CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20658

Trade Name: REQUIP

Generic Name: ROPINIROLE HYDROCHLORIDE

Sponsor: SMITHKLINE BEECHAM PHARMACEUTICALS

Approval Date: SEPTEMBER 19, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20658

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter			X	
Approvable Letter	X			
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI	X			
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)	X			
Correspondence				

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Application Number: NDA 20658

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-658

SEP 19 1997

SmithKline Beecham Pharmaceuticals
Attention: Eloise R. Scott, D.V.M.
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Dear Dr. Scott:

Please refer to your new drug application dated December 29, 1995, received January 2, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Requip™ (ropinirole hydrochloride) 0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg, and 5.0 mg tablets.

We acknowledge receipt of your submissions dated:

January 8, 1997	March 28, 1997	May 6, 1997	August 19, 1997 (2)
January 23,1997	April 9, 1997	June 20, 1997	August 25, 1997
February 13, 1997			

The User Fee goal date for this application is September 28, 1997.

This new drug application provides for the following indication:

> Requip™ is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.
>
> The effectiveness of Requip™ was demonstrated in randomized controlled trials in patients with early Parkinson's disease who were not receiving concomitant L-dopa therapy as well as in patients with advanced disease on concomitant L-dopa.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-658. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Robbin Nighswander, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely yours,

Robert Temple

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enc.: Draft labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20658

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

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NDA 20-658

JAN 2 1997

SmithKline Beecham Pharmaceuticals
Attention: Eloise R. Scott, D.V.M.
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Dear Dr. Scott:

Please refer to your December 29, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Requip™ (ropinirole hydrochloride) 0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg, and 5.0 mg Tablets.

We also acknowledge receipt of the following correspondence and amendments:

March 6, 1996	March 28, 1996	April 18, 1996 (2)	July 16, 1996
March 8, 1996	April 4, 1996	April 19, 1996	July 29, 1996
March 20, 1996	April 11, 1996	April 30, 1996	October 3, 1996
March 22, 1996	April 17, 1996	July 11, 1996	

We have completed the review of this application and it is approvable. Before the application may be approved, however, it will be necessary for you to develop labeling for Requip™ in accordance with the guidance offered in this letter and in the notes embedded within the text of the attached draft package insert. You will also need to provide additional reports and analyses both to comply with the usual pre-approval requirements (e.g., safety update, etc.) and to generate numerical estimates needed to complete product labeling.

Our review of the application has persuaded us that the reports contained provide sufficient evidence to support a conclusion that Requip, whether used with or without L-Dopa, can ameliorate some of the signs and symptoms of Parkinson's Disease. There are a number of unresolved issues, however.

The range of doses and dosing regimen under which Requip will be safe and effective for use.

Although the absolute numbers of patients exposed to ropinirole in the application appears, on face, to be sufficient to assess the safety of the drug, the exposure at the higher range of doses utilized in the controlled trials is limited, with only 176 patients receiving 24 mg/day and only 90 patients receiving a mean dose of 18 mg/day or more. Since the effectiveness trials were all of a titration design and provide data from patients having been exposed to a range of doses, it is not possible to recommend, with confidence, the range

of doses under which Requip will be both safe for use and effective in use. There is some evidence from Study 54 that the higher doses (20-24 mg) are needed for a full effect but time in study and dose may be confounded.

Although the original NDA is based upon experience gained in 1364 patients who participated in phase 2 and 3 studies, your presentation of the extent and duration of exposure for a given dose did not permit us to assess the adequacy of exposure to the higher doses.

It is possible that a full assessment of the relationship of dose to effect and toxicity will require further dose-response evaluation, but we do not believe the available data have yet been fully explored. Accordingly, before approval, you will need to provide for review a tabulation of the extent and duration of ropinirole use at dose of 12 mg/day or greater. This tabulation should reflect not only the information submitted to the original application, but that which will be included in the safety update as well. In addition, although there was no randomized, parallel, fixed dose, dose-response study carried out, so that dose-response assessment for favorable and unfavorable effects will be limited, available data should be used to the extent possible, e.g., by examining the titration period to define the effective dose. This has been done to some extent, but you should reexamine all data in an integrated way. For example, although in Study 54 higher doses seemed needed for response in some patients, in Study 32 better response rates were achieved with doses of less than 10 mg/day. In Study 53, the mean dose never exceeded 8.3 mg/day. You should also examine dose/exposure data to seek a relationship, if any, between adverse events incidence and severity, especially postural effects and syncope, dose, cumulative dose, and duration of exposure.

PACKAGE INSERT

Orthostatic Hypotension/Syncope Associated with Bradycardia

A WARNING statement concerning orthostatic hypotension, syncope and bradycardia is needed. The Warning in our draft is presented in a more or less generic format because it is intended for use in virtually any dopaminergic agonist drug product labeling. However, before it can be used for Requip, its content must be expounded to reflect data that apply specifically to experience gained with Requip during pre-marketing development.

The text of this section must advise the prescriber that the severity and incidence of the cardiovascular events observed during pre-marketing development of Requip may systemically underestimate the true risks because patients with significant cardiovascular disease (undoubtedly a significant proportion of the entire Parkinson's Disease population), who might be presumed to be more vulnerable to these effects, were excluded from the clinical trials.

Hallucinations

Hallucinations may be terrifying for the individual patient. It is critical, therefore, that the possibility of their occurrence be emphasized in labeling.

Information for Patients

We have extensively revised your proposal; the format of the section we propose follows an outline that would apply to any dopaminergic agonist intended for use in the treatment of Parkinson's Disease.

Dosage and Administration

A suggested format for the presentation of dosing recommendations is provided in the attached draft labeling. As noted earlier, however, this section's content cannot be made final until the analyses of extent and duration of use across the range of daily doses have been submitted and reviewed.

Other Labeling Issues

Please submit final printed labeling (FPL) identical in content, with requested sections supplied to the enclosed marked-up draft labeling. Please submit sixteen copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of that FPL may be required.

BIOPHARMACEUTICS

Please adopt the following dissolution methodology and specification for all strengths of ropinirole HCL tablets:

Apparatus:
Speed:
Medium:
Volume:
Specification:

ENVIRONMENTAL ASSESSMENT

Please provide replacement pages and/or an EA addendum to address the following deficiencies.

1. There are several input chemicals for the drug substance synthesis that are denoted by a SmithKline Beecham product number. It is not clear whether these are proprietary chemicals. If they are proprietary then the location of production should be identified. If the production facility has not already been discussed in the EA, then manufacturing site information should be included in format item 6.

2. The study report is identified as "preliminary", however, this is not indicated in the EA narrative. The final report should be provided or the test results listed in format item 8 should be footnoted/annotated appropriately.

3. The summary of environmental data included in Appendix V appears incomplete/preliminary. For example, one note is included that states "do not cite until study is completed".

MANUFACTURING AND CONTROLS

1. With regard to drug product stability testing/expiration dating, we have concluded that the data submitted will support a 12 month expiration date for drug product packaged in PVC blisters and 24 months in bottles. Furthermore, we ask that you provide a quantifiable source of light for the commercial batch stability testing to replace

2.

3. Please provide a specific test for the drug substance identity in your drug product specifications, are inadequate. Upon submission of this additional information, we will initiate methods validation in FDA labs.

4. Please describe the identity testing that you perform for acceptance of plastic packaging components.

SAFETY UPDATE

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you have accumulated that relates to the conditions under which the drug will be recommended for use.

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The details concerning construction of this tabulation should be discussed with the Division (see below). Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings that would affect the conclusion that Requip is safe for use, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event since the NDA cut-off date.

6. We ask that the following information/analyses be provided.

   a. Using a definition of cardiovascular disease (CVD) based upon medication use and reported underlying CVD at baseline, re-analyze adverse events in Studies 54 and 44, calculating relative risks for patients with CVD and compare those to relative risks in patients without evidence of CVD.

   b. Provide follow-up for all patients meeting F3 and F4 laboratory flags (as defined in your application).

   c. Describe the cardiovascular effects on the patient volunteers in the phase 1 studies. For example, the change in standing blood pressure by dose.

   d. Provide a description of ocular abnormalities observed in studies 054 and 032.

   e. Provide a clinical description of the abdominal pain reported in US study 054.

   f. Provide a clinical description of the events coded as confusion in US study 054 and 044. In addition, discuss the outcomes from these events.

7. Please explore the data base for gout or use of uricosuric agents.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

To facilitate our review, we have a number of additional requests as to the format and content of your update. Below, we provide an example of the type of tabulation that will be most helpful. Again, however, we urge that you meet with Division staff to develop plans for the actual conduct of the analyses that will support these displays.

For phase 2/3 studies, not including their extensions, please construct the following table that shows person-time as a function of daily dose and time since starting study drug. Provide separate tables for each study drug (e.g., Placebo, bromocriptine, L-dopa, etc.).

	Requip™ Daily Dose			
	0.75 mg	1.5 mg	2.25 mg	etc.
Day 1				
Days 2-7				
Week 2				
Week 3				
etc... to..				
Week 24				

In each cell, show the person time with the number of patients contributing to that cell in parentheses. The total person time across all cells should equal the total person time from the studies. A patient can contribute person-time to one or more cells.

Foreign Regulatory Update/labeling:

Please provide an update regarding the status of all ropinirole actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. In addition, we ask that you provide us current foreign labeling for ropinirole, along with the English translations when needed.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or

mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Robbin Nighswander, R.Ph.
Regulatory Management Officer
Telephone: (301) 594-2777

Sincerely yours,

Robert Temple

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

cc:
Original NDA 20-658
HFD-120/Div. Files
HFD-2/M.Lumpkin
HFD-92
HFD-120/Leber 12/12/96
/Katz/Rouzer-Kammeyer 12-13-96
/Burkhart/Knudsen 12/13/96 RV 12/13/96
/Fitzgerald 12/13/96
/Blum/Scarpetti 12/13/96 12/13/96
HFD-710/Sahlroot/Jin
HFD-860/Baweja/Ibrahim RB 12/13/96; SI 12/13/96
HFD-101/L.Carter
DISTRICT OFFICE
HFD-40/DDMAC (with draft labeling)
HFD-560/D.Bowen (with labeling - for OTC Drug Products Only)
drafted: rmn/October 28, 1996
rev:12/13/96/leber/nighswander/burkhart/rouzer
r/d Initials:
Final:

APPROVABLE (AE)