed to 36/125 (29%) of placebo patients, a statistically significant difference.

Proportion of Patients with an Insufficient Response

A total of 14/116 (12%) ropinerole patients were judged to have had an

insufficient response, compared to 37/125 (30%) of placebo patients, a statistically significant difference.

Of the secondary measures described, only Responder Rate was seen to have a selegiline by treatment interaction.

Additional Studies

Two other studies were performed in patients with PD who were not concurrently receiving l-dopa. These studies were both multi-national, randomized, double blind, parallel group, active controlled trials. Study 53 was a 6 month trial comparing ropinerole to bromocriptine, and Study 56 was a 6 month study comparing ropinerole to L-dopa. Both trials utilized a titration design, with a maximum proposed dose of 8 mg TID. In both trials, the primary outcome was the change from baseline in UPDRS Motor score.

Study 53

In this trial, 335 patients (ropinerole 168, bromocriptine 167) were randomized at 37 centers in 13 countries. In this study, according to the sponsor, on UPDRS Motor score, there was a significant treatment by selegiline interaction, with ropinerole patients not receiving selegiline having a statistically significant improvement compared to bromocriptine patients, and no significant between treatment difference in the selegiline stratum. A statistically significant difference favoring ropinerole was also seen in the non-selegiline stratum for the comparison of responders, defined as in the earlier described studies. The same pattern of response was seen for the proportion of patients with improvement on the CGI, and there was no statistically significant difference in the proportion of patients requiring l-dopa rescue.

Study 56

A total of 268 patients (ropinerole 179, l-dopa 89) were randomized in a 2:1 ratio at 30 centers in 7 countries. No statistically significant differences between treatments on mean change from baseline in UPDRS Motor score or responder rate were seen, although on both measures, l-

dopa patients were favored numerically.

LATE PD

STUDY 44

This was a multi-center, randomized, double blind, parallel group placebo controlled trial in patients with PD receiving dopaminergic therapy and whose PD was not adequately controlled. The study duration was 6 months.

Patients were first screened in a 1 week placebo run-in, and then were randomized in a 2:1 ratio to ropinerole or placebo (randomization was stratified by concomitant selegiline use). Patients were required to have been on a stable dose of Sinemet, Sinemet CR, or both, for at least 4 weeks prior to the study; the same rule applied to those patients also receiving selegiline.

All patients were to be started on a dose of 0.25 mg TID (a total daily dose of 0.75 mg). Dose increments were to occur weekly to a maximum of 8 mg TID; all patients were to achieve a dose of at least 2.5 mg TID.

Once a dose of 2.5 mg TID was reached, there was to occur a mandatory reduction in the dose of Sinemet. The first reduction in dose was to be a reduction of 1/2 or 1 tablet, with each subsequent increase in study drug accompanied by a 1/2 or 1 tablet decrease in the dopaminergic therapy. If PD symptoms were not adequately controlled, the study medication was to be increased according to the algorithm, but the l-dopa dose was not to be decreased.

In the event of dopaminergic toxicity, there was a prescribed sequence of maneuvers that were to be followed. First, the l-dopa unit dose was to be lowered while maintaining the study medication dose. Then, if this was not successful, the frequency of the l-dopa was decreased, while maintaining the study drug constant. If this failed to ameliorate the adverse events, the study medication was to be lowered. If efficacy was lost, the l-dopa dose could be re-instated to baseline levels or even increased.

The primary outcome in the protocol was the degree of the reduction in the l-dopa dose. Based, at least in part, on discussions with the Division, the sponsor decided that in order for a clinically relevant effect to be documented, they would have to establish that the degree of l-dopa dose reduction was not accompanied by a loss of control of PD symptoms. Toward that end, the primary outcome was changed to a comparison between treatments of the proportion of patients who both tolerated a 20% reduction in the l-dopa dose **and** who experienced a 20% reduction in the proportion of awake time spent in the "off" condition (a period during which patients are particularly immobile). For purposes of the analysis, the only l-dopa reductions considered were those that were mandated by the protocol; i.e., dose reductions undertaken to control dopaminergic adverse events were not included. To document the amount of "off" time, patients were to fill out a diary card for 2 days during the week prior to a study visit. On these cards, the day was broken into 30 minute intervals, and the patient was to document whether, for each 30 minute interval, they were "on", "off", or asleep.

Secondary measures assessed included the proportion of patients with a 20 % reduction in l-dopa dose, the proportion of patients with a 20% decrease in the amount of awake time spent "off", CGI (method of analysis undefined), the mean reduction in l-dopa dose, the mean reduction in awake "off" time, and the number of patients who required reinstatement of their baseline dose (or greater) of l-dopa.

RESULTS

A total of 149 patients were randomized at 16 centers in the United States The following chart displays the disposition of patients:

	Ropinerole	Placebo
Randomized	95	54
Completed	74 (78%)	35 (65%)

Approximately half the patients in each treatment group were being treated concomitantly with selegiline.

The following chart displays the results of an LOCF analysis of the intent to treat cohort of the primary outcome, the Proportion of Responders, as defined above:

	Proportion of Responders	P-value
Ropinerole (N=94)	26/94 (28%)	
Placebo (N=54)	6/54 (11%)	<0.05

Similar results were seen for an analysis performed on the data at the time of 70% retention in the trial, as well as for other analyses. Dr. Jin in his review states that a significant treatment by selegiline interaction was seen again, which appeared to suggest that a significant treatment effect was seen only in the non-selegiline group (28% percent responders in the ropinerole group and 0% in the placebo group), but not in the selegiline group (27% in the ropinerole patients and 20% in the placebo patients). Dr. Jin suggests that this interaction was likely an artifact, related to their being zero responders in one group.

Secondary Outcomes

Proportion of Patients With a 20% or Greater Decrease in L-Dopa Dose

A total of 46/94 (49%) of ropinerole patients experienced such a change, compared to 9/54 (17%) of placebo patients, corresponding to an odds ratio of 6.1, which was statistically significant.

Mean Percent Change From Baseline in L-Dopa Dose

The total daily dose of L-Dopa decreased by 19.4% in ropinerole treated patient, compared to a decrease of 3% in placebo patients, a difference that was highly significant ($p<0.001$).

Proportion of Patients With a 20% or Greater Decrease in Percent of Awake Time Spent "Off"

A total of 52/88 (59%) of ropinerole patients met this criterion, compared to 23/52 (44%) of placebo patients, a difference that was not statistically significant (odds ratio 1.8, 95% CI of 0.89, 3.70).

Mean Percent Awake Time Spent "Off"

The following chart displays the baseline, endpoint, and % Change From Baseline for this variable:

	Ropinerole	Placebo
Baseline	39.3	43.4
Endpoint	29.3	37.8
% Change	+9.2	+4.3

Here, ropinerole patients appeared to have spent more awake time in the "off" condition. However, Dr. Jin and the sponsor agree that these results were influenced by the contribution of a few outliers who had very low baseline values, and subsequent very large positive changes. The sponsor attempted to correct for this by performing a covariate analysis that resulted in a statistically significant treatment difference in favor of ropinerole. Dr. Jin instead calculated the median % Change From Baseline in Awake Time Spent "Off", because the means were too sensitive to the outliers. This analysis revealed the median % Change Spent in "Off" for ropinerole patients to be approximately decreased by 30%, compared to a 15% decrease in placebo patients, a difference that clearly favors the ropinerole group.

CGI

A total of 55/94 (59%) of ropinerole patients were categorized as improved, compared to 17/53 (32%), a statistically significant difference. Much of this difference, arose from the following differences: 23/94 (25%) of ropinerole patients were rated Much Improved, compared to 6/53 (11%) of placebo patients, while 8/94 (8.5%) of ropinerole patients were Minimally Worse, compared to 11/53 (21%) of placebo patients.

Proportion of Patients Reinstated to Baseline L-Dopa Dose or Above

A total of 22/95 (23%) of ropinerole patients had to have their l-dopa dose re-instated, compared to 23/54 (43%) of placebo patients, a statistically significant difference ($p<0.001$).

In addition to Study 44, the sponsor presented the results of 5 other controlled trials in patients receiving concomitant dopaminergic therapy, and whose PD was not adequately controlled. They were all double blind, randomized, parallel group, placebo controlled trials.

Following is a brief description of these additional studies.

Study 30

This was a 2 center, multi-national (UK, France) trial of 12 weeks duration in which ropinerole dose was titrated to a maximum dose of 4 mg BID (total daily dose of 8 mg). The primary outcome measure was the proportion of patients who experienced at least a 30% decrease in the percent of awake time spent "off".

A total of 46 patients (ropinerole 23, placebo 23) were enrolled. In the ropinerole group, 65% of patients were classified as responders, compared to 39% in the placebo group, a difference that failed to achieve statistical significance. Significantly more patients improved on the CGE on ropinerole; 78% vs 35%. The ropinerole group was again numerically, though not statistically, favored on the percent of awake time spent "off", as was also the case for the percent change from baseline in UPDRS Motor score.

Study 34

This trial was conducted at 8 centers in 2 countries (UK, Israel) of 12 weeks duration. The design was similar to Study 30, though with a maximum dose of 5 mg BID. Investigators were to decrease the l-dopa dose after a certain study drug dose was achieved.

The primary outcome was the proportion of patients achieving a decrease in l-dopa dose of at least 20%. Also evaluated was the mean change in l-dopa dose.

A total of 68 patients (ropinerole 46, placebo 22) were randomized. A total of 20/41 (49%) of patients in the ropinerole group were considered responders, compared to 8/22 (36%) in the placebo group, a difference that was not significant. The mean change from baseline in l-dopa dose in ropinerole patients was 22% compared to a 19% decrease in placebo patients, and 67% of ropinerole and 55% of placebo patients improved on the CGE. None of these differences were statistically significant.

Study 36

This was a multi-center, multi-national study in which 29 patients (ropinerole 20, placebo 9) were treated for 12 weeks. The primary outcome was the proportion of patients experiencing a decrease in "off" time of at least 20%. A total of 11/19 (58%) of ropinerole and 4/9 (44%) of placebo patients met this criteria, a difference that was not significant.

Study 38

This was a multi-national study in which 36 patients (24 ropinerole, 12 placebo) were treated for 12 weeks. The primary outcome was the proportion of patients who experienced improvement in the amount of awake time spent "off". No significant difference was detected, although the results numerically favored ropinerole.

Study 40

This was a randomized controlled trial in which patients were randomized to either 0.5 mg BID, 1.0 mg BID, 2.0 mg BID, or placebo. The trial duration was 9 weeks; 1 week placebo run-in, 3 week titration, 4 week treatment phase, and 1 week follow-up. The primary outcome was the reduction in the proportion of awake time spent "off" for each week of the treatment phase. A total of 125 patients (4 mg-30, 2 mg-32, 1 mg-32, Pbo-31) were

enrolled in 15 centers in the United States.

Although results for the primary outcome, and other secondary outcomes numerically favored the 4 mg BID dose group, no statistically significant differences were seen.

SAFETY

Experience in a total of approximately 1514 subjects was included in the NDA. Included in this total are 103 (or 104) healthy subjects and 47 PD patients in Phase 1 studies, and 1364 PD patients in Phase 2/3 studies. The total number of PD patients exposed to ropinerole for greater than 6 months was 972, and the number of patients treated for at least 1 year was 599.

A total of 176/1364 (13%) of the PD patients achieved a dose of 24 mg/day, the highest dose recommended by the sponsor in its proposed labeling. A total of 352 early therapy PD patients received a mean daily dose of at least 4.6 mg for at least 6 months, as did a total of 423 late PD patients.

DEATHS

In the development program, a total of 32 deaths occurred (or the event leading to death began) within 30 days of cessation of treatment with study drug (ropinerole, bromocriptine, placebo-no deaths were reported in patients randomized to l-dopa as a control). A total of 15 of these deaths occurred in ropinerole treated patients, 6 of which occurred during controlled trials. While it is difficult to make a direct comparison of mortality rates between ropinerole and bromocriptine or placebo in the controlled trials for the entire database, Dr. Burkhart in his review (Pages 25-26) has calculated 6 month mortality risks for ropinerole and bromocriptine (1.4/100 patients and 2.1/100 patients, respectively) in Study 043, a 6 month controlled trial in late PD patients, and for Study 053 (0.6/100 patients and 3.4/100 patients, respectively), a 6 month study in early patients.

For the overall PD database (including randomized, blinded, controlled and open, uncontrolled studies) Dr. Burkhart has calculated the following mortality rates for ropinerole, bromocriptine, and placebo:

	Rate/1000 Patient Years		
	Ropinerole	Bromocriptine	Placebo
Early patients	7.8	34.5	28.6
Late Patients	16.9	31.8	26.0

According to Dr. Burkhart, 12 of the 15 ropinerole deaths could have been considered to have been cardiovascular in origin. Examination of these cases revealed no obvious relationship to dose (deaths occurred at doses as low as 1.5 mg/day, although most occurred at doses of at least 6-9 mg/day) or duration (deaths occurred from 1 week after 1 day of treatment to up to 1 year). Similarly, no obvious drug related syndrome emerges, although it is fair to say that, of the 12 described in some detail by Dr. Burkhart, many deaths were attributed to MI for which there was no evidence to support this diagnosis, and in patients with no prior history of cardiovascular disease. In at least 1 case, a patient suffered a witnessed syncopal episode; she died several weeks later, presumably sometime after a fall in which she bruised her leg, and was shortly thereafter diagnosed with deep vein thrombosis. Several days later, she died in her sleep.

DISCONTINUATIONS

Early patients

A total of 140/515 (27%) of early PD patients discontinued treatment with ropinerole as of 5/31/95. This compares to 23% of the placebo patients, 17% of l-dopa patients, and 28.5% of bromocriptine treated patients (again, it is not necessarily the case that all 140 of the ropinerole patients discontinued during a controlled trial; an unknown percentage may have discontinued during open [extension] protocols).

The comparative rates of discontinuation due to adverse events in this same population are as follows:

Ropinerole	Placebo	L-Dopa	Bromocriptine
88/515 (17.1%)	19/147 (13%)	14/89 (15.7%)	25/167 (15%)

As Dr. Burkhart notes in his review (page 29), the risk of (all cause) discontinuation in Study 54 rises sharply (and separates from the risk of discontinuation in placebo patients) after week 10, and approaches the (relatively constant) rate in placebo patients by week 20. Because this is a titration study, the effects of duration of treatment and/or dose on this rate of discontinuation cannot be isolated (and the NDA does not report daily dose at time of discontinuation). However, by protocol, most patients were to have achieved a dose of at least 4.5 mg/day by week 10.

Late Patients

A total of 249/849 (29%) of late PD patients discontinued treatment with ropinerole; the comparative rates were placebo-39%, bromocriptine-22%. The following were the rates for discontinuation due to adverse events:

Ropinerole	Placebo	Bromocriptine
147/849 (17.3%)	24/151 (16%)	29/188 (15.4%)

Again, as with the early patients, we cannot be sure of the distribution of ropinerole patients treated under controlled and uncontrolled conditions.

Again, Dr. Burkhart examined the risk over time for (total) discontinuation, this time using data from Study 44. In this trial, the risk in the placebo group rises relatively sharply after week 10, while the risk over time for discontinuation in the ropinerole group varies, but minimally, and not coherently as a function of time.

Serious Adverse Events Leading to Discontinuation

A total of 26/515 (5%) of early ropinerole patients experienced an adverse event leading to discontinuation of treatment that was characterized as serious; the corresponding rate for placebo was 5.4%. According to Dr. Burkhart, of the 26 serious ropinerole AEs, 8 were cardiovascular. These 8 included 4 cases of bradycardia, 2 cases of hypotension, and 1 case each of MI, PVC, V Tach, Bigeminy, A Fib, SVT, Sick Sinus Syndrome, Orthostasis, and chest pain (a given patient may have had several of these events). Duration of treatment ranged from 6-274 days with 6 of the cases occurring after at least 100 days on treatment. The doses at which these events occurred are not easily obtainable from the sponsor's tables or the safety review. Two (2) of the above cases were also associated with syncope (one of these was associated with sick sinus syndrome, one with sinus bradycardia). Of the 8 patients in the placebo group with serious AEs, 4 had events related to the cardiovascular system (Myocardial ischemia, angina, V Tach, MI).

The following Investigator Verbatim terms were used to describe the remaining 18 serious AEs that led to discontinuation in the ropinerole group: CVA (2), hypokinesia, dyskinesia, convulsion, benign brain tumor, esophageal cancer, hematuria, hallucinations, thrombophlebitis, arthritis, back pain, abnormal gait, vertigo, confusion, headache.

A total of 45/849 (5.3%) of late ropinerole patients experienced an adverse event leading to discontinuation of treatment that was considered serious; the corresponding placebo rate was 9/151 (6%). Of these 45 serious ropinerole discontinuations, 10 patients had events referable to the cardiovascular system. These 10 included 4 cases of hypotension (2 orthostatic), 3 cases of hypertension (1 listed as hypertensive crisis), 2 cases of syncope and 1 case each of chest pain/tightness, congestive heart failure, arrhythmia, SA block. The duration of treatment at the time of discontinuation ranged from 1-275 days. Of the 9 placebo discontinuations, 2 patients appeared to have events referable to the CV system; MI and a flutter/fib.

The following investigator terms were used to describe the events in the remaining 36 patients that were considered serious and led to discontinuation of ropinerole: hallucinations (11), worsening PD (7),

dyskinesia (7),depression (4), psychosis (4), confusion (3), anxiety (3), delirium (2), gangrene (2), and 1 case each of nausea, dystonia, CVA, anemia, vomiting, akinesia, prostate CA, shoulder pain, subarachnoid hemorrhage, ataxia, sepsis, agitation, ulcer, polymyalgia rheumatica, attempted suicide, and overdose.

Other Adverse Events Leading to Discontinuation

The most common reasons for discontinuation from all studies in the 515 early PD patients treated with ropinerole were Nausea (4%), Hallucinations (1.7%), Vomiting (1.7), and dizziness (1.4%). Other reasons for discontinuation, all in fewer than 1% of patients, included syncope, dyskinesia, anxiety, headache.

In controlled trial 54, adverse events associated with discontinuation seen at an incidence that was greater than both 1% and that of the placebo group included, in decreasing frequency, nausea, dizziness, somnolence, bradycardia, palpitation, and dyspepsia.

The most common reasons for discontinuation from all studies in the 849 late PD patients treated with ropinerole were hallucination (3.2%), nausea (2%), dyskinesia (1.4%), confusion (1.3%), vomiting, dizziness, and worsening PD (1.2%). Postural hypotension was reported as being the reason for discontinuation in 5 patients (0.6%).

In controlled trial 44, the following adverse events were seen in 2 patients (all other events associated with discontinuation were seen in only 1 patient): dyskinesia, vomiting, confusion, depression, and nervousness. The incidence of these AEs was greater than the placebo incidence of these events in this trial.

Other Serious Adverse Events

Of 1423 patients exposed to ropinerole, the most common serious events seen were, in order of decreasing frequency: injury (2.7%), poor therapeutic response (1.9%), neoplasm, CNS events (including amnesia, confusion, delirium, depression, paranoid reaction, and psychosis), arrythmia (including bradycardia, extrasystoles, a fib, SVT, v tach, and

palpitation), and syncope, the last occurring in 1% of patients.

According to Dr. Burkhart, a number of adverse events reported as serious are worthy of mention. These included 2 patients with skin reactions, 1 patient with a seizure, 3 patients with hematologic disorders, 3 patients with GI bleeds, and 4 patients reportedly with renal failure. Review of the summaries of these cases provided by Dr. Burkhart reveals that for the significant majority of these cases, other causes for the events could be identified, or insufficient data was available on which to base a judgment about causality. One patient who was diagnosed with life threatening thrombocytopenia, which apparently followed a viral illness, is of concern, though there was no follow-up or bone marrow.

One patient was reported to have had persistently elevated CPK (maximum of 944 IU/ml-ULN=200 IU/ml) She was asymptomatic, and had normal EMG. No muscle biopsy was performed, and the patient continued on treatment with ropinerole.

All Adverse Events

Many adverse events were seen more frequently in ropinerole treated patients than in placebo patients. In the 515 early PD patients, the most common events seen were nausea (48%), dizziness (24%), somnolence (22%), headache (13%), and vomiting and insomnia (12%). The most important adverse event seen at an incidence greater than placebo was syncope, which was reported to have occurred in 35/515 (7%), compared to 2/147 (1.4%) of placebo patients.

In placebo controlled trials in 157 early PD patients, syncope was reported in 11.5% of patients, compared to 1.4% of 147 placebo patients. Postural hypotension was seen in 6.4% of ropinerole patients, compared to 4.8% of placebo patients.

In the 849 late PD patients, the most common adverse events seen were dyskinesia (26%), nausea (26%), dizziness (19%), and worsening PD (16%).

In placebo controlled trials in 298 late PD patients, syncope was reported in 3.4% of patients, compared to 1.3% of 151 placebo patients. The

incidence of postural hypotension in the ropinerole patients (11.1%) was lower than the corresponding placebo rate (13.2%).

Syncope/Orthostatic Hypotension

In clinical pharmacology studies, 9/110 (8%) of healthy volunteers experienced orthostatic hypotension or were so symptomatic on standing that blood pressure was not measured; in 8/9, there was an associated bradycardia. One of the 9 subjects experienced 26 seconds of asystole associated with orthostatic hypotension upon standing 1 hour after a 1.0 mg dose. Of the 47 patients with PD in Phase 1 studies, there were 2 episodes of orthostatic hypotension. In general, in Phase 1 studies, ropinerole caused a dose related decrease in standing BP, peaking at 1 and 2 hours after dosing.

In Study 54 (early PD patients), syncope was one of the 3 most common reasons for discontinuation, and syncope/orthostatic hypotension accounted for 6/22 adverse events reported as serious in ropinerole treated patients in this study. In addition, syncope was one of several adverse events which occurred at an incidence of >5% and more than twice as frequently as in the placebo group. Of these latter events, syncope had the greatest difference in risk compared to placebo: 10.3% vs 1.6%.

In Study 44 (late PD patients), syncope was not among the serious adverse events reported, nor did it occur at >5%. Indeed, across all placebo controlled trials in late PD patients, syncope the incidence of syncope was 3.2%, compared to 1.2% in placebo treated patients.

These findings (orthostatic hypotension/syncope associated with bradycardia) are consistent with findings seen in animals, which the sponsor suggests is related to presynaptic inhibition of noradrenaline release.

The findings in early PD patients are of concern, in particular because patients with significant cardiovascular disease were excluded from trials (as were patients with significant CV disease and late PD). While this would not stand as an absolute bar to approval, labelling would need to explicitly state the incidence and characteristics of

syncope/hypotension and bradycardia associated with standing, and the lack of information about the potential occurrence and/or effects of these events in patients with significant cardiovascular disease. It should be noted, however, that mortality in both PD populations was less in ropinerole treated patients than in the control groups.

SUMMARY

The sponsor has submitted the results of numerous studies in PD patients who were and were not receiving concomitant dopaminergic treatment. A detailed review of Studies 32 and 54, placebo controlled trials in patients not receiving dopaminergic therapy revealed statistically significant differences between ropinerole and placebo patients in the protocol specified primary outcomes related to the Motor scale of the UPDRS; secondary measures including global scales, time to l-dopa rescue, etc., were also, in general, nominally significant.

In Study 44, a placebo controlled trial in PD patients receiving concomitant Sinemet or Sinemet CR, there was also a statistically significant treatment difference in favor of ropinerole on its primary outcome, a comparison of the proportion of patients who were classified as responders. In this study, a responder was a patient who experienced a decrease in l-dopa dose of at least 20% **and** a decrease of at least 20% in the amount of awake time spent in the "off" state. Dr. Jin has raised objections to this compound outcome in his review. His view is that because the difference between drug and placebo on the proportion of patients with a 20% or greater decrease in l-dopa dose was so great in favor of ropinerole, the compound outcome still would have been positive even if a considerable proportion of ropinerole patients did worse than placebo patients with regard to the amount of wake time spent "off". In such a case, the compound outcome would not have served its purpose, which was to ensure that a decrease in l-dopa dose was accompanied by a clinically meaningful effect. To satisfy himself that, at least, the ropinerole patients were not having their l-dopa dose lowered at the expense of decreasing control of their PD symptoms, he concluded that there is no evidence that ropinerole patients were worse (as measured by reduction in awake time spent "off") than placebo patients. In addition, there was a significant effect on the Clinician's Global Improvement

score, as well as for the number of patients reinstated to their original l-dopa dose.

It is of some interest to note the existence of several studies, 2 in early and 5 in late PD, which, generally, did not distinguish ropinerole from controls. The 2 studies in early patients were large studies, but were active control trials; the lack of statistically significant differences between ropinerole and controls in these studies is not terribly worrisome. Neither of the studies documented statistically significant differences in favor of the control.

The 5 remaining studies were all placebo controlled. Although, in general, statistical significance was not achieved, the studies were all relatively small (enrollment in the ropinerole groups ranged from 20-46), and there was consistent numerical superiority in the ropinerole groups compared to the placebo patients on most outcomes assessed. For these reasons, I do not believe that these studies should raise serious concerns about the effectiveness of ropinerole.

Of some passing interest were the hints of treatment by selegiline interactions in a number of studies. Perhaps a more comprehensive evaluation of this issue might be worthwhile, although it does not appear to be particularly clear or problematic at this time.

Regarding the safety of ropinerole, most adverse events were expected, given its pharmacologic class and presumed mechanism of action. Not unexpectedly, typical signs of dopaminergic excess were seen to be more frequent in the studies in which ropinerole was added to a background of Sinemet.

The one adverse event of concern is the occurrence of syncope/hypotension and bradycardia associated with standing, which appeared to be a more significant problem in patients not receiving concomitant dopaminergic therapy than in those who were. The problem is particularly worrisome given that patients with significant cardiovascular disease, and therefore who might be presumed to be more vulnerable to these effects, were excluded from the trials. For this reason, we cannot say how a population of PD patients who do have CV

disease (undoubtedly a significant proportion of the entire PD population) will tolerate the treatment. Although I do not believe that the absence of this evidence should preclude approval, I do believe that the labelling should make explicitly clear the concerns about these adverse events, and our ignorance about the occurrence and/or consequences of these events in the (presumably large) proportion of PD patients with significant cardiovascular disease.

Of more concern, however, is the question of the total patient exposure to effective doses of ropinerole. Given that the effectiveness trials were all of a titration design, we cannot state unequivocally what the "effective dose" is; we can only conclude that a particular treatment strategy is effective. However, this strategy has resulted in patients having been exposed to a range of doses, and while the absolute number of patients exposed to ropinerole in the development of the drug appears reasonably large, the exposure at the higher range of doses utilized in the controlled trials is rather meager. For example, although the reviews do not specifically address this point, it appears that about 73% of the patients in Study 32 achieved doses of at least 6 mg/day, with at least 32% (and perhaps a much greater percentage) of all patients achieving doses of greater than 9 mg/day, while in Study 54, the mean dose was 15 mg/day. Examination of the total patient exposure by dose for these early PD patients reveals only 129 patients have received, by the cutoff date of 5/95, doses of 12 mg/day or greater for at least 6 months. Similarly, although the distribution of doses achieved in Study 44 is not immediately obvious, only 179 late PD patients received 12 mg/day or greater for at least 6 months.

While I have seen nothing in the database that would preclude the application being judged Approvable, I believe that the sponsor should be required to explicitly describe the distribution of doses achieved in these 3 controlled trials. Presumably, this will permit us to better judge how many patients in the entire database received daily doses equal to or greater than those achieved in the controlled trials. Additionally, of course, it is presumed that additional exposure at relevant doses would have accumulated since the NDA cutoff date of 5/95.

RECOMMENDATIONS

The sponsor should be issued an Approvable letter and the attached draft labelling. The letter and labelling should highlight the fact that nothing is known about the occurrence/risks of syncope/hypotension and bradycardia associated with standing in PD patients with significant underlying cardiovascular disease. In addition, the sponsor should be requested to make explicit the distribution of doses achieved in the controlled trials.

Russell Katz, M.D.

Cc:
NDA 20-658
HFD-120
HFD-120/Katz/Leber/Rouzer-Kammeyer
HFD-120/Burkhart/Knudsen/Nighswander
HFD-710/Jin/Sahlroot

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 13, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 20-658, Requip™ [ropinirole HCl tablets]

TO: File NDA 20-658
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys my endorsement of the review team's unanimous recommendation that the NDA 20-658 Requip™ Tablets, Smith Kline Beecham's brand of ropinirole, be declared approvable.

Introduction/background

Ropinirole is a dopamine agonist intended for the management of the signs and symptoms of idiopathic Parkinson's Disease (PD). By way of background, direct acting dopamine agonists have been used in the treatment of PD since the mid-1970's both as monotherapy (typically early in the course of PD) and as adjunctive treatment to l-dopa/carbidopa (among patients failing to respond adequately to the latter). Marketed members of the dopaminergic pharmacologic class include bromocriptine, pergolide and lisuride[1]. An application for yet another dopamine agonist,

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ON ORIGINAL

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[1] Lisuride, however, does not carry a claimed indication for use in PD

is currently under review[3].

Although I am unaware personally of any results of comparative clinical studies to support the belief, it is generally held that the dopamine agonists are, the differences in their milligram potency and specific receptor affinities aside, largely indistinguishable in regard to their clinical effects, both therapeutic and untoward [4].

It is noteworthy that the Division's reviews of the Requip™ and the Mirapex NDA's were carried out contemporaneously (the two applications were submitted to the agency within days of each other). Although the review team's assessment of the reports made to each NDA has been considered entirely from the perspective of whether or not they provide the evidence needed to support the marketing of a new drug, the strategies of assessment applied to the review of the evidence and the approach taken in developing the form and structure (not content) of product

labeling for the two products understandably have much in common.

Effectiveness

The reports submitted to the Requip™ NDA provide "substantial evidence" of ropinirole efficacy as a treatment for the signs and symptoms of Parkinson's Disease[5]. The evidence deemed substantial derives from studies that compared ropinirole to placebo both in patients with early (not concurrently using l-dopa/carbidopa) and in those with more advanced disease (using l-dopa carbidopa but not, despite the administration of maximally tolerable doses of the latter, having a fully satisfactory response.).

As the primary review documents detail, the evidence from each of the sponsor's studies is not of uniform strength or probative force; however, taken in aggregate, the data unequivocally establish (from a proof of principle perspective) that ropinirole has a beneficial effect on the signs and symptoms of Parkinson's disease.

Early PD

Of the 4 studies[6] conducted with early PD patients, both placebo controlled trials, **Study 32** (a 12 week long, nine center, non-USA (most in UK), RCT of some 63 subjects, 41 of whom were titrated to a **10 mg** maximum daily dose of ropinirole) and **Study 54** (a 24 week long, 25 center, USA, RCT of some 241 subjects, 116 of whom were titrated to a 24 mg maximum daily dose of ropinirole) achieved statistical significant differences on their primary outcome variables (the variables were not identical, but each was derived from changes observed on the United Parkinson's Disease Rating Scale; **UPDRS**) favorable to ropinirole. These

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[5] The primary reviews of the clinical effectiveness data were conducted by Dr. Rouzer-Kammeyer [7/15/96] and Dr. Kun Jin [10/15/96] did the statistical analysis; the overall findings are summarized in Dr. Katz's supervisory overview [11/25/96]

[6] Studies 32 and 54 employed a placebo control, Study 53 relied upon bromocriptine and Study 56 used l-dopa as the comparator treatment..

two studies, although nominally evaluating patients with early PD, not only differed in their entry and exclusion criteria, their maximum dose and their duration, but, in all likelihood, in how they were conducted. (e.g., there was a much higher non-completion rate in the longer US study). The point made is that although each provides proof of principle of ropinirole efficacy as a treatment of early PD patients not being treated with l-dopa, their observations are not suitable for pooling if the intent is to gain a single generalizable estimate of the benefits and risks of ropinirole use (see also the discussion on safety for use).

Late PD

The sponsor's NDA provides results of 7 completed trials[7] bearing on ropinirole use in PD patients who, despite receiving maximally tolerated doses of l-dopa/carbidopa, were not gaining as satisfactory response to the combination as they once had. The sample of PD patients admitted to these trials should not be viewed as a subset of Parkinson's Disease patients, however, but as a sample from a stage of the disease that occurs in virtually every PD patient after several years or so (i.e., typically 3 or more) of successful treatment with l-dopa/carbidopa.

Study 44

Among the 7 trials (6 placebo and 1 active control), only one, Study 44, a 6 month long, 16 site multiclinic, USA based, RCT of placebo add-on design provides statistically significant findings supporting the effectiveness of ropinirole as an adjunct to l-dopa/carbidopa therapy.

Study 44 employed a 2:1 randomization; 95 of the 143 patients enrolled were assigned to ropinirole. Randomization was stratified on the use of selegiline, a feature unique to this study among the 4 carried out to assess ropinirole efficacy in late PD. The scheme for ropinirole and l-dopa administration was complicated; essentially, patients were expected to be titrated, over a period of 4 weeks from a starting dose of a dose of 0.75 mg a day (given in 3 dived doses) upwards, at weekly intervals, to a maximum dose of 24 mg a days. When a dose of 7.5 mg (2.5,

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[7] Studies 30, 34, 36, 38, 40. 43 and 44

tid) was reached, however, a forced reduction in l-dopa/carbidopa was begun. If a deterioration in clinical response occurred, l-dopa could not be added back, but it also could not be further reduced. As a consequence, a reduction in dose of l-dopa accompanied by a loss of therapeutic response had to be managed with the study drugs (i.e, placebo or ropinirole).

The dosing scheme is important because the primary outcome of the study was initially to have been based solely on the reduction in l-dopa dose attained[8]. Because of concern that a dose reduction might have been achieved at a cost of ropinirole patients being allowed to tolerate a less than maximal overall therapeutic response, the Division persuaded the sponsor to adopt a compound outcome strategy that relied upon the percent of patients achieving both a 20% reduction in l-dopa and a 20% reduction in time off while awake.

The statistical reviewer subsequently objected to this compound variable, pointing out that the treatment with a larger percent l-dopa reduction might win on this measure although, overall, a smaller proportion of the patients assigned to that treatment attained a 20% reduction in time off[9]. Accordingly, for this and other reasons, we evaluated in addition to the primary outcome variable, the change in percent time off while awake from baseline time off while awake among ropinirole and placebo assigned patients. Ropinirole was superior to placebo at a statistically significant level on both this and the primary outcome measure.

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[8] Implicit in the choice of this particular outcome measure is the belief extent among some experts that l-dopa treatment, per se, may contribute to the pace of degeneration of nigral striatal neurons.

[9] For example, if no patient within the placebo group was able to tolerate a 20% reduction in l-dopa, the group would receive no credit even if all its members experienced a 20% reduction in time off while awake. In contrast, if 50% of the ropinirole assigned patients tolerated a dose reduction, and only 10% of them had a 20% or more reduction in time off while awake, ropinirole would, on the compound outcome measure, be declared the superior treatment--an incoherent result.

Other advanced PD studies

None of the remaining completed trials when considered individually provide statistically significant findings that support the sponsor's claims, although all but one of the 6, a bromocriptine controlled trial, are said to be directionally favorable to ropinirole (see following Table).

Table Summarizing other advanced PD studies.

Study	Max daily dose and control condition	duration in weeks	#Ropinirole and # control	Outcome: "+" is a directionally favorable result for Ropinirole
30	8, placebo	12	23/23	+
34	10, placebo	12	46/22	+, but marginally
36	10, placebo	12	20/9	+
38	8, placebo	12	24/12	+
40	1mg,2mg,4mg, and placebo	8	31/30 /29/31	+
43	24 mg vs 40mg of bromocriptine	24	367/188	direction unknown; but difference not significant

In sum, the reports of the effectiveness trials submitted, evaluated according to current agency interpretations of the effectiveness requirements of the FD&C Act, provide "substantial evidence" that Requip™ [ropinirole] will be effective for use when administered under the conditions of use recommended in the draft labeling developed by the Division.

Safety for use

Because no pharmacologically active drug substance is entirely free of

risk, the conclusion that a drug has been shown to be "safe for use," is actually no more than an opinion, albeit one offered by an individual reasonably knowledgeable in the management of the condition that is the intended target of treatment, that the benefits associated with the use of the drug are sufficient to outweigh its known risks of use.

Accordingly, risk to benefit assessments are inherently arguable, all the more so because each turns not only on personal sentiments about the nature of risks and the benefits of a drug, but upon incomplete and imperfect information concerning the drug's risks.

To illustrate, the Division's recommendation to declare the NDA for Requip™ approvable allows the inference that ropinirole has been found, upon review, to be reasonably free of a potential/capacity to cause death[10] and/or serious injury at an unacceptably high incidence[11]. The validity of this inference, however, turns on the truth of an implicit assumption about clinical experience gained with ropinirole (i.e., that it is of a kind and of an extent that is sufficient to detect all important risks likely to be associated with ropinirole's use). Unfortunately, in this particular instance, the assumption tends toward the sanguine because the extent of experience gained with ropinirole at the higher end of the range of doses the sponsor seeks to recommend for its use is not only limited in terms of the numbers of patients exposed, but in the extent to which patient attributes that might be expected to modify the risks associated with ropinirole use (e.g., co-morbidity, concomitant drug use, etc.) have been explored.

For example, Requip's use appears to be associated with a substantive

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[10] It is noteworthy, in fact, that the actual incidence of fatalities viewed in terms of deaths per patient-time is, on face, very favorable to ropinirole. Specifically, among patients with both early and advanced PD, the fatality rate was lower for those on ropinirole than for those on either placebo or bromocriptine. These relative risks, however, must be viewed with caution because they compare patients pooled across studies with very different subject selection and exclusion rules.

[11] I am fully mindful that I have begged the definition of what does or does not represent "an unacceptably high incidence."

incidence of syncope. Because we suspect that both orthostatic hypotension and bradycardia (presumed causes of syncope) are dose related, the relative paucity of clinical experience reported in the NDA with ropinirole at higher daily doses (12 to 24 mg/day) is disconcerting.

Consequently, although I believe that it is reasonable to conclude that ropinirole is safe for use at the lower end of the daily dosing range (e.g., the maximum daily dose was 10 mg in Study 32), additional data and analyses are required to permit the construction of labeling that can responsibly be deemed to satisfy the Act's requirement that the product be "safe for use" and "effective in use" under the conditions of use recommended in its approved labeling.)

For this reason, the approvable action letter and the draft division labeling advance requests for additional analyses of the clinical experience (i.e., original NDA and the Safety Update combined) that has been gained with ropinirole.

These qualifications and observations notwithstanding, there is nothing in the administrative file regarding the reports submitted to the Requip™ NDA that would lead me to conclude that the ropinirole is unsafe for use as a treatment for Parkinson's Disease. Again, it deserves emphasis that this in no way implies that the use of Requip™ will be free of risk. To the contrary, as noted, Requip™ can cause orthostatic hypotension, bradycardia, and syncope[12]. On the other hand, past agency actions document that this risk is readily acceptable in a treatment for PD. Specifically, dopamine agonists already marketed for the management of PD (i.e., bromocriptine, pergolide) cause the very same set of presumably autonomic nervous system mediated adverse events. Like these marketed drugs, ropinirole also causes hallucinations, nausea, vomiting and a host of other not so troubling AEs.

In sum, although the NDA can be declared approvable at this point in time, I urge strongly that the declaration of its approvable status be conveyed

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[12] While a simple faint is in and of itself not an especially dangerous phenomenon, it can cause harm, even serious injury and death, either as a consequence of when or where it occurs, or because it may cause a secondary medical event (i.e., stroke, seizure, heart attack).

to the firm in the company of a clear message that additional analyses of clinical data will be required before it will be possible to draft product labeling under which ropinirole can be legally marketed.

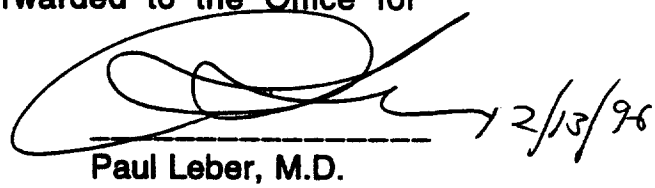
Labeling

For reasons related to the limitations described above, the draft of Requip™ product labeling developed by the Division is incomplete, many of its sections serving primarily as a means to convey comments and instructions to the sponsor about proposed revisions.

Conclusion and Recommendations

The sponsor has provided substantial evidence of ropinirole's efficacy as a treatment for the signs and symptoms of PD. The evidence submitted also supports a conclusion that ropinirole can be used without unacceptable risk in the management of patients with PD. However, before the application may be approved, additional information, some of which, unfortunately, I can only presume is available to the sponsor, must be assembled, analyzed and submitted. This additional information is critical because without it, we would be unable to draft labeling under which I could reasonably and responsibly conclude that Requip™ would be both safe for use and effective in use.

I am mindful that, in light of this view, a case could be made for declaring the NDA not approvable. I am persuaded, however, that although such an approach is defensible, it is less desirable than an approvable action conveyed in the company of the caveats and requests enumerated in the draft labeling and action letter being forwarded to the Office for issuance.



Paul Leber, M.D.
December 13, 1996

cc NDA 20-658
HFD-101
Temple
HFD-120
Katz
Rouzer-Kammeyer
Burkhart
Fitzgerald
Nighswander
HFD-710
Sahlroot
Jin

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 7, 1997

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Ropinirole; NDA 20-658

TO: Dr. Leber

We have here a clearly effective drug with adverse effects characteristic of the D2 agonist class but with one of them, those adverse effects, orthostatic hypotension and syncope, seemingly more prominent than usual and far more prominent than a contemporaneously evaluated drug of similar pharmacology. We do not know why these symptoms are so prominent and therefore do not know how they can be avoided. Part of the problem seems likely to be SKB's avoidance of well-designed dose-finding efforts, although they did examine results vs dose during titration and it is pretty clear this is a drug that will need titrating. It is reassuring, as Dr. Katz points out, that no one seems to die of these problems (mortality on ropinirole is lower, if anything, than controls) but syncope and falls in the elderly or infirm are not trivial and the combination of hypotension and bradycardia is capable of killing.

I would therefore like to inject a note of somewhat greater uncertainty into the approvable letter, i.e., point out the need to understand better the dose needed for effect and the doses associated with hypotension and syncope. It is possible a conspicuous warning will be needed if approval is eventually granted.

To see what we have to work with, let's consider, for the major studies:

1. Dose

2. Titration scheme

3. Evidence of effect over time (and thus in relation to titrated dose)

4. Rates of OH, syncope, for ropinirole and controls

5. Timing of syncope in relation to study and dose

1. Dose and Titration; effect over time.

Table 1 shows my understanding of dosing and the titration scheme used. The last column is either my "eyeballed" account of when effect was seen and the largest dose that could have been given by then, or results of the sponsor's assessment of response and dose. Study 54 shows reasonably clearly that much of the response did not show up till a dose of 20-24 mg was reached. [I think it shows this; the only time-related data in the review is categorical (response rate). It would be nice to see mean motor scores over time (with mean dose added to the time axis)].

Titration was slow by any standard (Table 2); i.e., it would be hard to attribute syncope and O.H. to excessively fast titration.

APPEARS THIS WAY
ON ORIGINAL

TABLE 1

Dosing			
Study	Dose Scheme	Top Dose	Maximum Effect Seen (wk/dose)
32 placebo- 12 week	Start 0.5 b.i.d. Titration ≤ 0.5 b.i.d./wk	5 mg b.i.d. wks. 10-12	9/4.5 mg b.i.d. (responder and CGI)
54 placebo- 6 mos	Start 0.25 t.i.d. titration x3 0.25/wk to 1 t.i.d. Titration x4 0.5/wk to 3 t.i.d. Titration x5 1.0/wk to 8 t.i.d. All had to reach 1.5 t.i.d./wk. After wk 4, pats seen q 2 wk	8 mg t.i.d.	(from table 20) Of 50 responders (30% improved motor score), 23 occurred at ≤ 12 mg (16 at ≤ 4 mg) but 20 needed 20-24 mg.
53 bromocriptine	Same as study 54		CGI improves from very early on ropinirole (but not bromocriptine) but full effect not till wk 16 or so. Mean dose never got past 8.3 mg.

TABLE 2

Study 54			
Dose by Week			
Time (week)	Dose, mean (mg)	Range (mg)	n
1	0.75		110
2	1.5		104
3	2.1		104
4	2.9		108
6	5.3		104
8	7.5		103
10	10.7		103
12	14.0		91
16	15.9		90
20	16.9		77
24	17.8		79

2. Orthostatic Effects and Syncope

Normal volunteers show a 15 mmHg systolic fall at one hour after a 1 mg dose, with an initial fall in HR of about 8 bpm. Nine of 110 volunteers on 1 mg had overt OH or were so symptomatic they could not stand up for BP measurement and one NV had syncope and 26 sec of asystole 1 hour after a 1 mg dose, surely as terrifying a phase 1 event as has been seen.

It is not hard to imagine that a more compromised vasculature would not have allowed the complete recovery seen in that NV.

The early patient studies are somewhat less complicated (no changing L-dopa). Studies 32 and 54 were placebo controlled trials with a total of about 300 patients. In study 54, there were two drop-outs associated with syncope, both late (163 d, 113 d) and both probably associated with other disease, sick sinus syndrome, and sinus bradycardia (safety MOR, p 31). Among the 515 early patients, only two others stopped because of a postural/orthostatic problem (at 41 and 175 days), the 175 d case associated with an AMI. This leaves only one reasonably timed (41 day is during titration) case of D/O due to orthostatic problems.

TABLE 3

Individual Cases

No deaths (Safety MOR, pgs. 26-28) seem directly related to syncope, but one patient (00043) may have died of the consequence of a fall (DVT following a fall, with sudden death, perhaps a PE).

APPEARS THIS WAY
ON ORIGINAL

Hypotension/syncope on ropinirole considered serious leading to D/C (Table 8.4)			
PID	AE	Duration	Study
007.001.00002	OH	4 d	C
020.001.00006	S. Bradycardia, Vasovagal episode, Syncope	1 d	A
023.003.00002	Sev. sympt post hypotension	20 (?)	A
040.004.00107	Syncope	217 d	A
043.076.01537	Orthostatis	85 d	A
053.026.00909	Bradycardia, hypoT (AMI)	175 d	E
053.035.01030	OH	41 d	E
057.001.00009	Bradycardia, dizziness, hypoT	12 d	C
099.010.00099	OH	43 d	A
054.002.00186	Syncope, SSS	163 d	E
054.019.00125	Syncope, sinus bradycardia	113 d	E

Placebo- None
Bromocriptine- None

A= Adjunct
E= Early
C= Clin Pharm

The safety review identifies three early patients dropping out associated with syncope of any severity or seriousness (Safety MOR, p 33 and Table 7.18), or 0.8%. Two are listed in Table 3 because they were considered serious. There is some doubt as to whether all cases were identified as syncope (MOR, p 33). Examination of study 54 (u=110) showed three drop-outs with syncope (2.6%), all coded as bradycardia. This includes the two 054 patients in Table 3, coded as serious. The third was not serious but led to D/O because of concerns caused by his daughter. There were some other drop-outs, e.g., in study 056 (not serious) that also were syncope associated.

Considering overall ADR's (See my Table 4) in early patients, postural hypotension and syncope are more common on ropinirole than placebo, but postural hypotension is not strikingly so, and not different from bromocriptine. Syncope (however defined) remains in excess compared to placebo or bromocriptine.

I remain somewhat uncertain about its meaning, however, as "syncope" occurs in 1.4% of the placebo group; I'd have thought passing out is rarer than that. Dizziness (See my Table 4) is not a very good indicator of drug-related effects.

Postural effects and syncope appear to occur at all doses (Safety MOR, Table 15.3), without an obvious excess at doses above 12 mg in either early or late PD patients.

TABLE 4

ADR Data, ET					
All				Study 54	
	Rop	Plbo	Brom	Rop	Plbo
n	515	147	167	116	
D/O AE	17.1	12.9	15.0		
D/O, Post/Syncope (See my Table 3) and MOR Table 7.18)	1.0 (?)	0	0	2.6 (MOR, p 33)	0
D/O Serious AE	5.0	5.4		6.9	3.2
ADR's				All Plbo control	
n	515	147	167	157	147
Hypotension				1.9	0
Hypotension, postural	7.0	4.8	10.8	6.4	4.3
Syncope	6.8	1.4	2.4	11.5	1.4
Dizziness	24.1	21.8	19.2	1.3	0.7
Bradycardia	?	?	?	1.9	2.0

Conclusion:

The description, dose-relationship, and timing of important orthostatic events still leaved something to be desired and more formal dose-finding may be in order. Study 32, after all, with a top dose of 10 mg (5 mg b.i.d.) showed effectiveness about as clearly as study 54 (top dose 24 mg, 8 mg t.i.d.) did; at the same time, it did appear that many patients in Study 54 needed 20-24 mg for full response. Titration studies, unfortunately, can be hard to analyze for D/R and safety D/R is particularly difficult.

All that said, however, it does appear that ropinirole is effective, acceptably tolerated by most patients and, with appropriate caution, usable in treating early and last PD. The hypotension/syncope, however, will need prominent discussion in labeling.

Robert Temple

Robert Temple, M.D.

SB hereby submits the following patent data in order to comply with the FDA Federal Register notice of October 3, 1994.

Pat. No.	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
4,452,808	December 7, 2002	drug/drug product composition	SmithKline Beckman Corporation	Stephen Venetianer, Vice President & Patent Counsel, Corporate Intellectual Property - UW2220 SmithKline Beecham Corporation 709 Swedeland Road King of Prussia, PA 19406
4,824,860	May 19, 2008	method of treatment	SmithKline & French Laboratories Limited	Stephen Venetianer, Vice President & Patent Counsel, Corporate Intellectual Property - UW2220 SmithKline Beecham Corporation 709 Swedeland Road King of Prussia, PA 19406

The undersigned declares that the U.S. Patent Number 4,452,802 covers the drug (compound) and drug product and composition for Ropinirole. The undersigned also declares that U.S. Patent Number 4,824,860 covers the method of treatment of Parkinson's disease with Ropinirole. This product is currently the subject of this application for which approval is being sought.

Stephen Venetianer
Vice President and Patent Counsel

EXCLUSIVITY SUMMARY for NDA # 20-658 SUPPL #_____

Trade Name Requip® Generic Name Ropinirole Tablets 0.25; 0.5; 1.0; 2.0; & 5.0 mg

Applicant Name SmithKline Beecham Pharmaceuticals HFD- 120

Approval Date Sept. 19, 1997

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /_X_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X_/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /_X_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #_____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND #_____ YES /___/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Signature 12-6-96
Date

Title: Project Manager

Signature of Division Director 12/13/96
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA # 20-658 Supplement # ____ Circle one: SE1, SE2, SE3, SE4, SE5, SE6

HFD-120 Trade (generic) name/dosage form: Requip (Ropinirole HCl) Tablets Action: AP (AE) NA

Applicant SmithKline Beecham Pharmaceuticals Therapeutic Class 1S

Indication(s) previously approved: None

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application: Primary and Adjunctive therapy in the symptomatic treatment of Parkinson's Disease.

(For supplements, answer the following questions in relation to the proposed indication.)

__ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

__ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. The applicant has committed to doing such stuilies as will be required.
___ (1) Studies are ongoing.
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

__ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

__ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Robert M. Hendrickson, PM — 12-6-96

Signature of Preparer and Title (PM, CSO, MD, other) **Date**

cc:Orig NDA
HFD-120/Div File
NDA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.
3/96

3.) Pediatric Studies are not needed.

The incidence of Parkinson's Disease in children is non-existant — with the possible exception of an occasional case in older adolescents.

— per Dr Gunther McCormick

SmithKline Beecham Pharmaceuticals

NDA 20-658

Requip™

Ropinirole Hydrochloride Tablets

DEBARMENT STATEMENT

SMITHKLINE BEECHAM PHARMACEUTICALS HEREBY CERTIFIES THAT SAID APPLICANT DID NOT USE IN ANY CAPACITY THE SERVICES OF ANY PERSON DEBARRED UNDER SUBSECTION (A) OR (B) [SECTION 306(A) OR (B) OF THE ACT], IN CONNECTION WITH THE NEW DRUG APPLICATION FOR REQUIP™ (ROPINIROLE HYDROCHLORIDE) TABLETS. THE APPLICANT FURTHER CERTIFIES THAT NO SUCH PERSON DEBARRED BY THE FOOD AND DRUG ADMINISTRATION WILL BE USED IN ANY CAPACITY IN FUTURE INVESTIGATIONS INVOLVING THIS DRUG PRODUCT, AT SUCH TIME AS SAID DEBARMENT BECOMES KNOWN TO THE SPONSOR.

(476)

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair, (HFD-530), NLRC Room 224

From: Division of Neuropharmacological Drug Products HFD-120
Attention: Frederick J. Abramek, Phone: 301-594-5526

8/8/95

Date: 8 August 1995

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: REQUIP NDA/ANDA# IND

Company Name: SmithKline Beecham Pharmaceuticals

Established name, including dosage form: ropinirole HCl, SK&F 101468-A oral tablets

Other trademarks by the same firm for companion products: N/A

Indications for Use (may be a summary if proposed statement is lengthy): symptomatic treatment of Parkinson's disease (tentative)

Initial comments from the submitter (concerns, observations, etc.):
None

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev May.94

Subject: Consult 476 revised

nsult #476 (HFD-530)

_QUIP Ropinirole Hydrochloride Tablets

A review revealed no names which sound like or look like the proposed name.

The Committee notes the proposed name has been submitted for review very early in the review process (IND stage). Under such circumstances, the Committee routinely recommends the proposed name be re-evaluated once an NDA has been submitted and the application is closer to approval since the universe of potential sound-alike/look-alike proprietary names is constantly changing.

The Committe has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

D L Boring, Chair

NOTE: The Committee believes the established for this product is -

Ropinirole Hydrochloride Tablets