CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 21024

Trade Name: PRIFTIN 150 MG TABLETS

Generic Name: RIFAPENTINE

Sponsor: HOECHST MARION ROUSSEL, INC.

Approval Date: 06/22/98

Indication(s): TREATMENT OF PULMONARY TUBERCULOSIS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 21024

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative 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)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 21024

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-024

JUN 22 1998

Hoechst Marion Roussel, Inc.
Attention: Ms. Libby Hayes, B.S.
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

Dear Ms. Hayes:

Please refer to your new drug application dated December 22, 1997, received December 22, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PRIFTIN® (rifapentine) 150 mg tablets.

We acknowledge receipt of your submissions dated as follows.

January 23, 1998	March 19, 1998	June 3, 1998
January 28, 1998	March 27, 1998	June 4, 1998
January 29, 1998	April 6, 1998	June 5, 1998
February 3, 1998	April 13, 1998	June 9, 1998
February 5, 1998	April 28, 1998	June 10, 1998
February 9, 1998	April 30, 1998	June 11, 1998
February 16, 1998	May 12, 1998	June 16, 1998
March 3, 1998	May 19, 1998	June 22, 1998
March 16, 1998	May 22, 1998(3)	
March 18, 1998	May 29, 1998	

The User Fee goal date for this application is June 22, 1998.

This new drug application provides for the use of PRIFTIN® (rifapentine) 150 mg tablets in the treatment of pulmonary tuberculosis.

We have completed the review of this application, including the submitted draft labeling, according to the regulations for accelerated approval and have concluded that adequate information has been presented to approve PRIFTIN® (rifapentine) 150 mg tablets for use as recommended in the draft labeling in the submission dated June 15, 1998, as revised on June 22, 1998. Accordingly, the application is approved under 21 CFR 314.510. Approval is effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on June 22, 1998. 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 21-024. 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 labeling may be required.

Products approved under the Accelerated Approval Regulations (21 CFR 314.510) require further adequate and well-controlled studies to verify and describe clinical benefit. The accelerated approval commitments are not specifically designated in your June 15, 1998, letter; therefore, they are listed as follows:

We remind you of your Phase 4 commitments specified in your submission dated June 15, 1998, and to our June 11, 1998, facsimile, and to our letter dated June 5, 1998. These commitments, along with any completion dates agreed upon, are listed below.

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secret and/or

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information

We also remind you that 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.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Please submit one market package of the drug product when it is available.

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 Brenda Atkins, Project Manager, at (301) 827-2127.

Sincerely yours,

/S/

M. Dianne Murphy, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21024

MEDICAL REVIEW(S)

Date Submitted:	12/22/1997
Date Received:	12/22/1997
Date Assigned:	12/29/1997
Date Advisory Committee:	5/5/1998
Date Review Completed:	6/19/1998
Reviewers:	Marianne Mann, M.D. (safety) Joyce Korvick, M.D. (safety and efficacy) /S/ 6/19/98
Applicant:	Hoechst Marion Roussel 10236 Marion Park Drive P.O. Box 9627 Kansas City, MO 62134-0627
Drug:	Established Name: Rifapentine Proprietary Name: Priftin®
Drug Class:	Rifamycin, Antibiotic 3{[(4-cyclopentyl-1-piperazinyl) imino] methyl}rifamycin.
Formulation:	150 mg oral tablet, for oral administration
Proposed Indication:	Treatment of Pulmonary Tuberculosis

TABLE OF CONTENTS:

I. Background

I.A. Abbreviations (Anti-tuberculosis Drugs)

For the purposes of this NDA review, the following abbreviations will be used:

INH = Isoniazid
R = Rifampin
Rpt = Rifapentine
EMB = Ethambutol
PZA = Pyrazinamide

I.B. Scientific Background

Tuberculosis is the leading infectious cause of morbidity and mortality worldwide. The World Heath Organization estimates that approximately 90 million persons will become infected with tuberculosis and 30 million will die of the disease in the 1990's throughout the world (1,2). While the United States has been fortunate to have been able to control this problem, between 1985 and 1992 the reported number of TB cases increased by 20% . In 1990, there were 25,701 new cases of tuberculosis reported in the United States: 9,883 more cases than anticipated on the basis of earlier trends (3).

Over the past 5 years, as a result of the renewed TB treatment and prevention, there was a decrease in the number of new tuberculosis cases (19, 855 new cases of TB in 1997). One of the most successful strategies employed insures adherence to therapy: Directly Observed Therapy (DOT) (4,5). Because of the contagiousness of the disease, and the length of treatment necessary to ensure a cure, interventions to ensure full adherence to therapy are recommended and are mandated for all patients undergoing TB therapy in most states. Strategies to reduce treatment costs will be important to ensure the success of such programs in the future when decreases in funding might be expected.

Rifapentine is a rifamycin derivative antibiotic and has a similar profile of microbiological activity to rifampin. An important advantage of rifapentine over rifampin is a longer elimination half-life which may allow less frequent administration. This might improve patient compliance and reduce the number of provider contacts for directly observed therapy (DOT) of tuberculosis patients.

Thoracic Society (ATS) guidelines in 1994 for short course chemotherapy of TB include the following recommended regimen (6).

INH/R/PZA DAILY X 2 MOS followed by
INH/R DAILY (or 2-3 X per week) X 4 MOS
***EMB is also recommended with initial therapy until sensitivities are reported unless:

- < 4% INH resistance in community where patient is from
- No history of exposure to INH resistant case

New in this recommendation is the advocacy of ethambutol until drug susceptibility is reported. This new focus is due to rising levels of drug resistance, most notably resistance to INH. Notably, intermittent therapy has been shown as effective as daily therapy:

Short Course Chemotherapy for Primary TB

Regimen	Follow-up	Relapse Rate	# Doses
2 mos daily INH/R/PZA/S 4 mos daily INH/R (SING)	24 mos	2%	180
2 mos daily INH/R/PZA/S 4 mos daily INH/R (EA)	18 mos	2%	180
2 mos daily INH/R/PZA/S 4 mos daily INH/R (ALG)	24 mos	3%	180
2 mos daily INH/R/PZA/S 4 mos thrice weekly INH/R (SING)	6 mos	2%	114
1 mos daily INH/R/PZA/S 5 mos thrice weekly INH/R (SING)	6 mos	1%	96
2 mos daily INH/R/PZA/S 4 mos twice weekly INH/R (POL)	30 mos	0%	96
6 mos thrice weekly INH/R/PZA/EMB (HONGKONG)	18 mos	2%	78
6 mos thrice weekly INH/R/PZA/S (HONGKONG)	18 mos	1%	78
6 mos twice weekly INH/R/PZA/S (GDR)	12-48 mos	2%	52

INH=isoniazid, R=rifampin, PZA=Pyrazinamide, S=streptomycin, EMB=ethambutol , Ref. (7)

Comparable efficacy has been demonstrated for regimens which require less frequent dosing than the standard 180 day dosing regimens. With the increasing need for directly observed therapy (DOT) to assure patient compliance, a therapeutic regimen which requires less frequent dosing is desirable. Rifapentine is well absorbed following oral administration and has a prolonged elimination half-life of approximately 15 hours. Based on this favorable pharmacokinetic profile and the drug's known activity against M. tuberculosis, the proposed study requires only 76 DOT visits for drug administration over 6 months (2 mos daily INH/PZA/EMB and twice weekly Rpt followed by 4mos once weekly INH/Rpt). This trial, PR0008, is the primary subject of this NDA review.

I.C. Regulatory Background

Few controlled clinical trials in pulmonary tuberculosis have been conducted with this formulation of rifapentine. The pivotal trial is the largest randomized controlled trial to date. CDC is conducting a pulmonary tuberculosis study of rifapentine as daily therapy in the last 4 months of a six month regimen. No other controlled studies have been performed with rifapentine for the treatment of pulmonary tuberculosis. A small trial of 23 patients was conducted in South Africa to determine the early bacteriacidal activity of rifapentine in pulmonary tuberculosis patients. Two uncontrolled treatment studies in 51 AIDS patients with Mycobacterium avium complex were performed in Europe. Finally two controlled nongonococcal urethritis studies utilizing a prototype HMR formulation have been reported in the literature.

The published literature available on rifapentine's effect on pulmonary tuberculosis describes a Chinese-manufactured rifapentine. Trials reported in these publications used drug product manufactured in China for which the bioavailability and specifics of the formulation of the drug is unknown. For this reason, these studies have not been submitted to the NDA and do not contribute to the overall evaluation of the HMR rifapentine.

I.C.(1) Approved Indications

Rifapentine is a new molecular entity and is not approved for any indication.

I.C.(2) Pivotal Study

Rifapentine is not approved for any indication in the United States. In support of the indication for treatment of newly diagnosed uncomplicated pulmonary tuberculosis, the applicant has submitted a single pivotal study:

Protocol 000473PR0008: "Efficacy and Safety of Rifapentine Combination Therapy Compared to Standard Therapy in the Treatment of Previously Untreated Pulmonary Tuberculosis".

The trial was an open-label, randomized, phase III comparative trial for treatment of pulmonary tuberculosis in South Africa, the United States, and Canada. Patients were randomized to receive one of two treatment regimens:

Treatment A (control): 2 mos daily INH/R/PZA/EMB followed by
4 mos twice weekly INH/R
Treatment B: 2 mos daily INH/PZA/EMB and twice weekly Rpt followed by
4mos once weekly INH/Rpt.

The dose of rifapentine is 600 mg. The endpoints include sputum conversion at the end of treatment and tuberculosis relapse at 6 months and 2 years after the end of therapy. The targeted enrollment was approximately 600 patients.

Since a single pivitol trial has been accepted by the FDA for submission, it is of interest to comment that the CDC is currently conducting a trial designed to study the use of rifapentine/INH (once weekly) versus rifampin/INH (twice weekly) during the continuation phase of therapy (month 3 through 6) for patients with acute pulmonary tuberculosis. As of January, 1998, they had enrolled approximately 850 of the desired 1000 patients for this trial. Complete clinical results from this trial are not available for this NDA review, however reference to this trial will be made regarding the published results of relapse which occurred in patients who were HIV-seropositive (see comment in Section V.B. of this NDA review). This study will lend additional information regarding the most effective regimen for rifapentine upon its completion and analysis.

Medical Officer Comment:
During development of rifapentine for TB, the applicant was encouraged to submit 6 month follow-up data from one study, under the accelerated approval regulations (21CFR 314Sup-Part H). There is a need for new anti-tuberculosis medications, and for medications which will potentially increase the adherence to dosing thereby decreasing the potential for the development of resistant organisms. It was anticipated that rifapentine would be such an agent. Six month relapse data would serve as a surrogate for 2 year relapse data predictive of long term clinical benefit. Additional information from the CDC study will be an important part of the phase IV commitments given the accelerated approval.

I.C.(3) Other Controlled and Uncontrolled Studies

Human studies which have been performed with rifapentine include two preliminary phase II clinical trials performed in male patients with nongonococcal urethritis (NGU) which employed older formulations of rifapentine made by Marion Merrel Dow Inc. These studies are summarized:

Nongonococcal Urethritis Study in Finland:

This study enrolled 100 males with NGU who were evenly randomized to receive:

Group A:	Rifapentine 600 mg single oral dose.
Groups B1 and B2:	Rifapentine 600 mg oral dose every 24 hours for 3 days
Group C:	Rifapentine 600 mg oral dose every 24 hours for 6 days

The results of the study indicated that a 6 day course of therapy with rifapentine was required to adequately treat NGU, with 6 doses of rifapentine comparable to a 10-14 day course of tetracycline or erythromycin. Rifapentine was well-tolerated and no adverse events were reported during the study. There were no hematological or biochemical laboratory test abnormalities during this study.

Nongonococcal Urethritis Study in U.K.:

This study enrolled 31 males who received rifapentine 600 mg orally daily for 3 days. The results indicated that the clinical response to this regimen was inadequate. Of 26 evaluable patients, on 18 (69%) were cured and 8 patients (31%) required additional therapy. There were no adverse events reported or laboratory abnormalities noted.

Early Bactericidal Activity (EBA) Study:

In order to place the pharmacokinetic information in the context of the microbiologic effect, an early bactericidal activity (EBA) study was performed. This type of study performes quantitative sputum cultures during the first two weeks of mono-therapy of TB. The EBA of rifapentine was investigated in a South African study of patients with newly diagnosed pulmonary tuberculosis. Sixty-five patients were enrolled, of whom 44 met all inclusion criteria for the EBA study. Summary statistics for mean EBA's were calculated on 18 rifapentine sputa, 12 isoniazid sputa, and 14 rifampin sputa. Unadjusted mean EBA's for rifapentine, isoniazid, and rifampin were 0.2347, 0.4982, and 0.2991 $\log_{10}$ CFU/ml/day, respectively.

II. Chemistry, Manufacturing, and Controls

Rifapentine is a rifamycin derivative differing from rifampin by the presence of a cyclopentyl ring instead of a methyl group at the piperazinyl moiety. This provides rifapentine with a more lipophilic character than rifampin.

The chemistry manufacturing and controls information was discussed with the chemistry reviewer, Dr. John Smith, and no clinical concerns were identified. Please refer to the review by Dr. John Smith for additional chemistry information.

III. Preclinical Pharmacology and Toxicology

The applicant has performed acute toxicity studies, multiple dose studies for up to 1 year in rats and monkeys, mutagencity tests, a teratology study and a reproductive study with rifapentine. This information was discussed with Dr. Owen McMaster, and no clinical concerns were identified.

Please refer to the review by Dr. Owen McMaster for additional pharmaco-toxicology.

IV. Microbiology

Microbiological studies of *in vitro* and *in vivo* activity against Mycobacterium tuberculosis and nontuberculosis mycobacteria have also been completed and are covered in the Microbiology review by Dr. Linda Gosey. Additional discussions regarding the microbiology in the clinical trial was discussed in detail with Dr. Gosey and are included in the review.

Please refer to the review by Dr. Gosey for further microbiology information.

V. Clinical Pharmacology and Biopharmaceutics

A brief summary of the pharmacokinetics of rifapentine in healthy volunteers and in people with AIDS follows. Although rifapentine has a 15 hour half-life, pharmacokinetic studies did not demonstrate accumulation of rifapentine.

Please refer to the review by Dr. Kofi Kumi as well.

V.A. Pharmacokinetics and Bioavailability in Healthy Volunteers

Single dose (150-1200 mg) and multiple dose (150-600 mg q 24 hours and 600 mg q 72 hours) oral dose pharmacokinetic studies have been performed in humans. Results indicate that rifapentine is well absorbed. Peak plasma concentrations are achieved at approximately 7 hours after administration with food. Absorption is increased by approximately 50% when rifapentine is co-administered with food. Rifapentine has a long plasma half-life of approximately 15 hours. It is metabolized to an active metabolite, 25-desacetyl rifapentine, which has mean peak plasma concentrations of
rifapentine. It is hepatically metabolized, and it induces liver enzymes; thus the potential for drug interactions exists. Adverse events associated with rifampin should also be considered with rifapentine. These include liver function abnormalities, gastrointestinal disturbances, ataxia or muscular weakness, visual disturbances, fevers, pains in extremities, and general numbness. The red-orange discoloration of urine, feces, saliva and tears noted with rifampin may be less severe with rifapentine. Changes in blood urea nitrogen, serum uric acid, thrombocytopenia, leukopenia, and anemia have all been noted with the rifamycins.

V.B. Pharmacokinetics and Bioavailability in AIDS Patients

Mean Cmax and AUC (0-∞) values of rifapentine were 20% and lower, respectively, in asymptomatic human immunodeficiency virus (HIV)-infected subjects (17 subjects) as compared to healthy, young male volunteers. However, Cmax and AUC(0-∞) values of 25-desacetyl rifapentine metabolite in asymptomatic HIV-infected subjects were 6% to 10% and 9% to 18% higher, respectively, as compared to healthy subjects. Mean

CLpo value of rifapentine was 29% to 30% higher in asymptomatic HIV-infected subjects as compared to healthy, young male volunteers. Rifapentine was well-tolerated in asymptomatic HIV-infected subjects.

V.C. Indinavir Drug Interaction Study:

In addition, a drug-drug interaction study between indinavir and rifapentine were performed: 600 mg rifapentine was administered twice weekly for 14 days plus 800 mg indinavir 3 times a day for an additional 14 days (24 subjects). Indinavir Cmax decreased by 55% while AUC reduced by 70%. Indinavir did not affect the pharmacokinetics of rifapentine.

Medical Officer Comment:

The bioavailability of rifapentine in asymptomatic HIV-infected subjects was reduced by approximately compared with healthy volunteers. This is concerning, and may result in lower efficacy of the product in this particular patient population. Although the pivotal clinical trial performed by Hoechst Marion Roussel excluded HIV-infected subjects, the CDC trial noted relapses in five of thirty HIV-seropositive patients randomized to once weekly rifapentine (6). Of note, 4 of these 5 relapses were with rifampin mono-resistant strains of TB. The CDC trial has since been modified to exclude HIV-seropositive patients from enrollment. Rifapentine, should be used with extreme caution in patients which HIV, and once weekly dosing in the continuation phase should be avoided. Additionally, any patients receiving indinavir should probably not receive rifapentine until further characterization of effective dosing is performed.

It should be noted that rifampin reduces the AUC's of protease inhibitors to a similar degree, if not larger, than those noted for rifapentine.

VI. Efficacy Review

VI.A. Pivotal Clinical Trial: 000473PR0008

The applicant has completed a single pivotal study which is the subject of this review entitled:

"Efficacy and Safety of Rifapentine Combination Therapy Compared to Standard Therapy in the Treatment of Previously Untreated Pulmonary Tuberculosis."

VI.B. Study Design of Pivotal Trial

The study was a phase III open label, randomized, multi-center study of patients with previously untreated pulmonary tuberculosis. Patients were evenly randomized to Treatment A, a standard regimen, or Treatment B who received rifapentine in combination with other therapies. The purpose of the trial was to determine if combination therapy with rifapentine dosed twice per week in the intensive phase and once weekly in the continuation phase is as safe and effective as a standard antituberculous regimen. The experimental regimen varies the frequency of the rifapentine and the INH administration from the control arm (Treatment A).

Treatment A: 2 mos daily INH/R/PZA/EMB followed by
4 mos twice weekly INH/R
Treatment B: 2 mos daily INH/PZA/EMB and twice weekly Rpt followed by
4mos once weekly INH/Rpt.

Medical Officer Comment:
The control arm (Treatment A) is a standard therapy for pulmonary tuberculosis, and is an acceptable active control. This design was selected at a time when daily therapy during the first two months of treatment (intensive phase), was more widely accepted by clinicians than intermittent therapy throughout 6 months of treatment. There is a potential for adherence problems with the rifapentine regimen which might influence the overall outcome, in that some patients may not understand that the need to attend clinic daily during the first two months and not just twice per week. For additional comments regarding adherence in this study and its effect on outcome, see comments in Section VI.D.(4).

VI.B.(1) Eligibility Criteria

Inclusion criteria:

a. males or females of any race,

b. females of childbearing potential and males who were sexually active must have used one of the following contraceptive methods: barrier methods including condom, intravaginal spermicide, and diaphragm, cervical cap, intrauterine device (IUD). Use of oral, intramuscularly injected, or subcutaneously implanted contraceptives were excluded.

c. presumed diagnosis of tuberculosis. The following were strongly recommended:
- •smear positive for acid fast bacilli within 10 days of study enrollment
- •or, if smear negative, a diagnosis of TB was likely based on clinical signs and symptoms and typical chest radiographic changes.

d. one or more sputum cultures were obtained at enrollment and sent to a designated central laboratory. Approximately 2-3 weeks are required to identify M. tuberculosis using BACTEC methodology. Patients with negative BACTEC results were discontinued from the study.

e. serum creatinine $\leq$ 2 X upper limit of normal (ULN), total bilirubin and ALT (SGPT) $\leq$ 3 X ULN.

f. patients had to be considered cooperative and compliant with medications and all outpatient visits or would be admitted to hospital if necessary.

g. patients were expected to be accessible throughout the 30 month study.

h. patients signed informed consent.

Exclusion criteria:

a. patients with resistant isolates were to be discontinued from the study and treated appropriately by the physician. (M. tuberculosis isolate was resistant to isoniazid, rifapentine, rifampin, or pyrazinamide.)

b. patients with a past history of diagnosis and treatment for tuberculosis.

c. patients who had received antituberculous therapy for their current episode for more than 7 days prior to entry. Antituberculous drugs include: isoniazid, rifampin, rifabutin, pyrazinamide, ethambutol, streptomycin, ethionamide, capreomycin, cycloserine, thiacetazone, or para-aminosalicylate sodium.

d. patients who had received more than 14 days of therapy within 30 days of study entry with other agents that have antituberculous activity such as: amikacin, kanamycin, ciprofloxacin, ofloxacin, sparfloxacin, levofloxacin, clofazimine, and dapsone.

e. patients who had received preventive chemoprophylactic therapy for TB which was discontinued within 30 days of study entry.

f. patients who had close contact with a person with multi-drug resistant TB.

g. patients who had significant hepatic, neurologic, endocrine, renal, or other major system disease.

h. patients with extrapulmonary tuberculosis.

i. patients taking systemic corticosteroids.

j. patients with known hypersensistivity to study drugs.

k. patients with history of complications due to alcoholism or alcoholic liver disease.

l. patients who had been using I.V. drugs recently.

m. patients who were HIV seropositive. A relatively small number of HIV seropositive patients who were inadvertently enrolled due to a delay in diagnosis, however, continued to participate in the trial.

n. patients who were unwilling to comply with study procedures or requirements for full 30 months.

o. females with a positive serum pregnancy test or who were breast-feeding.

p. patients who had received any investigational drug(s) within 30 days of enrollment.

q. Karnofsky score < 60.

VI.B.(2) Randomization Methods and Blinding

This was an open label, randomized study. Patients were evenly randomized into two treatment groups. Study medications were packaged and randomized in blocks/modules of two (One treatment A and one Treatment B), and were identified by treatment assignment

numbers. To ensure that a balanced subset of patients had been enrolled at each site, investigators were instructed to assign medication in sequential numerical order per module of medications received.

VI.B.(3) Study Sites

Sites were anticipated in approximately 20 sites in South Africa, 10 sites in Europe, and 10-15 sites in North America. The South African sites were asked to enroll between 10-100 patients per site; the North American and European sites were asked to enroll a minimum of 10 patients per site, however patient accrual might occasionally be less than 10 per site at some sites.

VI.B.(4) Study Drug Assignment

640 patients were to be evenly randomized to one of two treatment regimens as shown below

Treatment Regimens Proposed for Study

	Treatment A	Treatment B
Intensive Phase (60 days)	Isoniazid 300 mg/day	Isoniazid 300 mg/day
	Rifampin 450 or 600 mg daily*	Rifapentine 600 mg twice a week
	Pyrazinamide 1500 or 2000 mg/day*	Pyrazinamide 1500 or 2000 mg/day*
	Ethambutol 800 or 1200 mg/day*	Ethambutol 800 or 1200 mg/day*
	Pyridoxine 50 mg/day	Pyridoxine 50 mg/day
Continuation Phase (120 days)	Isoniazid 600 or 900 mg twice a week*	Isoniazid 600 or 900 mg once a week*
	Rifampin 450 or 600 mg* twice a week	Rifapentine 600 mg once a week
	Pyridoxine 50 mg/day	Pyridoxine 50 mg/day

*note: higher doses of study drugs were given to patients who weighed ≥ 50 kg, while those who weighed < 50 kg received lower doses.

note: ethambutol was administered daily until susceptibility tests returned. If M. tuberculosis isolated was susceptible to INH/Rpt/R/PZA, then ethambutol was discontinued from the treatment regimen. If M. tuberculosis was resistant to INH/Rpt/R/PZA, the patient was discontinued from the study and treated appropriately.

Medial Officer's Comment:

The bi-weekly dosing regimen used in the intensive phase was suggested because of the generally acknowledged activity of such rifampin containing regimens. The intensive phase of Treatment B is supported given the known long half-life of rifapentine and that the other agents were dosed in their standard daily dosages. In addition, concern is raised regarding the efficacy of the continuation phase in which both isoniazid and rifapentine are given only once weekly. The use of once weekly isoniazid is of particular concern given its relatively short half-life. If the use of once weekly isoniazid may be subtherapeutic, Treatment B could theoretically predispose to the development of rifampin/rifapentine resistance and perhaps to excessive relapses. This review will carefully focus on relapse rates and the development of

rifamycin resistant organisms.

VI.B.(5) Concomitant Medications

Concomitant antimicrobials with antitubercular activity were not allowed during the intensive or continuation phases of the trial and were to be avoided during the 2 year follow-up period or used for only a limited time period (< 28 days) if necessary for a non-tuberculous infection. The use of barbiturates other than phenobarbitol were not allowed during the active treatment portion of the study due to their effect on inducing hepatic enzymes.

VI.B.(6) Clinical Evaluations

Patients had pretreatment screening procedures on day 0. They then had study procedures performed on day 1, 15, 30, 60, 90, 120, 150, and 180 with follow-up visits at 3, 6, 12, 18, and 24 months following treatment.

Sputa were collected from each patient for smear and culture at the following timepoints:

- Day 0 (pretreatment)
- Day 1 (day of study drug initiation)
- Day 2 (day 2 of study drug administration)
- Days 14/15 or 15/16 (± 7 days)
- At the end of every month of active treatment
- After 180 days of active treatment
- At 3, 6, 12, 18, and 24 months of follow-up

Clinical laboratory data including CBC, chemistry, and urinalysis was collected:

- Day 0 (pretreatment)
- Day 15 (± 7)
- Day 30 (± 7)
- Day 60 (± 7)
- Day 120 (± 7)
- Day 180 (±7)
- At 3 month follow-up visit (± 30 days)

Female patients underwent additional serum and urine testing for human chorionic gonadotropin on Day 0 (pretreatment).

Medical history and physical examination were performed on:

- Day 0 (pretreatment)
- Day 60 (± 7) following intensive phase of treatment
- Day 180 (± 7) following continuation phase of treatment
- At each follow-up visit

Chest radiographs were performed on:

- Day 0 (pretreatment)
- Day 60 (± 7) following intensive phase of treatment
- Day 180 (± 7) following continuation phase of treatment

- at 6 month and 18 month follow-up visits

Finally, weight was determined on each patient on days 0, 30, 60, 90, 120, 150 and 180. Clinical signs and symptoms (including cough, expectoration, hemoptysis, dyspnea, fever, loss of appetite, and weight loss) were monitored on days 0, 15, 30, 60, 90, 120, 150, 180 and at each post-treatment follow-up visit.

VI.B.(7) Patient Adherence

All doses of study drugs in both the intensive and continuation phases were administered under DOT (directly observed therapy) guidelines. Adherence to study medication was defined as follows:

Intensive Phase Criteria for Adherence:

1. Received 60 doses INH/R/PZA (Treatment A)

OR

2. Received 60 doses INH/PZA plus 17 doses Rpt (Treatment B)

PLUS

3. Missed no more than 7 consecutive days or a total of 14 days of therapy.

If the patient did not receive the required induction therapy at the end of 60 days, the investigator was to add the required number of additional doses of study medication to complete the requirements of (1) and (2) as listed above.

Continuation Phase Criteria for Adherence:

1. Received 32 doses if INH/R plus missed no more than 4 consecutive doses of required study medications (Treatment A).

OR

2. Received 16 doses if INH/Rpt plus missed no more than 2 consecutive doses of required study medications (Treatment B).

If the patient had not received the needed continuation therapy within 120 days, the investigator was to provide additional doses to complete 32 doses for Treatment A and 16 doses for Treatment B.

VI.B.(8) Study Objectives and Endpoints

The primary objectives of the study were:

1. To compare the efficacy of rifapentine combination therapy with standard combination therapy in the treatment of pulmonary tuberculosis by:

1.a. Determining the relative percentage of patients per treatment group with a negative sputum culture at the end of 6 months of post-treatment follow-up; and

1.b. Supporting this objective by determining the percentage of patients per treatment group with a negative sputum culture at the end of every month during the 180 day active treatment period and at 3, 12, 18, and 24 months during the post-treatment follow-up period.

2. To evaluate and compare the safety of rifapentine combination therapy with standard therapy in the treatment of pulmonary tuberculosis.

The secondary objective was:

1. To estimate the rifapentine population pharmacokinetic parameters, estimate inter and intra-patient variability of these parameters, and ascertain if and how patient demographics, concomitant medications, and disease state affect the disposition of rifapentine.

Efficacy at the end of intensive phase was an early surrogate marker for long term treatment success. It was measured by determining the percentage of patients in each treatment group with negative sputum cultures after 60 (± 7 days) of treatment.

Efficacy during the continuation phase at the end of 90, 20, 150, and 180 days (± 7 days) was measured by determining the percentage of patients in each treatment group with 2 consecutive negative sputum cultures which remained negative throughout the end of 180 days of treatment.

VI.B.(9) Definitions of Success/Failure/Relapse

Treatment Success: This was defined as achievement of negative sputum cultures in the active treatment period which was sustained through at least 6 months of post-treatment follow-up (and for the remainder of the 2 year follow-up period). Patients who remained on study, but for whom a culture result was unavailable (due to missed study or culture contamination) were categorized as a treatment success if and only if they presented with negative culture results from scheduled visits both prior to and following the missing data point.

Treatment Failure: This was defined as those patients who either failed to achieve negative sputum cultures, or who achieved negative cultures but failed to sustain them through at least 6 months of post-treatment follow-up up (and for the remainder of the 2 year follow-up period) or patients who failed to remain on study (due to death, adverse event, loss to follow-up, etc) regardless of last culture result.

Treatment Relapse: This was defined as a positive sputum which occurred after the patient's sputum had converted to negative and he or she had completed therapy. Relapse consists of a single culture with a colony count ≥ 10 and/or 2 or more cultures with a colony count < 10. Investigators were encouraged to obtain 2 additional relapse cultures when possible to confirm the relapse. A restriction fragment length polymorphism (RFLP) genetic analysis was performed on any relapse specimens and on the initial specimen to confirm the relapse and exclude re-infection.

Medical Officer Comment:

In addition to the applicant's analysis, distribution of patient outcomes accounting for lost to follow-up patients were considered in the FDA analysis. Also, patients who could not produce sputum and were continued to be followed were considered cures in the FDA analysis (See Section VI.E.).

VI.B.(10) Criteria for Discontinuation from Study

Patient were discontinued from the study for the following reasons:

- initial sputum smear did not isolate M. tuberculosis
- initial sputum culture isolate of M. tuberculosis was resistant to INH/R/Rpt/or PZA
- pretreatment serum pregnancy test was positive or patient became pregnant during study
- pretreatment serum creatinine was > 2 times ULN or total bilirubin or ALT was > 3 times ULN
- treatment failure
- unacceptable toxicity to study drugs
- voluntary withdrawals

Sputum specimens were withdrawn from analysis for the following reasons:

- contaminated cultures
- interruption of treatment
- culture not available

VI.B.(11) Statistical Analysis Plan

Three sets of patients were defined for statistical analysis:

All Exposed Patients: Includes all randomized patients who were exposed to study medications.

Intent to Treat Patients: Includes all exposed patients with a pretreatment sputum culture positive for M. tuberculosis which was sensitive to INH/R/Rpt/PZA, and who had a negative serum pregnancy test, serum creatinine ≤ 2 X ULN and serum bilirubin and ALT ≤ 3 X ULN.

Protocol Correct Patients: Includes all intent to treat patients who:

- had newly diagnosed and previously untreated pulmonary TB and did not have extrapulmonary TB at enrollment.
- had not taken investigational drugs within 30 days of enrollment.
- met compliance criteria throughout continuation phase of treatment.
- had sputum samples which allowed determination of efficacy.
- had no regular use of systemic corticosteroids.
- had not received more than 7 days of treatment for their current episode prior to study entry.
- had not received other agents with known antitubercular activity for more than 14 days within 30 days of study entry.
- completed first 6 months of follow-up.

The primary efficacy analyses were performed on the Intent-to-Treat patients. In the Intent-to-Treat analyses, all patients with missing data because of inadequate sputum samples or patients lost-to-follow-up were considered treatment failures if there were no information to the contrary.

The primary measure of efficacy was an intent to treat analysis. It compared cure rates of rifapentine combination therapy with standard therapy at 6 months post-treatment follow-up. Equivalence was defined in terms of the 95% confidence interval for the differences between

treatment arms; the requirement was that the upper bound of the 95% confidence interval for the proportion of rifampin successes minus the proportion of rifapentine successes should not exceed 10%. Equivalence at the end of 2 years was shown if there was no greater than a 15% difference in cure rates.

Medical Officer Comment:
As this is an accelerated approval application (21CFR314 subpart H), the 6 month, follow-up endpoint is emphasized here, with a commitment for additional follow-up through 2 years by the applicant. It is expected that the majority of relapses will occur by 6 months of follow-up, however, the "gold-standard" is 2 year relapse rate. Additional comments regarding the influence of study design on analysis are made in Sections VI.D. and VI.E..

VI.C. Study Results

VI.C.(1) Baseline Comparability of Rifampin and Rifapentine Treatment Arms

The following table compares baseline demographic characteristics of the patients enrolled in each treatment arm:

Table C-8. Analysis of Demographics and Baseline Characteristics for (Intent-to-Treat) Patients in Controlled Clinical Study (Protocol 000473PR0008)C-8.

Baseline Characteristics	*Rifampin Combination (N=284)*	*Rifapentine Combination (N=286)*	*Total (N=570)*	*P value* [1]
Gender				
Male N (%)	208 (73.2)	230 (80.4)	438 (76.8)	0.0422
Female N (%)	76 (26.8)	56 (19.6)	132 (23.2)	
Age (years)				
Mean±SD	37±12	37±11	37±11	0.7110
Range				
Race				
Caucasian N (%)	11 (3.9)	9 (3.1)	20 (3.5)	0.9359
Black N (%)	173 (60.9)	179 (62.6)	352 (61.8)	
Asian/Oriental N (%)	6 (2.1)	7 (2.4)	13 (2.3)	
Multiracial N (%)	94 (33.1)	91 (31.8)	185 (32.5)	
Weight (kg)				
Mean±SD	54±9	55±10	54±9	0.5911
Range				
Height (cm)				
Mean±SD	167±10	168±10	167±10	0.1739
Range				
Karnofsky Score				
Mean±SD	84±9	84±9	84±9	0.3448
Range				

[1] P value from Kruskal-Wallis test for continuous factors and chi-square for categorical factors

Supporting Data: Appendix C.2.6.1, Statistical Analysis 1: Treatment Comparison of Demographics and Baseline Characteristics in Controlled Clinical Study 000473PR0008
Appendix C.2.6.2, Listing 6: Demographics and Baseline Characteristics in Controlled Clinical Study 000473PR0008

Baseline demographics were balanced between treatment arms. Notably, approximately three quarters of the patients studied were male, and over 90% were black or multiracial.

Medical Officer Comment:
Baseline demographics are balanced, except for the predominance of males.

The applicant submits that the rifapentine treatment arm had more males (80.4% in rifapentine versus 73.2% in rifampin) and that this may explain, in part, the occurrence of higher relapse rates in this arm since males have traditionally done less well in tuberculosis trials. However, there is no reference given for this statement. Also notable is the fact that 2 females relapsed in the rifampin arm and 3 females relapsed in the rifapentine arm. Thus, relapses were not solely restricted to male subjects.

Finally, this study population is somewhat different from the US population in that there are fewer Caucasians and more multiracial patients than would be expected in the US.

Baseline risk factors for tuberculosis are summarized in the following table:

Table C-9. Summary of TB Risk Factors (Intent-to-Treat Patients) in the Controlled Clinical Study (Protocol 000473PR0008)

TB Risk Factors	*Rifampin Combination (N=284)*	*Rifapentine Combination (N=286)*
Homeless or living in shelter >6 months		
NO N(%)	242 (85.2)	244 (85.3)
YES N(%)	42 (14.8)	42 (14.7)
Unemployed for >1 year		
NO N(%)	181 (63.7)	189 (66.1)
YES N(%)	103 (36.3)	97 (33.9)
Occupational exposure		
NO N(%)	216 (76.1)	214 (74.8)
YES N(%)	68 (23.9)	72 (25.2)
Migrant farm worker		
NO N(%)	273 (96.1)	268 (93.7)
YES N(%)	11 (3.9)	18 (6.3)
Illicit drug use		
NO N(%)	267 (94.0)	276 (96.5)
YES N(%)	17 (6.0)	10 (3.5)
Alcohol (≥1 drink per day) use		
NO N(%)	216 (76.1)	216 (75.5)
YES N(%)	68 (23.9)	70 (24.5)
Communal living		
NO N(%)	204 (71.8)	195 (68.2)
YES N(%)	80 (28.2)	91 (31.8)
Close contact with a person with active TB within the past year		
NO N(%)	232 (81.7)	226 (79.0)
YES N(%)	52 (18.3)	60 (21.0)
Other known TB risk factors		
NO N(%)	276 (97.2)	273 (95.5)
YES N(%)	8 (2.8)	13 (4.5)

Supporting Data: Appendix C.2.6.2, Listing 7: TB Risk Factors in Controlled Clinical Study 000473PR0008

The baseline risk factors for TB were balanced between arms. The most common risk factors were unemployment (one third of patients), alcohol use (one quarter of patients) and communal living (approximately 30% of patients).

Baseline clinical signs and symptoms of tuberculosis are summarized in the following table:

Table C-12. Summary of Clinical Signs and Symptoms at Baseline (Intent-to-Treat Patients) in the Controlled Clinical Study (Protocol 000473PR0008

Clinical Signs & Symptoms		*Rifampin Combination (N=284) N(%)*	*Rifapentine Combination (N=286) N(%)*
Cough	NO	7 (2.5%)	7 (2.4%)
	YES	277 (97.5%)	279 (97.6%)
Expectoration	NO	19 (6.7%)	25 (8.7%)
	YES	265 (93.3%)	261 (91.3%)
Hemoptysis	NO	233 (82.0%)	224 (78.3%)
	YES	51 (18.0%)	62 (21.7%)
Sweats	NO	57 (20.1%)	48 (16.8%)
	YES	227 (79.9%)	238 (83.2%)
Loss of appetite	NO	104 (36.6%)	94 (32.9%)
	YES	180 (63.4%)	192 (67.1%)
Weight loss	NO	45 (15.8%)	32 (11.2%)
	YES	239 (84.2%)	254 (88.8%)
Fever [1]	NO	205 (72.2%)	198 (69.5%)
	YES	79 (27.8%)	87 (30.5%)

[1] Patient 000473PR0008-0034-0009 (rifapentine combination) did not have a response checked for fever; thus, N=285 for computing percentages in that cell.

Supporting Data: Appendix C.2.6.2, Listing 10: Clinical Signs and Symptoms in Controlled Clinical Study 000473PR0008

Medical Officer Comment:

Baseline signs and symptoms were balanced between treatment arms, although other than expectoration, each symptom listed in the table was slightly more common in the rifapentine arm. These differences are quite subtle, however, and most likely do not reflect a clinically meaningful difference between treatment arms in the severity of disease at baseline.

A summary of chest radiograph findings at baseline follows:

Table C-14. Summary of Chest X-Ray Findings at Baseline (Intent-to-Treat Patients) in the Controlled Clinical Study (Protocol 000473PR0008)			
Result	*Rifampin Combination (N=284) N(%)*	*Rifapentine Combination (N=286) N(%)*	*Total (N=570) N(%)*
Abnormal	284 (100)	286 (100)	570 (100)
Cavities	205 (72.2)	208 (72.7) [1]	413 (72.5)
Bilateral	163 (57.4)	183 (64) [2]	346 (60.7)
[1] Chi-square P value versus rifampin combination = .884 [2] Chi-square P value versus rifampin combination = .107			
Supporting Data: *Appendix C.2.6.1, Statistical Analysis 2: Treatment Comparisons of Baseline Chest X-Ray Results in Controlled Clinical Study 000473PR0008* *Appendix C.2.6.2, Listing 11: Chest X-Ray Results in Controlled Clinical Study 000473PR0008*			

The chest x-ray was abnormal at baseline for every patient in the intent-to-treat population (see above). Cavities were present in approximately 70% of patients in each arm. There was slightly more evidence of bilateral chest disease in the rifapentine arm versus the rifampin arm (64% versus 57.4%, respectively).

Medical Officer Comment:
As noted above, bilateral chest x-ray findings were slightly more common in the rifapentine arm. The applicant states that this supports their contention that rifapentine patients were more ill at baseline, and is perhaps the most supportive evidence for this contention. Further discussion in analysis Section VI.E..

The applicant asked Dr. Lynch (their central reader) to perform a retrospective analysis of baseline chest x-rays which were available in 235 of 284 (82.7%) rifampin combination patients and in 238 of 286 (83.2%) rifapentine subjects. Results of this analysis showed more cavitation total surface area in the rifapentine combination arm (mean of 17.0 ± 17.2 cm^2) compared to the rifampin combination arm (mean of 13.8 ± 13.8 cm^2). This analysis had a p-value of .032. In addition, Dr. Lynch assessed the relative percentage of patients with bilateral chest x-ray disease and found that 43.4% of the rifampin versus 53.8% of the rifapentine patients had bilateral disease (p-value of 0.032). Notably, these results differ somewhat from the site-read chest x-ray on all 284 rifampin and 286 rifapentine patients which revealed bilateral lung disease in 57.4% of rifampin versus 64% of rifapentine patients.

Medical Officer Comment:
The applicant performed an analysis per protocol on the site-read chest x-ray findings which revealed a somewhat higher incidence of bilateral disease in the rifapentine combination arm. This finding was not, however, of statistical significance. Retrospectively, the applicant then performed an analysis of baseline chest x-rays by the central reader that included approximately 80% of the patients in each treatment arm. This selective subgroup

analysis demonstrated a significantly higher incidence of bilateral disease in the rifapentine arm. It was this same selective subgroup analysis which revealed greater affected lung surface area in the rifapentine arm. It is apparent that the retrospective analyses are limited by the fact that only 80% of the patients in the database are available. They may also be biased since trial results were known, and this may have affected the reader's interpretation of the films (even if he was blinded).

It is also, not clear how one would actually use the data in a clinically meaningful way in interpreting the results.

VI.C.(2) Study Site Breakdown

Results of enrollment reveal that patients were enrolled at a total of 39 investigative sites. About 90% of the patients were enrolled at 29 sites in South Africa, with the remaining 10% of patients enrolled at 10 sites in North America (5 each in the United States and Canada).

Medical Officer Comment:

FDA's Division of Scientific Investigations inspected several sites in South Africa. The overall impression of the inspector was that the patients lived under conditions of extreme poverty and, overall, patients appeared malnourished.

VI.C.(3) Study Drug Exposure

The mean duration of study drug exposure for the intent-to-treat (ITT) patients was computed for those ITT patients who did not discontinue the study drug during a treatment phase (i.e. the intensive phase or the continuation phase). Results of this analysis revealed that the duration of study drug exposure during the intensive phase was comparable between treatment regimens (65.2 days for rifampin versus 64.2 days for rifapentine subjects). The mean duration of study drug exposure during the continuation phase was somewhat greater for rifampin subjects (117.4 days) compared to rifapentine subjects (112.5 days). This difference, however, probably simply reflects the less frequent dosing schedule for rifapentine patients who therefore completed the continuation phase somewhat earlier.

At FDA request, the applicant also provided the mean duration of study drug exposure for all patients who received at least one dose of study drug. Patients who discontinued study drug during a treatment phase were thus included in this analysis. Results of this analysis revealed that the duration of study drug exposure during the intensive phase remained comparable between treatment arms (62.2 days for rifampin versus 62.5 days for rifapentine subjects). The mean duration of study drug exposure during the continuation phase remained slightly greater for rifampin subjects (112.9 days) compared to rifapentine subjects (108.7 days). Again, this small difference reflects the different dosing schedules rather than any true difference in study drug exposure.

Medical Officer Comment:

Study drug exposure during both the intensive phase and continuation phase of therapy was comparable between treatment arms in at least two different analyses. Further analysis of adherence to drug in the intensive phase will be considered in the analysis section VI.E.(4).