

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-024/S-005

ADMINISTRATIVE DOCUMENTS

NDA 50-752

Hoechst Marion Roussel, Inc.

rifapentine 150 mg tablet

13/14. Patent Information/Certification

13/14. Patent Information/Certification

U.S. Patent 4,002,752 covering the active ingredient Rifapentine expired January 11, 1994.

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: 021024 **Trade Name:** PRIFTIN (RIFAPENTINE) 150 MGS TABLETS
Supplement Number: 005 **Generic Name:** RIFAPENTINE
Supplement Type: SE7 **Dosage Form:**
Regulatory Action: OP **COMIS Indication:** TREATMENT OF PULMONARY TUBERCULOSIS
Action Date: 12/21/99

Indication # 1 treatment of pulmonary tuberculosis

Label Adequacy: Adequate for SOME pediatric age groups

Formulation Needed: Other

Comments (if any): August 1, 2000: The Division issued a Written Request to NDA 21-024 on June 19, 1998. This request stated that reports of the requested study must be submitted to the Agency on or before five years from June 19, 1998, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act. The June 19, 1998 Written Request further states that "It is preferred that the applicant develop a pediatric formulation; however, an alternative would be to develop directions for compounding a suspension from tablet for younger patients." The June 22, 1998 approval letter for NDA 21-024 states that "You commit to evaluate the pharmacokinetics of rifapentine and its major metabolite in children under 12 years of age. The currently available 150 mg film-coated tablet may not be suitable for administration to very small children." During a May 3, 2000 telephone conversation between Ms. Carol Childers of Aventis and Ms. Willard of the Division of Special Pathogen and Immunologic Drug Products, Ms. Childers stated that the current timeline is to begin pediatric studies by the 3rd or 4th quarter of 2000 and complete these studies by the 3rd or 4th quarter of 2001. It should be noted that the Pediatric Rule does not apply to SE7 supplements.

<u>Lower Range</u> 3 months	<u>Upper Range</u> 12 years	<u>Status</u> Deferred	<u>Date</u> 6/19/03
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This page was last edited on 10/19/00

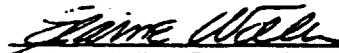
Signature - _____

Date

10/19/00

Debarment Certification

Hoechst Marion Roussel, Inc. hereby certifies that we did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) in connection with this application.



Elaine Waller, Pharm D
Vice President,
North American Drug Regulatory Affairs

22 Dec 97

Date

HFD-590
D. Willard

Memorandum of a Meeting

Meeting Date: April 10, 2000
Application: NDA 21-024/SLR-004 and SE7-005
Priftin (rifapentine) Tablets, 150 mg
Sponsor: Aventis Pharmaceuticals, Inc.
Subject: December 17, 1999 submission

Attendees:

Aventis

Carol Childers, Pharm. D. Regulatory Analyst, US Regulatory Affairs

FDA

Mark Goldberger, M.D., M.P.H.	Director, DSPIDP, HFD-590
Joyce Korvick, M.D., M.P.H.	Medical Officer, HFD-590
Linda Gosey	Microbiologist, HFD-590
Kofi Kumi, Ph.D.	Clinical Pharmacology and Biopharmaceutics, HFD-880
Owen G. McMaster, Ph.D.	Pharmacology/Toxicology Reviewer, HFD-590
Ellen C. Frank, R. Ph.	Chief, Project Management Staff, HFD-590
Diana Willard	Regulatory Health Project Manager, HFD-590

Background

The June 22, 1998 approval letter for Priftin (attached) outlined two accelerated approval commitments for Priftin as follows:

1. The final clinical Study Report issued upon completion of Clinical Study 008 will be submitted to the Agency for review. The projected timing is June 1999. In this final report both safety and efficacy data for the 2 years of follow-up will be included.
2. Aventis will continue to provide support for USPHS 22, conducted under the Center for Disease Control's (CDC) Investigational New Drug (IND) application for rifapentine, and to provide support for the pharmacokinetic sub-study undertaken in Study 22, developed because of the occurrence of rifampin monoresistance in four HIV-infected patients who relapsed in the rifapentine

treatment arm. It is agreed, since this study is being conducted by CDC under a separate IND, that CDC will submit study results upon completion of the study.

The December 17, 1999 submission to this NDA proposed revisions to the labeling to incorporate a Geriatric Use subsection and to add information to the labeling based on the Final Clinical Study Report for Protocol 008 (Item 1 above).

Meeting Objectives

1. To discuss division of the December 17, 1999 submission into two supplements: SLR-004 (a geriatric labeling supplement) and SE7-005 (to address Item 1 under accelerated approval commitments in the June 22, 1998 Priftin approval letter).
2. To discuss when NDA 21-024 would be removed from accelerated approval.
3. To discuss the status of USPHS 22.
4. To discuss other issues regarding review of the December 17, 1999 submission.

Discussion

Administrative Split of the December 17, 1999 Submission

The Division stated that the December 17, 1999 submission will be administratively split into two supplements, a geriatric labeling supplement and an efficacy supplement that addresses Item 1 of the commitments for accelerated approval stated in the June 22, 1998 Priftin approval letter. No User Fee will be assessed for this submission, as it will be classified as an SE7: Efficacy Supplement, Subpart H.

Removal from Accelerated Approval

The Division stated that submission of both Items 1 and 2 under accelerated approval in the June 22, 1998 approval letter are needed in order to remove Priftin from accelerated approval.

Status of USPHS 22

Ms. Childers stated that by early 2001 the last patient enrolled in USPHS 22 should have completed the 2 year follow-up period. The Division stated that a significant proportion of events occur very early after therapy ceases. The availability of these data to incorporate into the label could be beneficial: an earlier report could be submitted that did not contain all the data for the 2 year follow-up period. The Division recommended that Aventis contact the CDC regarding projected timelines for both interim and final study

reports. Ms. Childers stated that Aventis would seek clarity from the CDC regarding timeframes for availability of these reports and share that information with the Division. She further added that there is a partnership between the CDC and Quintiles that guides the sharing of data. Quintiles will be involved in when and how data are submitted to the Division.

March 20, 1999 Facsimile Transmission from Division to Aventis

A March 20, 2000 facsimile transmission (FAX) requested information regarding a listing of patients and outcome categories. Dr. Korvick inquired as to the timeline for a response to the March 20, 2000 FAX. Ms. Childers stated that a response to the March 20, 2000 FAX was submitted April 6, 2000. Ms. Willard stated that she would check with the Document Room for this submission.

Pharmacology Issue

Dr. McMaster noted that labeling in the December 17, 1999 submission proposed to add, under Precautions/Information for Patients, a statement regarding the potential for use of Priftin to produce a reddish coloration of breast milk. While noting that there is no information available regarding rifapentine and/or its' metabolites in breast milk, Ms. Childers stated that the purpose of the proposed revision is to bring the US labeling for Priftin in line with global labeling. There have not been any studies conducted to address this proposed labeling change. Aventis has no data regarding the expression of Priftin in breast milk.

Phase IV Commitments

The June 22, 1998 approval letter for Priftin outlined Phase IV microbiology studies to be conducted. Ms. Childers stated that in February of 1999 a submission containing proposed study designs was made to address the Phase IV microbiology commitments. Ms. Gosey stated that as the types of microbiology studies requested as Phase IV commitments for Priftin are routinely requested of sponsors, a guidance document is being prepared to assist with study design. This guidance document is currently about 50% complete. She stated that although the guidance document has not been completed and finalized, review of the February 1999 submission could begin.

Summary

The December 17, 1999 submission will be administratively divided into a geriatric labeling supplement and an efficacy supplement. Before Priftin can be removed from accelerated approval, data from USPHS 22 must be submitted to the NDA. Ms. Childers will contact the CDC to determine the timelines for availability of interim and final reports for USPHS 22.

NDA 21-024/S-004
April 10, 2000

Addendum

During a May 3, 2000 telephone conversation with Dr. Korvick and Ms. Willard, Ms. Childs stated that the last patient in USPHS 22 will complete the 2-year follow-up period in March of 2001. Ms. Childs further stated that the CDC plans to submit the preliminary report for USPHS 22 in June or July of 2000.

Some preliminary data for USPHS 22 was presented by the CDC during the American Thoracic Society meeting in Toronto on May 8, 2000.

Minutes Preparer: _____
Diana Willard

/S/

Concurrence, Meeting Chair: _____
Mark Goldberger, M.D., M.P.H.

/S/

Concurrence:

HFD-590/MGoldberger/5/10/00/E-mail
HFD-590/JKorvick/4/24/00/E-mail
HFD-590/LGosey/4/24/00/E-mail
HFD-880/KKumi/4/19/00/E-mail
HFD-590/EFrank/4/19/00/E-mail

cc:

Division Files
HFD-590.DWillard

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Special Pathogen
and Immunologic Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: January 7, 2000

To: Carol Childers, Pharm.D.
Regulatory Analyst

Address: Aventis Pharmaceuticals
10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Fax: (816) 966-6794
Phone: (800) 821-2630, ext. 5381

From: D. Laurie Bernato, Regulatory Project Manager

Through: Joyce Korvick, M.D., MPH, Medical Officer

Subject: NDA 21-024/SLR-004, PRIFTIN® (rifapentine) 150 mg tablets

The FDA is asking for clarification of the clinical study section of the proposed labeling changes. Please explain the discrepancies between your proposed labeling changes and the study report submitted June 29, 1999. Specifically, Table 2-2 lists the status of patients through 24 months of follow-up. You supplied a listing under tab 7 to support this data. However, review of your study report dated June 29, 1999, does not agree with the numbers reported as sputum negative. Specifically, Table 21, p. 74 reports the intent to treat analysis for treatment success at the end of 24 months. This number is 51.2% for Rifampin combination and 49% for the Rifapentine combination in the ITT analysis.

We are providing this information via facsimile for your convenience. Please feel free to contact me on (301) 827-2127 if you have any questions regarding the contents of this transmission or if a teleconference is needed.

/s/

D. Laurie Bernato,
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: March 20, 2000

To: Carol S. Childers, Pharm.D.
Regulatory Analyst
U.S. Drug Regulatory Affairs, Marketed Products

Address: Aventis Pharmaceuticals, Inc.
10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627 —
Fax: (816) 966-6794
Phone: (816) 966-5381

From: D. Laurie Bernato, R.N., MN, Regulatory Project Manager

Through: Joyce Korvick, M.D., MPH, Medical Officer
Linda Gosey, Microbiology Reviewer

Subject: NDA 21-024/, PRIFTIN® (rifapentine) 150-mg tablets

Thank you for your response of January 17, 2000 to the FDA facsimile dated January 7, 2000. This response did clarify the differences in analysis between the study report and the proposed labeling changes.

With regard to table 2.2 in your proposed label, we are having some difficulty in identifying the patients who changed categories from the initial label. The following requests will aid us in our final assessment of the proposed changes:

1. Please submit a listing of patient's response categories for the original label using the same format as the listing in TAB 7 of your submission dated December 17, 1999.
2. Regarding the outcome at the end of treatment for rifapentine: the denominator remains the same (it is assumed that all of the original patients are included), however, the numerator changes by one. Is this patient 50-0009? Provide the reason for the reclassification.
3. Regarding the treatment outcome for rifampin: the original denominator decreased by one patient. Please document the PID of the patient and the reason for change. The numerator changed by 3. Please identify the PID of these patients and state the reason for reclassifying the outcome.

4. Regarding the status in follow-up: we would like to discuss this with you after receipt of the line listing from request #1.

Regarding the proposed rewording of the resistance, which follows the table, please respond to the following:

1. Please explain why serial 2 fold dilutions of rifapentine and rifampin were not used when conducting in vitro susceptibility testing for the Phase III clinical trials.
2. Please explain how the MIC value of 0.25 ug/ml was obtained for isolates 55-0001 and 55-0002 when the following concentrations were tested: 0.125, 0.5, 2.0 and 8.0 ug/ml.

We are providing this information via facsimile for your convenience. Please feel free to contact me or Diana Willard, Regulatory Project Manager, at (301) 827-2127 if you have any questions regarding the contents of this transmission or if a teleconference is needed.

/s/

D. Laurie Bernato
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products